

## Borderline type leprosy with variation of clinical manifestations and histopathology: two case reports



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### ABSTRACT

**Background:** Leprosy is a chronic disease caused by *Mycobacterium leprae*. This disease can be diagnosed if one of the four criteria is met. Histopathological examination can vary depending on the spectrum of the disease. The following describes two cases of borderline-type leprosy that aimed to increase understanding of the diagnosis and management of leprosy, especially the borderline type.

**Cases:** Both cases had complaints of numb spots on the body. The first case had more lesions than the second one with borderline-borderline histopathological examination results, while the second one had borderline lepromatous histopathological examination results. Both patients received the same therapy (multidrug therapy for multibacillary leprosy). During observation, there were no drug side effects that the patient could not tolerate. The prognosis in both cases is dubia, depending on the patient's adherence to treatment.

**Conclusion:** The diversity of clinical and histopathological features can occur, including cases of leprosy. Early diagnosis and prompt treatment should be started as possible to prevent disabilities.

**Keywords:** borderline, case report, histopathology, leprosy, *Mycobacterium leprae*.

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## INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. The bacteria reproduce slowly, and the average incubation period for the disease is 5 years. Symptoms can occur within one year but last for 20 years or more.<sup>1,2</sup> There were 127,558 new cases of leprosy detected globally in 2020, according to data from 139 countries from 6 regions of the World Health Organization (WHO).<sup>1</sup> New leprosy cases are detected each year in (sub)tropical regions such as India, Brazil, Indonesia, Bangladesh, and Ethiopia. In 2017, there were 15,920 new cases in Indonesia, which included 70 new cases in Bali Province.<sup>2</sup> Based on the Register of Dermatology and Venereology Outpatient Clinic at the Prof. dr. I G. N. G. Ngoerah General Hospital as the tertiary hospital in Bali, there were 32 new cases of leprosy in 2021.<sup>3</sup>

Leprosy was classified into five groups in 1962 by Ridley and Jopling based on

clinical, bacteriological, histological, and immunological features; polar tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), lepromatous borderline (BL) and leprosy polar lepromatous type (LL), while for therapeutic purposes, WHO classifies leprosy into paucibacillary (PB) and multibacillary (MB) types. TT and BT are generally included in PB-type leprosy, while MB leprosy includes BB, BL, and LL.<sup>4</sup> The borderline form of leprosy (BT, BB, BL) is immunologically unstable. Mid-borderline leprosy can mostly downgrade to polar lepromatous, especially if left untreated.<sup>5</sup> In BL-type leprosy, the immune system is weak enough to stop bacterial proliferation but sufficient to suppress inflammation that causes tissue damage.<sup>6</sup> In the following, we report two cases of borderline leprosy with various clinical and histopathological manifestations two. This case aimed to increase understanding of the diagnosis and management of leprosy, especially the borderline type.

## CASE REPORT

The first case was a 26-year-old male complaining of numb, red spots appearing on his body, back, and legs 3 months before going to the polyclinic. Initially, it appeared a little, and over time, some of these spots protruded and multiplied. The patient also complained of joint pain, especially in the elbows and knees, which had been felt for the past two weeks. There are no other complaints. The patient had never had complaints like this before. History of other diseases such as high blood pressure, diabetes, asthma, liver, kidney, heart disease, other skin diseases, and malignancy was denied by the patient.

The patient works as a private employee and is not married yet. His uncle had the same complaint and received routine treatment from the public health center, but he did not know his illness. Besides that, the patient's sister was also said to have a similar disease but did not receive treatment.

The second case was a 33-year-old male complaining of numbness on his feet and reddish spots since two months ago. History of other diseases was denied. The patient was treated and given an ointment when the first complaint appeared. However, the symptoms did not improve. The patient works as a private employee, and no family member has the same symptom.

The present and general status was obtained within normal limits on the physical examination of the first case. Dermatological status on right superior palpebral region obtained solitary erythematous nodule oval in shape, well-defined margin, 1 cm in diameter, shiny surface, soft consistency, painless on pressure. There were infiltrates in both ears. In the thoracoabdominal anterior and posterior region, inferior extremities, there were multiple well-defined plaques, erythematous, geographical in shapes, varying in size from 1 x 1 cm to 5 x 10 cm, scattered discretely, some in the form of “punched out” lesions and a “Swiss cheese” appearance. On the thoracoabdominal anterior and posterior also, and left and right superior extremities, there are erythematous macula-patch, well-defined margins, geographical in shape, the size varies from 0.3 x 0.8 cm – 1 x 2 cm, and multiple erythematous papules, well-defined margin, round in shape, 0.3 - 1 cm in diameter, scattered discretely as well (Figure 1).

