The Unique Characteristic Skin Lesions of Borderline Leprosy with Severe Reversal Reaction: The Uncommon Case

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Keywords: borderline leprosy, reversal reaction, multi drug therapy, leprosy reaction therapy

Abstract: Leprosy is a chronic granulomatous progressive infectious disease caused by *Mycobacterium leprae*. Clinical features of leprosy is dependent upon the equilibrium between bacillary multiplication and the host cell-mediated immune response. Borderline leprosy is the immunologic intermediate of the granulomatous spectrum and is the most unstable area. The characteristic skin changes in borderline leprosy are said to be annular lesions with sharply margined interior and exterior margins. It could be complicated by potential intermittent hypersensitivity or leprosy reactions. Reversal reaction is one of leprosy reaction that most commonly occurs in the borderline cases. We report here a case of the unique characteristic skin lesions of borderline leprosy with reversal reaction. It was the uncommon manifestation because the lesions are distributed in all over the body. Because of the reversal reaction, the lesions become more prominent and have more sharply margined borders. This case report aims to describe the characteristic of skin lesions and clinical aspects of reversal reaction in leprosy. A 39-year-old man was diagnosed with borderline leprosy with reversal reaction who was treated by methylprednisolone for 2 weeks adding up to the multi drug therapy. There was clinical improvement and no side effect found during this study.

1 INTRODUCTION

Leprosy is one of a deliberately progressive infectious disease caused by *Mycobacterium leprae*. It was complicated by potential intermittent hypersensitivity reactions or lepra reactions. It is a disease which primarily affects the skin and peripheral nerve, and in highly bacillated state, any internal organ except central nervous system can be affected too. The damage to peripheral nerves results in sensory and motor impairment with characteristic dreadful abnormalities and debilities (Kumar and Kar, 2017).

Leprosy reaction are considered as acute or subacute episode, distinguished by cutaneous and systemic involvement. Those are caused by changes in the status of patient’s immune responses (Nery et al., 2013). This immunologically mediated episodes can be manifested as acute or subacute inflammation affecting the skin, nerves, mucous membrane and/or other sites which interrupt the chronic and placid course of leprosy. It can results in deformity and disability unless promptly and sufficiently treated. Well-timed initiation of treatment for reaction can reduce morbidity and prevent further deformities (Kumar and Kar, 2017). So that, this case report aims to describe the clinical aspects, immunopathogenesis, and the therapy of reversal reaction in leprosy.

2 CASE

A 39-year-old Indonesian man was referred to our hospital in September 2017 with a 3-month history of thickened red patches on almost all over his body. It was also accompanied with pain sensation on the site of lesions. Redness plaques appeared with whitish fine scales. He was also have a slight intermittent fever everytime he felt that the plaques thickened. Firstly, he got red patches on his trunk and face since about 8 months before admission. He was diagnosed with multibacillary leprosy for about 6 months in public health care and he have gotten the multidrug treatment for lepromatous leprosy (MDTL) since then.
According to the patient, he felt that the macule became thicker gradually after he took MDTL. When the rash became thicker, he took some medication from general practitioner (prednison) but he forgot about the dose that he took. There were no history of suffering from such disease before. History of taking or applying any traditional medicine before was denied. There were no history of food or drug allergy. History of contact with other persons who had leprosy was denied.

Figure 1: (A-D) The unique characteristic annular skin lesions of borderline leprosy with severe reversal reaction before management of leprosy reaction; (E-H) Clinical improvement of reversal reaction after 2 weeks of oral methylprednisolone along with MDT treatment. The redness macules still persist but thinner than before.

Physical examination discovered slight fever and multiple thick erythematous annular plaques that sharply marginated, some punched out lesions, some are covered with white fine scales and hypoesthetic (Fig. 1 A-D). No madarosis of the eyebrows or eyelashes was observed. There were no saddle nose or diffuse infiltrate on the face, and lagophthalmos. Thickened peripheral nerves were detected on the left and right ulnar nerves and accompanied with tenderness on palpation. In addition, peripheral neurological symptoms, including motoric, sensory and autonomic nerve disturbance were not detected based on a neurological assessment that included light touch, pin – prick test, thermal sensory test, manual muscle strength test and monofilament test.

