31. Dapsone hypersensitivity syndrome overlaps reversal reaction in leprosy patient

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Case Report

Dapsone hypersensitivity syndrome overlaps reversal reaction in leprosy patient

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Abstract

Background: Leprosy is a chronic granulomatous infectious disease that primarily involves the skin and peripheral nerve and is caused by *Mycobacterium leprae*. Clinical features may vary depending on the patient's immune response. Reversal reaction due to increased immunity is common after treatment in patients with borderline leprosy. Dapsone hypersensitivity syndrome (DHS) is an adverse effect from dapsone therapy that may occur in 5-6 weeks to 6 months after initial treatment.
Case Illustration: A 47-year-old female complained of a spreading red patches on the skin of her trunk and extremities for three weeks duration. She also felt itchiness and tight sensation of rash. She experienced fever, pain, and numb lesions. She was diagnosed with leprosy and already had her sixth Multi Drug Therapy-Multi Bacillary (MDT-MB) regimen. From physical examination, on thoracic, abdominal, and extremities regions, multiple erythematous macules with hypoesthesia, sharply marginated ranging from size 3 to 5 cm along with discrete erythematous papules were found. Bacteriology index was zero. Patient was diagnosed with borderline leprosy with reversal reaction. After treated with prednisone, the patches became better, but the rash was still progressive. The rash had gotten significantly better after dapsone therapy was discontinued.
Discussion: Borderline leprosy is immunologically unstable and can be complicated by reversal reactions. Reversal reaction due to increased immunity and usually occurs after MDT treatment.
Conclusion: Reversal reaction got better with prednisone, while DHS was significantly improved after stopping dapsone therapy. Drug patch test should be conducted after the lesion resolves in order to establish DHS.

Keywords*: dapsone hypersensitivity syndrome, leprosy, reversal reaction*

Background

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M. leprae*). It primarily affects the peripheral nervous system, and later can affect skin, eyes, muscles, bones, testes and other organs, with the exception of the central nervous system. This disease is also known as morbus Hansen (MH), or Hansen's disease after the founder's name Gerhard Armauer Hansen.[1-3] To date, leprosy is still considered a significant health problem in the world. Its prevalence rate worldwide in the first quarter of 2014 reached 180,618 cases, with 116,396 cases from Southeast Asia. Indonesia is ranked as the third highest country in the world in terms of number of leprosy cases.[4] The East Java Provincial Health Office stated that East Java is the largest contributor of leprosy patients among other provinces. The incidence of leprosy in Indonesia in 2012 reached 18,853 people while the incidence of leprosy in East Java in 2012 reached 4,807 people (25.5% of national incidence) .[5]

One of the problems in leprosy is the reaction. Leprosy reaction occurs due to an imbalance of the host's immune response towards *M. leprae,* leading to clinical manifestations on the skin, nerves, and other organs. Leprosy reaction is an acute episode in the chronic course of the disease. Leprosy reactions may occur before, during and after treatment, but most commonly during or after treatment.[6,7]

Dapsone is an antibiotic and anti-inflammatory drug that can be used for treatment of various

diseases, namely: leprosy, vesicobullous dermatosis, vasculitis, malaria, and *Pneumonitis carinii* pneumonia. Dapsone has rare, but life-threatening side effects, known as dapsone hypersensitivity syndrome (DHS) or sulfon syndrome. It may occur in 5-6 weeks to 6 months after initial treatment in leprosy patients. DHS symptoms are recognized as a triage of fever, skin eruption, and organ involvement (lung, liver, nervous system, etc.[8]), and may also be accompanied by malaise, exfoliative dermatitis, jaundice with liver necrosis, lymphadenopathy, methemoglobinemia, and anemia.[9]

Case Illustration

A 47-year-old housewife complained about red spots getting progressively worse on her body and extremities starting 3 weeks prior. According to the patient, the red spots were thick and numb. She complained of pain and fever that started recently. The patient denied any untreated foot injury or dental also complained of slowly emerging rashes, which grew in number and were accompanied by itch and sensation of tightness. In addition, the patient cavity. The patient had been diagnosed with leprosy and was on the sixth month of Multi Drug Therapy - Multi Bacillary (MDT-MB) treatment, which she received from the public health center. There was no previous contact or past history regarding leprosy. History of allergic diseases, asthma, and rhinitis in patient's and her family was also refuted.