On the sensibility examination, there was a decrease in touch, pain, and temperature sensation in several lesions. On examination of the peripheral nerves, there was enlargement and tenderness of the left ulnar nerve. Examination of the Semmer-Weinstein monofilament on palmar manus dextra et sinistra obtained and plantar pedis dextra et sinistra resulted sensory impairment. In the voluntary muscle test (VMT) examination, the results for hand muscle strength were 5555/5555 and leg muscles 5555/5555.

On physical examination of the second case, the general status was within normal limits. Dermatological status in the left inferior extremity region has multiple hypopigmented patches, well-defined margin, geographical in shape, varying in size from 1 x 1 cm – 2 x 3 cm, and also solitary hypopigmented plaque,



**Figure 1.** Papule-plaque multiple and some show “punched out” lesions and “Swiss cheese” appearance.

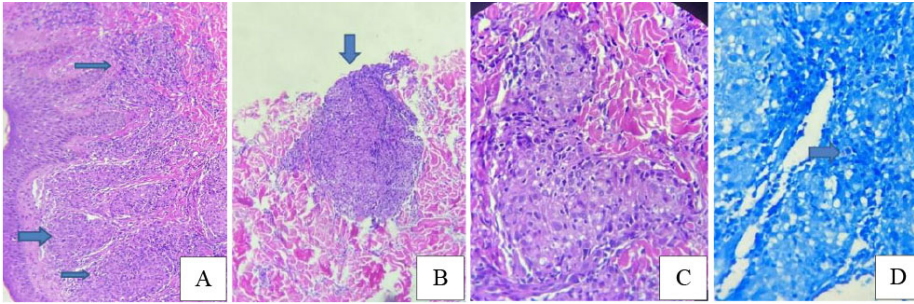


**Figure 2.** On the left inferior extremity region, there are punched-out lesions and hyperpigmented plaques on the posterior part of the right interior extremity.

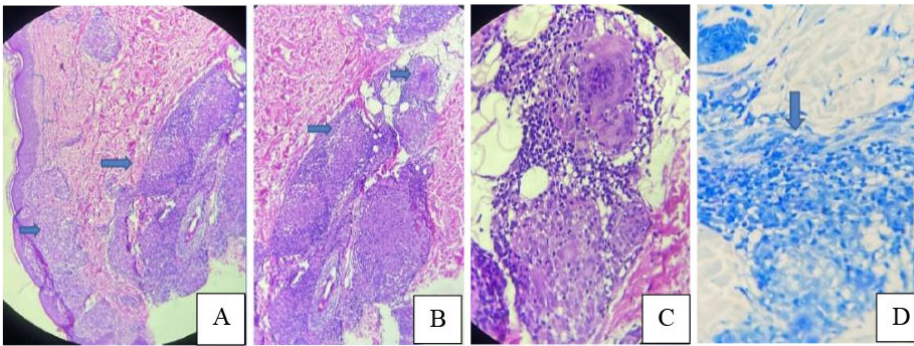
well-defined margin, geographical in shape, measuring 3x4 cm in the form of a “punched out” lesion. In the right inferior extremity region, there is a solitary erythema-hyperpigmented plaque geographical in shape, 1x2 cm in size (Figure 2). There was a decrease in touch, pain, and temperature in the sensibility examination. Examination of the peripheral nerves revealed enlargement of the left ulnar nerve. The Semmer-Weinstein monofilament on the palmar was blue, and the plantar was purple. On the VMT examination, the result was normal.

No acid-fast bacteria were found in the slit skin smear examination on both earlobes and skin lesions. KOH examination found no fungal elements, and laboratory examination complete blood and chemistry were also normal in both cases.

Histopathological examination from the first case obtained a result of the epidermis without signs of atypia and sub-epidermal area containing groups of granulomas that appear to be fused (back to back) and several groups in the dermis area. It appears that the granuloma contains a dense distribution of epithelioid



**Figure 3.** At 100x magnification, it appears that the sub-epidermal area contains groups of granulomas that seem to coalesce (back to back) (A). Groups of granulomas can be seen in the dermis area (B). At 400x magnification, the granuloma appears to contain a dense distribution of histiocyte epithelioid cells, and several Virchow cells can be observed, as well as a distribution of lymphocyte inflammatory cells among them (C) and positive AFB(D).



