Maculopapular drug eruption in a patient with human immunodeficiency virus (HIV) infection, wasting syndrome and pulmonary tuberculosis: A case report

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Case Report

Maculopapular drug eruption (MDE) is the most typical type of hypersensitivity reaction. Patients with human immunodeficiency virus (HIV) infection may develop some complications, including wasting syndrome, contributing to immune system dysregulation. The late stage of HIV infection increases the risk of pulmonary tuberculosis (TB), in which the administration of anti-tuberculosis drugs (ATD) often induces drug eruptions. A 41-year-old man complained of itchy skin rash on his hands, body, and feet. The rash appeared after a streptomycin injection on the 9th day, accompanied by complaints of fever, weakness, dizziness, and chronic cough followed by fever at night. The patient was treated and diagnosed with a new case of pulmonary TB; and he also received first-line ATD. The streptomycin injection was given because systemic manifestation still appeared. The researchers diagnosed the patient with HIV infection with wasting syndrome. He was hospitalized and given methylprednisolone injection, paracetamol infusion, omeprazole injection, oral cetirizine, and moisturizer. After that, clinical improvement occurred, and he was discharged on the fourth day. Patients with HIV infection often develop MDE. Clinical manifestations of maculopapular drug eruption are generally mild without systemic complaints; however, in certain conditions, such as HIV infection with wasting syndrome, more severe systemic symptoms can appear due to excess secretion of several proinflammatory cytokines. Several studies have also reported an increased incidence of maculopapular drug eruption caused by first-line anti-HIV drugs, especially in patients with HIV infection.
peningkatan insiden erupsi obat makulopapular yang disebabkan oleh obat anti-HIV lini pertama, terutama pada pasien dengan infeksi HIV.

**INTRODUCTION**

Maculopapular drug eruption is a hypersensitivity reaction to drugs that most often occurs with skin lesions such as macular rash or reddish papules, symmetrically distributed on the body and extremities, followed by itching. The rash can be polymorphic, with purpuric, targetoid and eczema-like lesions, blisters, and pustules. There has also been a report of an erythrodermic rash with skin separation. Mucosal involvement, such as conjunctivitis, oral mucositis, and/or genital mucositis, can also develop. These symptoms can last for months after the causative medication has been stopped.² Oktarina et al. reported that the prevalence of maculopapular drug eruption at Dr. Sardjito General Hospital Yogyakarta from 2011-2015 counted up to 50.88%.³ The MDE is generally caused by beta-lactam antibiotics, sulfonamides, antiviral class nonnucleoside reverse transcriptase inhibitors (nNRTIs), allopurinol, antiepileptic drugs, and non-steroidal anti-inflammatory drugs (NSAIDs).¹,⁴,⁵ Other predisposing factors that can cause MDE are HIV, Epstein-Barr virus (EBV), or Cytomegalovirus (CMV) infection.⁵ The differential diagnosis of MDE is Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a drug reaction that results in skin rash and impaired function of several organs. The clinical manifestations of DRESS appear two to three months after exposure to the alleged causal drug.⁶⁻⁷ The RegiSCAR is most often used to diagnose DRESS. Furthermore, in order to ruled out the DRESS syndrome, laboratory tests should be performed, including a complete blood count, liver enzymes, blood electrolytes, renal function test, urine analysis, and baseline thyroid function tests.⁸ It can be difficult to diagnose MDE because it is a common condition with a number of clinical mimics.⁹ Patients with HIV infection have a higher potential for drug reactions than do the population in general. Half of HIV patients have MDE, especially those caused by sulphonamide antibiotics.¹⁰ Precipitating factors of the drug eruption on HIV patients are polypharmacy, slow drug acetylation rate, a relative decrease in serum glutathione levels, CD4+ T cell levels < 200 cells/mm³ or > 25 cells/mm³, latent infection of EBV and CMV and CD8+ T cell levels > 460 cells/mm³. Systemic symptoms can also be found in HIV patients with MDE, such as fever, headache, muscle aches, arthralgia, granulocytopenia, thrombocytopenia, and elevated liver enzyme levels.¹¹

Furthermore, wasting syndrome is a condition in the late stage of HIV infection associated with weight loss. The criteria for the wasting syndrome based on the Centre for Disease Control and Prevention (CDC) include weight loss > 10% initial body weight accompanied by chronic diarrhoea (at least two bowel movements per day for 30 days), fever, and body weakness for 30 days without accompanied by any condition that causes chronic weight loss.¹² The pathogenesis of wasting syndrome is multifactorial, including metabolic disorders, cytokine dysregulation, endocrine dysfunction, malnutrition, and malabsorption, which can increase morbidity and mortality in HIV patients.¹³

