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THE EFFECT OF METHOTREXATE AS AN ALTERNATIVE THERAPY IN CUSHING SYNDROME INDUCED BY METHYLPREDNISOLONE IN MULTIBACILLARY MORBUS HANSEN WITH ERYTHEMA NODOSUM LEPROSUM

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ABSTRACT
Long-term high-dose corticosteroid therapy in Erythema Nodosum Leprosum (ENL) and Multibacillary Morbus Hansen (MB-type MH) can cause side effects, one of which is Cushing's Syndrome. A 25-year-old male patient with ENL and MB-type MH experienced Cushing's Syndrome due to a history of treatment with oral methylprednisolone 32 mg/day for 1 year with supervision as a management of his disease. Management during hospitalization with Multidrug Treatment-Multibacillary (MDT-MB), methotrexate 25 mg/week, folic acid 1 mg/day and topical therapy in the form of 10% urea cream twice a day. After 4 days hospitalized, this patient's condition improved. Methotrexate is a therapeutic option for ENL because of its anti-inflammatory mechanisms that specifically target the pathogenic pathways that cause ENL, especially inflammation and cytokine storm caused by neutrophils. Administration of methotrexate as an alternative therapy in treating ENL and MB-type MH with Cushing's syndrome can be considered.

Keywords: cushing syndrome; erythema nodosum leprosum; methotrexate; methylprednisolone; morbus hansen

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INTRODUCTION

Morbus Hansen is a chronic infectious disease caused by Mycobacterium leprae. In multibacillary cases, complications such as Erythema Nodosum Leprosum (ENL) may occur, leading to systemic inflammation and potential nerve damage. The global burden of leprosy remains substantial, particularly in Southeast Asia, including Indonesia. Corticosteroids are the mainstay therapy for ENL due to their potent anti-inflammatory effects. However, prolonged administration at high doses is associated with serious adverse effects, including Cushing's syndrome. This case report highlights the use of methotrexate as an alternative therapy to corticosteroids in a patient with ENL who developed steroid-induced Cushing's syndrome following prolonged methylprednisolone use. Reports regarding the use of methotrexate in ENL patients with severe corticosteroid-related complications remain limited. This case demonstrates the potential benefits of methotrexate as an affordable and relatively safe corticosteroid-sparing agent in the management of ENL, aiming to reduce corticosteroid dependence and improve the patient's quality of life.

METHOD

This study is a case report of a 25-year-old male diagnosed with Multibacillary Morbus Hansen and ENL who developed Cushing's syndrome following prolonged corticosteroid therapy obtained through history taking, physical examination, dermatological examination, and supporting laboratory tests. The patient approved clinical finding documentation and publication.

RESULT

The patient presented with fever, dyspnea, nausea, muscle weakness, and numbness in extremities. He had a history of MB-MH treated with MDT-MB and methylprednisolone 32 mg/day for one year. Physical examination revealed moon face, anemia, tachycardia, and dermatological lesions including multiple hyperpigmented nodules, xerosis, and hypoesthesia. Laboratory results showed leukocytosis (20,330/µL), anemia (hemoglobin 11.7 g/dL), and hypokalemia (potassium 3.3 mmol/L). Ziehl-Neelsen staining was positive.

The patient was diagnosed with ENL and steroid-induced Cushing's syndrome. Treatment consisted of continuation of MDT-MB, methotrexate 25 mg/week, folic acid 1 mg/day, urea 10% cream, and supportive therapy. The patient's condition improved after four days hospitalized, with no complaints of fever, nausea, vomiting, or muscle weakness. Follow-up laboratory examinations also demonstrated improvement compared with the previous day, including white blood cell count (8.98 × 10^3/µL), hemoglobin level (11.0 g/dL), and potassium level (4.0 mmol/L).

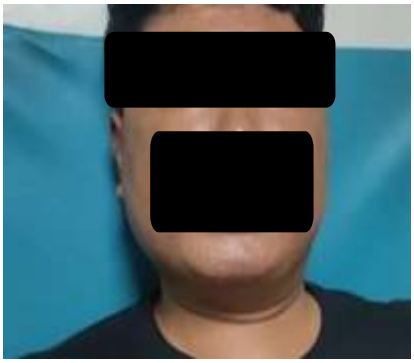

Figure 1. Moon facies in the facial region

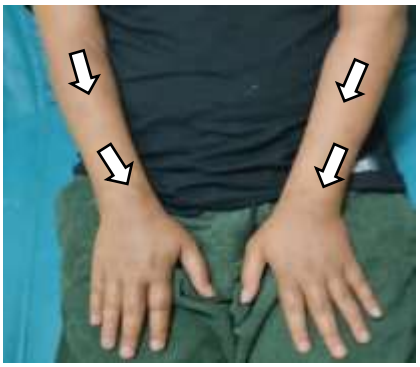

Figure 2. Multiple hyperpigmented nodular lesions on the right and left antebrachial regions, accompanied by clubbing fingers

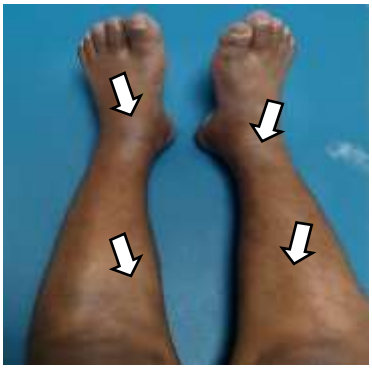

Figure 3.
Multiple hyperpigmented nodular lesions accompanied by scales and xerosis on the right and left cruris.