**Figure 4.** At 100x magnification, the skin epidermis is visible without signs of atypia with basket weave orthokeratosis type keratin. In the sub-epidermal area, (arrows) groups of granulomas appear that seem to coalesce (A). The granuloma appears to contain a dense distribution of epithelioid cells, histiocytes, Virchow cells, and several multinucleated giant cell types (B). Magnification 400x The granuloma appears to contain a dense distribution of epithelioid cells, histiocytes, Virchow cells, and several multinucleated giant cell types (C). Positive for acid fast bacilli at 400x magnification (D).

cells, histiocytes, and some Virchow cells can be observed. There was also a distribution of lymphocyte inflammatory cells among them. The morphological description is more suitable for BB-type leprosy. On Ziehl-Nielson's histochemical smear, it appears to contain acid-fast bacilli (Figure 3A-D).

In the second case, a microscopic picture of the biopsy tissue fragments appeared to be coated with the epidermis of the skin without signs of atypia with basket wave type keratin, orthokeratosis, and stroma of the dermis connective tissue and subcutaneous fat. In the sub-epidermal area, granuloma groups appear together, and several other groups appear in the dermis area. The granuloma appears to contain a dense distribution of epithelioid cells, histiocytes, Virchow

cells, and several multinucleated giant cell types. There is also a distribution of lymphocyte inflammatory cells, and several intact peripheral nerve foci can be observed. The morphological description corresponds to that of BL-type leprosy. On Ziehl-Nielson histochemical examination, acid-fast bacilli were found (Figure 4A-D).

The first patient's diagnosis was BB-type leprosy, and the second case was BL-type leprosy. Management for both patients was an MDT MB regimen, neurotropic vitamins B<sub>1</sub>, B<sub>6</sub>, and B<sub>12</sub> 1 tablet every 24 hours intraorally, and 10% urea cream every 12 hours topically. Tolerable side effects, such as color changing while urination, were observed and relieved without additional treatment. None of the patients reported having a leprosy reaction. Both patients will undergo

routine treatment considering the long-term therapy given and will report any side effects of the treatment that has been informed.

## DISCUSSION

Leprosy is a chronic granuloma infection affecting the skin, peripheral nerves, and other organs.<sup>7</sup> The course of the disease is determined by host immunity.<sup>8</sup> According to clinical, histopathological, and immunological criteria, leprosy is grouped into 6 forms according to the Ridley-Jopling classification.<sup>4,5,9</sup> Borderline leprosy covers a spectrum between that polar tuberculoid and polar lepromatous. In this type, two forms of leprosy are often found in one patient. This dimorphic appearance reflects the instability of borderline leprosy.<sup>5</sup>

Leprosy can occur at various ages but is most often found at 20-30 years or young adults. Men are most commonly affected with a male-to-female ratio of 2:1.<sup>10-13</sup> Based on research from Barua et al., 1 out of 132 leprosy patients who visited the clinic, and men dominated 68.2%. In this case, were two males aged 26 and 33.<sup>7</sup>

The diagnosis of leprosy can be made if one of three criteria is found or the histological characteristics typical for leprosy are found. The main signs of leprosy include (1) hypopigmented or erythematous skin lesions, such as macules or plaques, with loss of skin sensation; (2) thickening or enlargement of the peripheral nerves and signs of damage to them, such as loss of sensory, paralysis, or motor function with or without nerve enlargement; (3) Presence of acid-fast bacilli (AFB) in scrapings of skin lesions and/or biopsies. Early and correct diagnosis of leprosy is crucial to prevent permanent nerve damage.<sup>9,14-16</sup>

In the first case, two cardinal symptoms of leprosy were found, numb skin lesions and involvement of the left ulnar nerve. As in the second case, it met the diagnostic criteria for leprosy. In BB-type leprosy, the patient has an asymmetric annular plaque appearance. The classic BB lesion is a dimorphic appearance. The dimorphic lesion is typically annular in shape with an indistinct outer border and a well-defined "punched out" inner border. Patients may experience symmetrical or

asymmetrical nerve hypertrophy and/or neuritis. Several lesions in patients 10-30. Whereas in BL type leprosy, it can have macular, papular, or nodule lesions of various sizes and shapes with more than 30 lesions, in addition to the appearance of dimorphic lesions. An asymmetrical lesion with a shiny surface. Most lesions show a lepromatous appearance but also have a tuberculoid appearance. There is also asymmetrical involvement of the peripheral nerves.<sup>5</sup> All borderline patients have skin infiltration, varying from a few too many lesions in one or many body areas.<sup>4</sup>