However, acid-fast bacilli were not detected by the slit – skin smear test of the ear lobes and lesion (Bacterial Index: 0; Morphological Index: 0). Histological examination of the ear lobe skin reveals atrophy and short-flattening of rete ridge on the upper epidermis, there were some group of histiocyte or foam cell on superficial to deep dermis (Fig. 2 A-B). No specific microorganisms were identified by Ziehl – Nielsdon and Fite – Faraco staining. Serologic test by detecting antiphospholipid glycolipid I (anti PGL-1) antibody was positive by the score of IgM = 1553 (cutt off = 605 u/mL) and IgG = 927 (cutt off = 630 u/mL). In addition, the *M. leprae* deoxyribosenucleic acid (DNA) was detected from a skin sample by polymerase chain reaction (PCR) (Fig. 2 C).

Based on these findings, from physical and laboratory examination, the diagnosis of multibacillary, borderline (BB) leprosy was established. The patient also had severe reversal leprosy reaction but fortunately no disabilities was detected at that time. The patient were observed for

Figure 2: (A) Histologic examination of ear lobe. There were atrophy and short-falttening of the rete ridge of the epidermis. The group of histiocytes or foam cell on superficial to deep dermis and some bacteria are observed by Fite Farraco staining. So the conclusion were borderline (BB) leprosy; (B) *M. Leprae* deoxyribose – nucleic acid (DNA) was detected from a skin sample by polymerase chain reaction (PCR).
the period of time to observe the amendment of his condition.

Adding up to the multi drug therapy (MDT) that have been taken by him for about 6 months, we added methylprednisolone (32 mg/day) for a week. The original regimen dose of MDT were rifampicin (600 mg/month), clofazimine (300 mg/month and 50 mg/day), and dapsone (100 mg/day). After that, we found some improvement on the skin lesion. The redness macules still persist but thinner than before. So we tapered off the dose of methylprednisolone every 4-5 days to 4 mg/day. There was clinical improvement of reaction after 2 weeks of oral methylprednisolone along with MDT treatment (Fig. 1 E-H).

3 DISCUSSION

Leprosy is a chronic granulomatous infection caused by M. leprae. Based on the immunological response of the host to M. leprae, leprosy is classified into 5 major types: TT (tuberculoid), BT (borderline tuberculoid), BB (borderline), BL (borderline lepromatous), and LL (lepromatous) according to the Ridley – Jopling scale (Hattori et al., 2016).

Clinical features of leprosy is dependent upon the equilibrium between bacillary multiplication and the host cell-mediated immune response. This can reflect its pathology. The severity of the disease may be different from the presence of a not worth mentioning hypopigmented anesthetic skin patch to widespread damage to peripheral nerves and sign and symptoms suggestive of systemic involvement. Leprosy is exceptional infectious disease for the width of spectrum of signs and symptoms that it demonstrates. (Kumar and Kar, 2017).

Borderline leprosy is the immunologic intermediate of the granulomatous spectrum and is the most unstable area. It means that the patients can be quickly up- or downgrade to a more stable granulomatous bearing with or without a clinical reaction. Characteristic skin changes are said to be annular lesions with sharply margined interior and exterior margins, large plaques with islands of clinically normal skin within the plaque, giving a “Swiss cheese” appearance, or the classic dimorphic lesion. Because of its instability, the BB lesion is short lived and such patients are rarely seen (Lee et al., 2008). The characteristic skin lesions of borderline leprosy can be seen in our case. It shows us the unique annular plaque that become generalized to all over his body. It has sharp borders in both interior and exterior margins, it is also accompanied with normal skin within the plaque. From the clinical manifestation, our case simply show us the characteristic of the diagnosis of borderline leprosy.