DISCUSSION

ENL is a type 2 MH reaction involving a very high bacterial count and can occur before, during, or after treatment, but is most common in the second year of MDT treatment. ENL is an inflammatory complication of MH that occurs in 50% of lepromatous patients and 5-10% of borderline lepromatous (BL) patients. This can occur because during treatment, many M. leprae bacteria are killed, resulting in numerous antigens reacting with antibodies and forming immune complexes. The resulting immune complexes enter the bloodstream and are deposited in various organs, causing symptoms such as painful erythematous nodules, particularly on the arms and legs. In this

patient, the symptoms appeared after the start of the second year of treatment. Dermatologically, the face showed moon face and megalobule formation. Hyperpigmented nodular lesions were symmetrically distributed on both sides of the body, including the right and left hands and feet, accompanied by scaling, xerosis, hypoesthesia of the hands, right and left feet, and clubbing of the fingers and toes.

ENL therapy is based on whether the reaction is mild or severe. Very mild reactions can be treated with non-steroidal anti-inflammatory drugs (NSAID) such as ibuprofen. More severe leprosy reactions are treated with corticosteroids. Clofazimine can be used to treat severe and recurrent ENL reactions that are steroid-dependent. Thalidomide is effective in treating moderate to severe ENL reactions, but some countries have discontinued its use. The purpose of administering these drugs is to relieve pain, control inflammation, prevent the spread or formation of new lesions on the skin and nerves, and prevent disability. Methotrexate is an alternative therapy for leprosy reactions, both ENL and reversal reactions (RR). Methotrexate is a folate antimetabolite with antiproliferative properties and anti-inflammatory effects by increasing adenosine levels and anti-inflammatory cytokines, which play a role in reducing inflammatory reactions. Adenosine is found in the anti-inflammatory pathway, has the capacity to counteract inflammatory processes, and is a purine nucleoside considered an endogenous anti-inflammatory compound. Absolute contraindications for methotrexate include pregnancy, breastfeeding, significant leukopenia or thrombocytopenia, renal impairment, hematologic disorders, hepatic impairment, diabetes mellitus, and HIV infection, which are relative contraindications. In this patient, there are no contraindications to methotrexate use, so oral methylprednisolone therapy can be replaced with methotrexate 25 mg/week and folic acid 1 mg/day as an alternative therapy. Methotrexate is very affordable and readily available in hospitals. During methotrexate therapy, patients were monitored through clinical evaluation and laboratory tests to assess their response to therapy. Clinical monitoring included assessing ENL lesion improvement and reduction of inflammatory symptoms. Laboratory testing included a complete blood count and electrolyte evaluation, particularly potassium levels, given the patient's history of long-term corticosteroid use and the presence of hypokalemia. Folic acid supplementation was administered concurrently to minimize methotrexate-related toxicity.

Cushing's syndrome is an endocrine disorder characterized by increased production of adrenocorticotropic hormone (ACTH), which leads to excessive release of cortisol from the adrenal glands. Cushing's syndrome has two main causes: endogenous hypercortisolism and exogenous hypercortisolism. Endogenous Cushing's syndrome is rare, with an incidence of 0.7–2.4 per million population per year. The most common cause of Cushing's syndrome is exogenous hypercortisolism resulting from long-term glucocorticoid use. Cortisol functions as a glucocorticoid, but in high concentrations it can cause hypokalemia through the renin-angiotensin-aldosterone system. The renin-angiotensin-aldosterone system regulates plasma sodium concentration and arterial blood pressure and can indirectly contribute to hypokalemia. Signs and symptoms of Cushing's syndrome vary and can include moon face, weight gain, and muscle weakness. This patient had clinical signs of moon face, muscle weakness, and clubbing of the fingers and toes on the right and left sides. Laboratory tests showed hypokalemia and leukocytosis. This study has several limitations. Objective endocrine evaluation including serum cortisol and adrenocorticotropic hormone (ACTH) levels could not be performed due to limited diagnostic facilities as an investigative test in establishing the diagnosis of corticosteroid-induced Cushing's syndrome. Another limitation is the short timeframe for further evaluation of the long-term effectiveness of methotrexate therapy as an alternative to corticosteroid use.

CONCLUSION

Prolonged corticosteroid therapy in ENL may result in serious complications, including Cushing’s syndrome. Methotrexate represents a promising alternative therapy that may reduce corticosteroid dependence while effectively controlling inflammation.

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