In the first patient, clinical features were found in macula-patches, papules, and erythematous plaques. Besides that, in some of the first and second patient's lesions, an annular plaque appears with a firm inner edge and the outer edge sloping towards the surrounding skin, which is called a symmetrical punched-out lesion on the left and right legs. This picture is found in mid-borderline and borderline lepromatous leprosy. Normal skin in this plaque shows a "Swiss cheese" appearance.<sup>17</sup> The number of lesions that are more than 30 shows clinical manifestations of borderline lepromatous type of leprosy.<sup>5</sup> In the second case, a punched-out lesion was found on the patient's left leg, and a hyperpigmented macular lesion was found on the patient's right leg. Besides that, enlargement of the right ulnar nerve was also found. This manifestation corresponds to the mid-borderline type of leprosy.

Smear is a specific examination, but 70% of leprosy patients can have a negative result.<sup>18</sup> In this case, supporting examinations to help establish the diagnosis and determine therapy are slit skin smear examination, histopathology, routine blood tests, and blood chemistry. Slit skin smear examination in both cases did not find AFB.

Histological features in leprosy differ depending on the clinical form.<sup>18</sup> On histopathological examination, epithelioid cells were found in tuberculoid, BT, BB leprosy, and LL-type leprosy. Histiocytes and foamy macrophages are also present in BL and LL lesions.<sup>19</sup> Histological examination of BB leprosy can also show a dichotomous picture. On the one hand,

there are granulomas with epithelioid macrophages with less clear boundaries than the tuberculoid form; on the other hand, there are macrophages with abundant granular cytoplasm. Langerhans cells were not found. Large numbers of mycobacteria may be found. Histologically of BL-type leprosy is characterized by macrophages with abundant granular, sometimes foamy cytoplasm (Virchow cells) characteristic of the lepromatous form. Presence of peri adnexal granulomas consisting of clusters of epithelioid cells and foamy macrophages with many lymphocytes surrounding or part of the granuloma. There is a Grenz zone in most cases. The bacteria are easy to find and are more numerous than the other borderline forms. The infiltrate contains few to a few perineural lymphocytes.<sup>8,20</sup> In the first case, the histopathological picture found groups of granulomas containing a dense distribution of epithelioid cells, histiocytes, and several Virchow cells, and a distribution of lymphocyte inflammatory cells was also seen among them. In addition, on the histochemical staining of Ziehl-Nielsen, it appears to contain acid-fast bacilli organisms. The description corresponds to the BB type of leprosy. In the second case, clusters of granulomas contained densely distributed epithelioid cells, histiocytes, Virchow cells, and several multinucleated giant cells. There is also a distribution of lymphocyte inflammatory cells, and several intact peripheral nerve foci can be observed. On Ziehl-Nielsen histochemical examination, acid-fast bacilli were found. This morphological picture corresponds to BL-type leprosy.

The discrepancy between clinical manifestations and histopathological picture in leprosy patients often occurs, especially in BB-type leprosy, because of its unstable nature, where this type is prone to downgrading or upgrading. This is because the immune response still changes according to the course of leprosy and the patient's immunological status. Inadequate collection of biopsy specimens can also lead to clinical and histopathological manifestations discrepancies.<sup>11</sup>

A case report from Mayasari et al. showed differences in the clinical picture of leprosy with the histopathological examination results.<sup>21</sup> Histopathological differences between clinical and

histopathological diagnoses can arise because the clinical picture shows the overall morphology of the lesion caused by the underlying pathology. In contrast, the histopathological picture shows the microscopic and more accurate overall tissue response. Various factors can affect the histopathological diagnosis, including differences in sample size, location of the biopsied lesion, and selection of the site for biopsy plays an important role in histopathological diagnosis because clinically different lesions biopsied from the same patient may show different types of lesions, patient's immunological status and treatment at the time of biopsy.<sup>21,22</sup> The correlation of clinical and histopathological features and bacteriological index is more useful in determining the type of leprosy than considering a single parameter alone.<sup>22</sup> If discrepancies are found between clinical and histopathological diagnosis, patients are diagnosed and treated according to the more severe type to prevent inadequate treatment.<sup>7,21,22</sup> However, clinical features still play a major role in determining the diagnosis of leprosy. In this case, the patient received an MB MDT therapy regimen for 12-18 months.