Around 13% of new cases of pulmonary tuberculosis worldwide are coinfected with HIV, especially at a late stage. Therefore, the management of pulmonary tuberculosis patients with HIV infection using ATD can cause drug eruption, so it is necessary to consider switching to other drugs or giving second-line ATD. Precipitating factors of drug eruption in patients coinfected with HIV are complex drug interactions, overlapping drug toxicity, and tuberculosis-associated immune reconstitution inflammatory syndrome, which can increase mortality and the risk of drug resistance and accelerate the transmission of tuberculosis infection.¹⁴ Based on this description, the researchers report a case of MDE on a HIV patient with wasting syndrome and pulmonary tuberculosis to provide information regarding the relationship between HIV infection and wasting syndrome and between tuberculosis lungs and MDE.

**CASE DESCRIPTION**

A 41-year-old man living in Surakarta, Central Java, Indonesia, came to the Pulmonary Department and then was consulted to the Dermatology and Venereology Polyclinic, Dr. Moewardi General Hospital, Surakarta. The patient complained of itchy red skin rash on the hands, body, and feet. Autoanamnesis history of his present illness reported that the patient...
complained of red skin rash on the hands and stiffness that had been itching for the previous 3 days, followed by fever. Two days later, he said that the red rash spread to the stomach, chest, and face accompanied by a slight feeling of heat, weakness, dizziness, and chills. One month earlier, the patient was taking ATD regularly. Still, after one week, the patient complained of nausea, vomiting, and heartburn, so he returned for treatment at the Pulmonary Polyclinic. The ATD regimen was changed to a single drug, while the pyrazinamide was discontinued and replaced by a daily streptomycin injection. On the 9th day of the streptomycin injection, redness of skin rash occurred in several parts of the body, so he was consulted to the Dermatology and Venereology Polyclinic for further treatment.

Autoanamnesis of previous medical history reported that since the last three months he had complained of frequent vomiting, diarrhea, and decreased appetite, so his weight decreased. Two months later, he complained of frequent coughing with phlegm and sometimes fever, especially at night. Again, his body weight decreased, and his tongue became bitter. Then he went to a general practitioner and received medicine, but there was no improvement. One month earlier, the cough worsened with complaints of shortness of breath, chest pain, dizziness, muscle aches, body weakness, and canker sores that did not heal for four months. A general practitioner referred the patient to PKU Muhammadiyah Hospital Sampangan because his condition worsened. The patient was diagnosed with a new case of pulmonary TB with suspected HIV infection; then, he received ATD therapy, such as isoniazid, rifampin, pyrazinamide, and ethambutol. Still, after taking these drugs, several complaints appeared, so he was referred to Dr. Moewardi General Hospital; however, antiretroviral (ARV) drugs have not yet started due to consideration for the treatment of active pulmonary tuberculosis. Autoanamnesis of sexual history reported that ten years before marriage he often had sexual intercourse with several women without using a condom.

The physical examination showed that his general condition was moderately ill with normal GCS. Vital signs showed that his blood pressure was 174/115 mmHg, his respiratory rate was 22 times per minute, his pulse was 85 times per minute, his temperature was 39.4°C, and his oxygen saturation was 99%. Dermatological status examination on the body area (superior and inferior extremities) showed several discrete scattered erythematous macules and papules. The oral and genital mucosa showed no erosions, and no conjunctivitis was found (Figure 1). Examination of the lymph nodes did not reveal enlarged cervical, axillary, or inguinal lymph nodes.

The results of laboratory tests showed 11.9 g/dl (12.1-17.6 g/dl) of hemoglobin levels, 14,300/mL (4,500-11,000/mL) of leukocytes, 3,830,000/mL (4,500,000-5,900,000/mL) of erythrocytes, 84.90% (55.00-80.00%) of neutrophils, 2.8% (0.0-4.0%) of eosinophil, 8.50% (22.00-44.00%) of lymphocytes, 3.3 g/dl (3.5-5.2 g/dl) of albumin, 128 mmol/L (132-146 mmol/L) of blood sodium, and 1.13 mmol/L (98-106 mmol/L) of blood chloride. The result of the calculation of the Regi-SCAR score for the DRESS diagnostic criteria was 0. Based on the history, physical examination, and laboratory data, the researchers established the diagnosis of maculopapular drug eruption due to suspected streptomycin. Thus, he was advised to be hospitalized due to fever, body aches and body weakness. His therapy included a high-calorie and high-protein diet (1,700 kcal), NaCl infusion (0.9% 20 drops per minute (DPM)), methylprednisolone injection (62.5 mg per day) followed by a tapering off dose, omeprazole injection (40 mg per day), paracetamol infusion (1 g per day for three days), and cetirizine oral (10 mg per day). Then Soft u-derm® moisturizer was applied to the whole body twice a day.