During physical examination, the patient was found to be in good general conditions and there were no signs of anemia, jaundice, cyanosis, and respiratory distress. The patient's blood pressure was 120/80 mmHg, heart rate was 88 times per minute, respiration was 20 times per minute, and axillary temperature was 37 degrees Celsius. During dermatology examination, multiple erythematous macules with hypoesthesia and well-defined border, ranging from 3 to 5 cm in size were found, along with multiple papules that spread evenly (**Figure 1**). Also, there were enlarged left and right ulnar nerves with pain during palpation. Muscle strength was within normal limits. There was a decrease in sensation on the red patches on the trunk, hands, and feet. There were no madarosis, lagophthalmus, and thickening of the ear lobe. Level of disability was 0 in the eyes and feet.

Complete blood test results showed that white blood cell count were 7.14 x 10^3 /µL, hemoglobin concentration was 12.6 g/dL, red blood cell count was 3.91 x 10^6 /µL, platelet was 217x10^3 / µL, and eosinophil count was 0.046. Based on the liver function test, AST and ALT levels were 23 U/L, and 33 U/L, respectively. On the examination of renal function, BUN level was 10 mg/dL and creatinine level was 0.9 U/L. Fasting blood glucose level was 62 mg/dL and 2 hours post-prandial blood glucose level was 103 mg/dL. Bacterial index was zero. Histopathology examination showed atrophy and rete ridge shortening on the epidermis. Granulomas composed of histiocytes and epitheloid cells with a few lymphocytes and neutrophils in the vicinity were found in the dermis, which corresponded to MH Borderline type with type 1 reaction. Acid fast bacilli were found using Fite-Faraco staining.

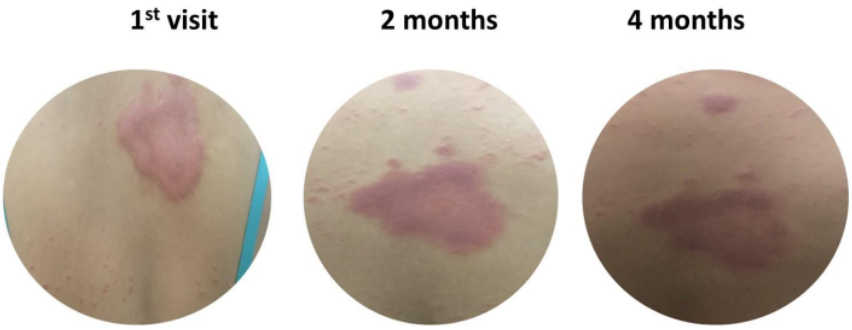

Figure 1. Lesions progression in number and size within four months.

The patient was diagnosed with borderline type leprosy with type 1 reaction. The patient continued the next MDT-MB therapy and received 25 mg/day of prednisone for two weeks and the dose was periodically tapered off every two weeks. In the initial four weeks of treatment, the patient's complaints were improved, the red spots decreased, but the patient complained of increasing number of rash (**Figure 2**). Treating the focal infection was advised and the patient decided to treat dental infections by the sixth week.

Unfortunately, the rash persisted and the itch and sensation of tightness became more prominent. Prednisone dose was increased to 25 mg/day and she also received 50 mg sodium diclofenac twice daily, but the clinical features did not improve. The patient was not taking others medication and denied applying any topical medication. She also received supportive therapy, such as 1 tablet of vitamin B complex once daily.

Three weeks later, in the 9th MDT-MB treatment, the complaint persisted and laboratory evaluation was performed. Complete blood count results showed white blood cell count was 8.6 x 10^3 /µL, hemoglobin concentration was 10.7 g/dL, red blood cell count was 3.38 x 10^6 /µL, platelet count was 292 x 10^3 / µL, and eosinophil count was 0.131.

She was suspected with DHS and managed to discontinue dapsone regimen. The patient's condition improved significantly and the rash disappeared a few weeks later. In the twelfth week, the patient no longer experienced itching and sensation of tightness and prednisone dose was decreased to 10 mg / day.