The discovery of MDT by WHO in 1982 has led to a significant reduction in the incidence and prevalence of this disease throughout the world.<sup>7</sup> For adults, MB-type MDT (MDT-MB) in 1 package consists of Rifampicin 600 mg, Dapsone 100 mg, and Clofazimine 300 mg taken once a month under healthcare control, followed by Dapsone 100 mg and Clofazimine 50 mg once a day taken alone.

Sulfones (diamino diphenyl sulfone - DDS), or dapsone, have mainly bacteriostatic action with weak bactericidal activity. This drug acts as a para-aminobenzoic acid (PABA) antagonist, preventing its utilization in folic acid synthesis by *M. leprae*. Dapsone is well tolerated, with many side effects, which usually do not lead to treatment discontinuation. Side effects can be caused by gastritis, headache, hemolysis, methemoglobinemia, hemolytic anemia, agranulocytosis, hepatitis, dapsone syndrome, peripheral neuropathy, and nephrotic syndrome.<sup>6,17,23</sup>

Rifampicin (RMP), a semi-synthetic

derivative of rifamycin B, has mainly bactericidal action. This drug acts by inhibiting the enzyme RNA polymerase in bacterial multiplication. The effect often occurs when using this drug is a change in the color of body fluids, such as urine, to red or orange. In addition, liver toxicity, thrombocytopenia, although not common, shock, dyspnea, hemolytic anemia, and renal failure may also occur. Red face and neck, rash and pruritus, decreased appetite, nausea, vomiting, diarrhea, abdominal pain, malaise, loss of appetite, jaundice, purpura, epistaxis. Apart from the mentioned side effects, RMP is well tolerated by most patients.<sup>6,17,23</sup>

Clofazimine (CLF) has a mild bactericidal effect, acts slowly on *M. leprae*, and kills 99% of bacteria in approximately 5 months. CLF has an anti-inflammatory effect. The most important side effects of CLF are skin pigmentation, xerosis, hypersensitivity to light, gastrointestinal manifestations, and edema of the lower limbs. Pigmentation can be reduced after reducing sun exposure. In many cases, after stopping treatment, pigmentation persists for a year or more.<sup>6,17,23</sup>

Before starting multidrug therapy, basic laboratory monitoring should include complete blood count, liver and kidney function tests, and urinalysis. A glucose-6-phosphate dehydrogenase (G6PD) level is recommended before starting dapsone because patients with G6PD deficiency are at risk for severe hematological side effects, especially hemolytic anemia and methemoglobinemia. Complete blood tests were repeated every 3-6 months for patients taking dapsone and/or rifampicin.<sup>6,17,19,23</sup> In both cases, routine hematological examinations were performed, and complete blood count and blood chemistry were obtained at normal limits. Thus, the MDT MB package could be given in both cases.

The most important transmission mode is droplet infection via the nasal mucosa, followed by the development of a localized primary lesion, similar to tuberculosis. However, transcutaneous transmission after direct skin contact with untreated, ulcerated, multibacillary lepromatous nodules is also considered a possible transmission route.<sup>8</sup> Based on this, the information provided to patients

is about the side effects of treatment and routine control and possible transmission.

The prognosis of leprosy depends on several factors, such as the severity of the disease at diagnosis, earlier initiation of therapy, ease of seeking treatment, and adherence to therapy.<sup>24</sup> However, the limited availability of MDT therapy may interfere with patient adherence to treatment.

## CONCLUSION

Two cases of Borderline type leprosy have been reported with various clinical and histopathological manifestations in two men. Discrepancy of clinical manifestation, laboratory and histopathology finding affected by multifactorial including host immune response. Early diagnosis and treatment are important to prevent disability for leprosy cases.

## ETHICS IN PUBLICATION

Patients have given informed consent and agreed to share their clinical picture and history for publication and educational purposes.

## CONFLICT OF INTEREST

The author declares no competing interests.

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## AUTHORS' CONTRIBUTIONS

All the authors have read and agreed to the final manuscript.

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