Leprosy reactions are periodic episodes of acute inflammation caused by immune responses to M. leprae or its antigen overlaid on the chronic course of leprosy. These episodes have been classified into two types: reversal reaction (RR) and erythema nodosum leprosum (ENL). These are also known as type 1 and type 2 reactions respectively. RR occurs in the borderline cases and is a reflection of immunological instability. It is because of increasing in the delayed cellular hypersensitivity (DTH) or type IV hypersensitivity which is reflected by increase in lymphocyte transformation response (Kumar and Kar, 2017).

Reversal reactions most commonly occur in borderline and lepromatous forms of leprosy. Clinically, patient display abrupt inflammatory changes of the skin, nerves, or even both. Existing skin lesions become erythematous and edematous and may display ulcerative changes. Accompanying edema is common, whereas systemic symptoms are unusual (Kamath et al., 2014).

Reversal leprosy reaction result from the activation of cell immunity, expressed clinically by exacerbation of skin and peripheral nerve inflammation. It leads to sensory and motor alterations. Inappropriately, the activation of macrophages with the resulting obliteration of bacteria that can cause irreversible nerve damage and aggravating sensory and motor alterations. There is predominance of the pattern of Th-1 (IL-1β, TNF, IL-2, IFN-γ) in reversal reaction lesions. It is more dominant over the pattern of Th-2 (IL-4, IL-5, and IL-10), which predominates in multibacillary leprosy (Nery et al., 2013).

The high level of TNF-α, soluble IL-2 receptor and adhesion molecules indicate the concentration of local inflammation. Increasing of the expression of TNF-α mRNA in peripheral nerves and skin of patients with the borderline form, was observed in type 1 reactions. It seems that reversal reactions can be facilitated through Th1 lymphocytes, and cells of reactional lesions express the pro-inflammatory cytokines interferon-gamma (IFN-γ), interleukin 12 (IL-12), and oxygen free radicals (Nery et al., 2013).

According to Nery et al. (2013) reversal reaction episodes occur mainly during the first six months of polychemotherapy. This reaction can occur at any time but most frequently appears after starting multiple drug therapy. This reaction may be resolved spontaneously first, but worsen gradually. The patient suffered from the leprosy lesions that became
more thick and pain in palpation. He got tenderness on ulnar nerve as the symptom of neuritis. Fortunately, we did not find any deformity yet.

Treatment of reversal reaction intends to suppress the cellular immune response during the reaction. Early diagnosis and the initiation of the anti-inflammatory therapeutic are fundamental in order to avoid possible nerve damage. The identification of risk factors is advantageous since it leads to a more attentive monitoring of patients (Nery at al., 2013). Although, the exact events that trigger reversal reaction are unknown. Risk factors for this reaction include increasing age and the postpartum period (Kamath et al., 2014). Nery at al. (2013) said that the risk of reversal reaction was increasing due to several factors, such as vaccination, chemotherapy and puerperium. It can be happened since there are factors such as improvement in cell immunity among others, and this condition could be happened right after pregnancy, intercurrent infections, stress, trauma, and use of contraceptives.

Management of reversal reaction includes giving antileprosy treatment. Multidrug therapy has to be started or continued, if already started. This is important since this is required for continuous killing the M. leprae to reduce the bacterial/antigenic load in the skin and nerves (Kumar and Kar, 2017).

World Health Organization (WHO) recommends corticosteroid as the drug of choice for reversal reaction. It is because of its anti-inflammatory effects (Andrade et al., 2015). The exact mechanism of corticosteroid in reversal reaction has been discussed in several studies.

Corticosteroids encourage reduction in vascular permeability and vasodilation through inhibition of mediators, such as metabolites from arachidonic acid (prostaglandins) and inhibition of the discharge of platelet-activating factor (PAF), vasoactive amines, neuropeptides, interleukin-1 (IL-1), tumor ecrosis factor (TNF), and nitric oxide. Glucocorticoid also induce inhibition of the phagocytic capacity and production of oxygen free radicals (burst cell) and reduction in the number of eosinophils circulating in peripheral blood that causes rough granulation in polymorphonuclear neutrophils. It has a role in inhibition of tissue migration of monocyte and lymphocytes, with an increase in endothelial adhesion of lymphocytes. Not only that, but it also inhibit the vascular permeability as well as cellular migration and activation (Nery et al., 2013).