Discussion

Leprosy is common in developing countries due to the country's limited ability to provide adequate services in terms of health, education and socio-economic welfare to the community.[5]

To establish the diagnosis of leprosy, it is necessary to look for major signs or cardinal signs, namely: lesions (abnormalities) on the skin with decreased sensibility, skin disorders or lesions that may be numb, whitish or reddish spots, peripheral nerve thickening, accompanied by impaired neurological function and the discovery of *M. leprae* on bacteriological examination.[10] Multiple numb reddish spot and decreased sensibility in this patient corresponds to the cardinal signs of leprosy.

There are several types of classification for leprosy including the classification of Madrid, Ridley-Jopling, and the WHO classification.[10, 11] The Ridley-Jopling classification system is widely used in leprosy research because it defines the relationship between bacterial interactions with immunological response of a person, especially the response to cell-specific immunity.

The five types of leprosy according to Ridley-Jopling are based on patient immunity status, which are: tuberculoid leprosy (TT) with more stable cellular immunity response (CMI), borderline tuberculoid (BT), mid borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL). Given this classification, it is clear that the clinical manifestations of leprosy show a spectrum related to immunological status, especially CMI to *M. leprae*. This patient's symptoms correspond to multi-bacillary classification from WHO and borderline type (BB) from Ridley-Jopling classification, prompting the need for 12-month MDT-MB regimen.

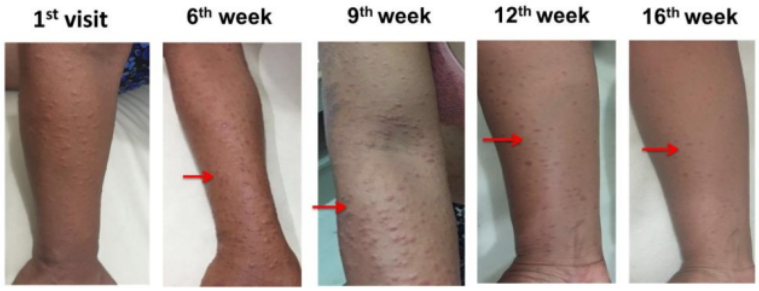

Figure 2. The progression of rash (arrow) in the upper extremity.

Leprosy reaction is defined as an acute inflammatory episode that can occur throughout the phases of leprosy. Reactions need to be managed because they are capable of causing impairment due to nerve damage. There are two types of leprosy reactions, type 1 reaction or reversal reaction (RR) and type 2 reaction or erythema nodosum leprosum (ENL). Both types of reactions are characterized based on the role of immunity, and may occur either before, during, or after MDT.[11, 12]

Type 1 leprosy reaction, also known as Reversal Reaction (RR), is caused by an increase in cellular mediated immunity (CMI) response to *M. leprae*, causing inflammation.[11, 12] This reaction is primarily characterized by skin lesions or nerve damage.[13] Borderline leprosy is at higher risk to develop type 1 reactions, although a small percentage of polar-type leprosy patients can also experience it.[14] Most type 1 reactions occur within the first 6 months of leprosy treatment.[13] Type 1 reaction is actually one of the delayed-type hypersensitivity reactions toward *M. leprae* antigen, located in the neuron (Schwann cells) and the skin (macrophages).[14] The immunopathology of type 1 reactions is mediated by elevated CMI through activation of CD4 T cells and macrophages that trigger the production of Th1 cytokines, such as tumor necrosis factor (TNF) -α, interferon IFN) -γ, interleukin (IL) -2, and IL-12. Increased levels of pro-inflammatory cytokines eventually lead to inflammatory symptoms of edema and pain.[12] In general, type 1 reaction occurs in BB-type leprosy. The term reversal or upgrading reaction refers to an increase in CMI.[2, 11]

Type 1 reaction can cause clinical symptoms, such as edema and erythema of existing skin lesions, the appearance of new lesions, neuritis, loss of motor and sensory function, and edema of the extremities and face. Type 1 reaction rarely shows systemic symptoms. Occasionally, widespread edema of the extremities or face may occur in some BL-type patients.[14] The RR criteria are found in this patient, such as red spots that become progressively worse located on her trunk and extremities during the sixth MDT-MB regimen. It can occur due to the instability of BB-type at the peak of Ridley-Jopling spectrum.