The patient was consulted to the Pulmonary Department and diagnosed with clinically confirmed new pulmonary tuberculosis and HIV under treatment with first-line ATD. During the first month of the intensive period, a drug
eruption appeared. Treatment from the Pulmonary Department was nasal oxygen up to 2-3 liters per minute (LPM) if necessary, and ATD was discontinued. The patient was also admitted to the Internal Medicine Department and was diagnosed with the 4th stage of HIV infection with wasting syndrome, hypotension due to delirium, and hyponatremia. Therapy from the Internal Medicine Department included infusion of ringer lactate up to 500 cc, NaCl infusion (0.9% 30 DPM), cotrimoxazole (oral 900 mg once daily), and administration of ARV (lamivudine, tenofovir and efavirenz). After four days of hospitalization, he experienced clinical and skin lesions improvement. The patient was discharged from the hospital and was allowed outpatient control (Figure 2).

DISCUSSION

Maculopapular drug eruption (also known as morbilliform or exanthematous eruption), is the most common form of drug eruption on the skin. The lesions generally appear as erythematous macules and papules without bullae, pustules, or systemic complaints. The skin lesions first appear on the body in less than one week and spread symmetrically to the periphery, and repair of the lesions occurs within 7 to 14 days. A study conducted by Rajendran et al. reported that the maculopapular drug eruption mostly occurred in men (54.6%) and in the age group of 40-60 years (38.4%). Common complaints are pruritus, but in some cases it can be accompanied by fever, erythroderma, disorders of several organs, and severe drug reactions resembling DRESS. The
Figure 2. Superior and inferior extremities show recovered discretely scattered erythematous with a partial hyperpigmented rash on 4th day of treatment (A-E).

most common causes of MDE include antibiotics, anticonvulsants, antihypertensives, and anti-inflammatory drugs. Drugs rarely cause drug reactions, including antihistamines, digoxin, local anaesthetics, steroid hormones, acetylsalicylic acid, acetaminophen, and, coumarins. Other precipitating factors that can cause MDE are viral infections such as HIV, CMV, EBV, or hepatitis B. 5,15

In this case, a 41-year-old male patient was consulted with red rash on the hands, body, and feet after receiving ATD (streptomycin). The skin rash is itchy and slightly hot with fever, weakness, dizziness, and chills. His skin lesions first appeared on the body and legs on the 9th day after he received the streptomycin injection. Dermatological status, body area, superior and inferior extremities showed several discrete scattered erythematous macules and papules. No conjunctivitis or oral and genital mucosal erosions were found. He was also diagnosed with HIV positive for 1.5 months before going to the hospital. Based on the history and dermatological status, this case is more suitable for the diagnosis of MDE.

The differential diagnosis is DRESS, a drug reaction that results in skin rash and impaired function of several organs. Clinical manifestations of DRESS usually appear two to three months after exposure to the alleged causal drug. Its symptoms appear as fever, skin rash, lymphadenopathy, hepatitis, and leucocytosis with eosinophilia—haemorrhagic crusts. The lesions are symmetrically distributed over the face, trunk, and extremities. In the early stages of the disease, facial and periorbital edema may be seen. Cervical, axillary, and inguinal lymphadenopathy is found in almost 70% of patients, especially in the early
stages of the disease.\textsuperscript{17} Severe cases of DRESS may have oral mucosal involvement, although less often than Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN). The most common DRESS-causing drugs include carbamazepine, dapsone, phenytoin, salazosulphapyridine, phenobarbital, allopurinol, and zonisamide. The Regi-SCAR scoring system is generally used to establish a diagnosis, and a result of the calculation value > 5 is declared as DRESS.\textsuperscript{17}

On the 9th day of the streptomycin injection, a skin rash appeared. Dermatological status on the body, upper and lower limbs showed discrete scattered erythematous macules and papules. There were no skin lesions or edema in the facial area; and then, cervical, axillary, and inguinal lymphadenopathy were not found. The laboratory examination results did not reveal eosinophilia, atypical lymphocytes, or impaired liver or kidney function. The results of the calculation of the Regi-SCAR obtained a value of 0. Therefore, DRESS can be ruled out.