High dose prednisone (1 mg/kg/day) provides rapid symptomatic relief and helps reverse nerve function impairment. The regimen must be personalized individually based on whether nerve tenderness and motor or sensory deficits are present. Symptoms should be reconsidered every 2 weeks. If nerve function improves, the dose can be decreased by 2.5 to 5 mg; if there is no improvement or worsening of nerve function, the dose should be increased. Treatment may last up to 6 months or even years for those with neuritis (Kamath et al., 2014).

Initial dose of 40 mg prednisone was adequate to control most of reversal reaction. The patients with neural involvement may be need higher doses, corresponding to 1 mg/kg/day (60 mg) and sometimes even higher (2 mg/kg/day). The prednisone dose should be reduced following evidence of clinical improvement and upon reaching the dose 20 mg/day. It should be maintained for a long period of time until there is clinical regression and complete recovery of neural functions (Nery et al., 2013).

The standard dose of prednisolone schedule at referral center uses starting dose 1 mg/kg body weight/day to be continued until improvement of skin lesions is visible or nerve tenderness and pain diminishes. Then the dose should be decreased by 5 mg every 1-2 weeks. The crucial maintenance dose should be around 15-20 mg for several weeks or months. In the follow-up period, the dose should be decreased by 5 mg every 2-4 months. Graded sensory testing with monofilaments and voluntary muscle testing can guide the tapering of prednisolone. The duration should be long enough to cover the period during which antigen load is able to induce the CMI response. BT leprosy has to be 4-9 months, BB leprosy in 6-12 months, and BL leprosy in 6-24 months (Kumar and Kar, 2017).

In acute phase the inflamed nerves must be maintained in resting position. Appropriate splinting and padding gives relief. When the acute phase is over, passive and active exercises should be initiated. Additional nonsteroidal anti-inflammatory drugs (NSAIDs) may be required for relieving pain (Kumar and Kar, 2017).

In our case, we continued to give the multidrug therapy (MDT) that have been took by him for about 6 months. We added methylprednisolone (32 mg/day) for a week. The original regiment dose of MDT were rifampicin (600 mg/month), clofazimine (300 mg/month and 50 mg/day), and dapsone (100 mg/day). But we did not continue to give clofazimine treatment to the patient because of its melanogenic side effect. After that, we found some improvement on the skin lesion, so we tapered off the dose of methylprednisolone every 4-5 days to 4
mg/day. There was clinical improvement of reaction after 2 weeks of oral methylprednisolone along with MDT treatment.

4 CONCLUSION

Leprosy is a chronic granulomatous progressive infectious disease caused by *Mycobacterium leprae*. Borderline leprosy is the immunologic intermediate of the granulomatous spectrum and is the most unstable area. Characteristic skin changes are said to be annular lesions with sharply marginated interior and exterior margins, large plaques with islands of clinically normal skin within the plaque, or the classic dimorphic lesion. It was complicated by potential intermittent hypersensitivity reactions or lepra reactions. Leprosy reaction are considered as acute or subacute episode, distinguished by cutaneous and systemic involvement. These episodes have been classified into two types: reversal reaction (RR) or type 1 reaction and erythema nodosum lepromatous (ENL) or type 2 reaction. RR occurs in the borderline cases and is a reflection of immunological instability. Management of reversal reaction includes giving or continuing antileprosy treatment, good rest, splinting or padding, and analgetics. If it is accompanied by neuritis or severe reaction we can treat the patient with corticosteroids. If it is left untreated, surgical decompression of nerve that is inflamed may be useful for treating reversal reaction.

ACKNOWLEDGEMENT

The authors would like to express their genuine thanks to the Dermatovenereology Ward and Outpatient’s Clinic of Dr. Soetomo General Hospital Surabaya and patient who participated in this study.

REFERENCES