Therapeutic management of leprosy reactions involves four main principles: controlling acute neuritis to prevent anesthesia, paralysis and contractures; preventing optical nerve damage and blindness; pain control; and killing the bacteria to prevent the spread of disease.[15] Identifying the type of reactions that occur and then identifying the severity of the reaction type must be done before initiating the therapy. According to WHO, one of the disability prevention stages is the management of reactions. Various problems may arise in the management of reactions, such as recurrence, side effects, steroid resistance, and difficulty in obtaining medications; therefore research is continuously conducted to find alternative therapies for leprosy reactions.

One of the most important precursors to the treatment of leprosy reactions is the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in mild reactions and steroid administration in severe reactions.[7] Prednisone 25 mg/day is given in order to control acute symptom of RR, while sodium diclofenac is given to reduce the pain. The patient's condition got better at the first 4 weeks, but she suddenly experienced rashes followed by itch and sensation of tightness. The rash kept increasing in number; despite the fact that the focal infection was already resolved.

DHS was first proposed by Allday, Lowe, and Barnes as a hypersensitivity reaction of vitas vasculitis syndrome. DHS incidence ranges from 0.5-3% out of all of hypersensitivity reactions and can occur within the first 6 weeks to no later than 6 months. This condition is also known as "fifth week dapsone dermatitis". Patients would experience early reactions of skin peeling after 3 months therapy. Classic triad of DHS consists of fever, involvement of internal organs (liver, kidneys, hematological system, etc.), and skin eruptions.[8,16] In these patients, there are liver involvement characterized by nausea, jaundice, increased AST/ALT. Additionally, changes in hematologic systems were characterized by weakness and anemia and changes in the kidneys were characterized by elevated blood urea levels.

DHS has many clinical manifestations; hence it can be misdiagnosed as other diseases, such as leprosy reaction, drug reaction syndrome with eosinophilia and systemic symptoms, Stevens-Johnson Syndrome (SJS), as well as hematological diseases, such as leukemia and lymphoma, interstitial pneumonia, paraneoplastic disorders, and abnormalities of certain connective tissue. Clinical manifestations of DHS can be more serious than SJS and toxic epidermal necrolysis. In DHS, new skin lesions with edema may appear, not in previous skin lesions. Continuous fever with liver dysfunction may help to rule out the diagnosis of reversal reactions in

leprosy.[16] The pathogenesis of DHS is not yet clear, some studies suggest differences in production metabolism (increased activity or quantity of the P450 cytochrome polymorphic enzyme) and the detoxification of reactive metabolites (glutathione synthetase deficiency) play an important role in the hypersensitivity reaction of sulfonamide sensitivity. Toxic metabolite production (hydroxylamine) due to metabolism of dapsone imbalance can be a risk factor for hemolytic anemia.

General management includes discontinuation of dapsone as a suspected cause of the eruption, systemic steroid of oral prednisone 1 mg/kg/day or equivalent dose of methylprednisolone, and supportive therapy as well as minimizing the use of other drugs. Tapering off prednisolone (more than one month) is recommended as dapsone may be systemically present in the body for thirty five days by bonding with protein.[17, 18] Corticosteroids significantly reduce the symptoms of DHS, although no control studies have shown its efficacy.[17] Dexamethasone, another alternative of corticosteroids, is administered in the form of injection because it is more practical and works faster. Dexamethasone is administered in the dose of 3 x 5 mg for the first 12 days; after showing signs of recovery and the critical period has passed, the dose was tapered off. In this case, significant progression was seen after the discontinuation of dapsone regimen. The rash was resolved by the sixteenth week.

Conclusion

There are several possible causes for rashes and patches in leprosy patients; therefore, clinicians are expected to be able to distinguish clearly between reversal reaction and dapsone hypersensitivity syndrome so that they can provide appropriate therapy. The reversal reaction that occurs in these patients improves with prednisone therapy of 25 mg/day, which is slowly tapered off every 2 weeks. Increased rash and itch after the symptoms improved is a clinical marker to suspect dapsone hypersensitivity. This is supported by the fact that the patient's symptoms and lesions were significantly improved after the discontinuation of dapsone. The diagnosis of dapsone hypersensitivity can be established using drug patch test after the complaints and lesions have healed.

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