This patient had wasting syndromes, a frequent complication of late-stage HIV infection that is defined by fever, recurrent diarrhea, and weight loss of more than 10% of the initial body weight within 30 days. Therefore, malignancy, tuberculosis, cryptosporidiosis, or enteritis should be ruled out.\textsuperscript{6} The pathogenesis of wasting syndrome remains unclear and multifactorial. Furthermore, proper treatment is needed to prevent morbidity and mortality.

Patients with HIV infection often have drug eruptions where ATD causes as many as 75% of cases. Based on the Coombs and Gell criteria, the T helper immune response mediates a maculopapular drug eruption type IVa hypersensitivity reaction, with macrophages serving as the primary effector cells that secrete interferon-gamma (IFN-\textgamma), which causes an inflammatory response through tumour necrosis factor alpha (TNF-\textalpha) and interleukin-12 (IL-12).\textsuperscript{10} HIV patients with wasting syndrome have immune system dysregulation which is characterized by increased levels of IL-1\textbeta, IL-6 and TNF-\textalpha; in addition, increased levels of immunoglobulin E (IgE) and hypereosinophilia also can increase the risk of drug allergic reactions. Another predisposition that causes drug eruption in HIV patients with wasting syndrome is the decreased drug acetylation rate and inhibition of reactive oxygen species (ROS) binding. Thus, toxic drug metabolites level increase. Low levels of glutathione peroxidase can also inhibit the synthesis of cytochrome P450 in the liver, which has the potential to cause drug eruption.\textsuperscript{10,19}

In this case, the patient had a history of chronic vomiting and diarrhoea that led to significant weight loss in the last three months. He also complained of a bitter taste on the tongue, decreased appetite, and chronic cough. His sexual history is at high risk due to engaging in free sex frequently with several sexual partners without using a condom. Unexpectedly, when he received treatment at the Dr. Moewardi General Hospital, he was identified as late-stage HIV with wasting syndrome related to pulmonary tuberculosis. Wasting syndrome is a clinical manifestation generally found in the late-stage HIV due to several factors, including immune system dysregulation.\textsuperscript{5} The levels of several cytokines are elevated in HIV patients with wasting syndromes such as TNF-\textalpha, IL-1, and IFN-\textgamma, resulting in too much lipid synthesis and decreased lipoprotein lipase concentration in the liver. This situation affects the clearance process of triglyceride-rich lipoproteins and drug metabolism.\textsuperscript{15}

Tuberculosis infection is often found in late-stage HIV patients, so early ATD administration is necessary to prevent a worsening prognosis. Hypersensitivity reactions related to ATD have also been reported in previous retrospective studies. From 2014–2017, the prevalence of maculopapular drug eruptions caused by ATD at Dr. Sardjito General Hospital was 66.7%, as reported by Rahmawati et al.\textsuperscript{14} The World Health Organization (WHO) distinguishes the toxicity of adverse drug reactions into two types, type A and B. Type A is more common and related to the pharmacological properties of a drug, which is predictable and generally dose-related. Type B reactions occur in 10–15% of cases; hypersensitivity reactions mediate these reactions, which are unpredictable and occur in people with certain predisposing factors. Drug intolerance, hypersensitivity, or drug cross-reactions are forms of type B drug reactions.\textsuperscript{18}

The patient was diagnosed with a new case of pulmonary TB and received first-line ATD. Still, the patient complained of nausea, vomiting, and heartburn, so his doctor stopped the drug and replaced it with parenteral streptomycin. On the 9th day of streptomycin injection, skin rash
appeared, and second-line ATD was considered. Drug eruption caused by ATD can occur as mild to severe hypersensitivity reactions. Consequently, maculopapular drug eruption can be classified into type A or type B reactions depending on the clinical symptoms and the suspected causative drug. Several studies suggest the first-line ATD regimen to be replaced with another drug or to administer second-line ATD in patients with drug eruptions.

CONCLUSION
Patients with HIV infection often experience drug eruption, and is most common form is the maculopapular type. Several studies have reported an increased incidence of MDE due to first-line ATD, which is similar to this case report as the eruption occurred after the administration of streptomycin. Since this situation can potentially increase patients’ morbidity and mortality, it is crucial to consider the second line of ATD in patients with HIV infection to prevent a poor prognosis.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTIONS
All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

LIST OF ABBREVIATIONS
WHO: World Health Organization; MDE: Maculopapular Drug Eruption; HIV: Human Immunodeficiency Virus; ATD: Anti-tuberculosis drugs; nNRTIs: Non-nucleoside reverse transcriptase inhibitors; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; DPM: Drops per minute; LPM: Liters per minute; SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis; TNF-α: Tumour Necrosis Factor-α; IFN-γ: Interferon-γ; IL: Interleukin; ROS: Reactive oxygen species.

REFERENCES