Case Report

Cutaneous Adverse Drug Reaction due to Anti-TB Drug Allergy in TB-HIV Patient: A Case Report

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Abstract

Background: In people living with HIV/AIDS (PLHIV), tuberculosis (TB) is the leading cause of death, with a 20 times higher risk of developing active TB compared to people without HIV. PLHIV are also at higher risk of experiencing cutaneous adverse drug reactions (CADR) caused by anti-TB drugs. The delayed therapy of TB caused by CADR might make TB management more difficult.

Case: A 23-year-old male with clinically confirmed pulmonary TB on intensive phase anti-TB therapy experienced erythroderma due to allergies to anti-TB drugs and stage III HIV. In the drug challenge, it was found that the patient showed an allergic reaction in the form of a reddish rash that spread widely on the anterior and posterior thorax and abdomen after consuming rifampicin and pyrazinamide.

Discussion: The patient's treatment was then added with cetirizine and methylprednisolone. The anti-TB drugs will be given for 9 months, with the intensive phase of 2 months, and the continuation phase of 7 months.

Conclusion: There is a very high risk of CADR in TB patients with HIV infection. Monitoring the side effects of anti-TB regularly and identifying immediately which anti-TB drug causes the allergy is significant as the key to managing CADR in TB-HIV patients. Anti-TB drug provocation tests for each drug and a gradual dose increase are carried out if the clinical CADR has disappeared or improved.

Keywords: anti-TB Drugs, CADR, Cutaneous Adverse Drug Reaction, People living with HIV/AIDS (PLHIV), tuberculosis

INTRODUCTION

Tuberculosis (TB), which is caused by *Mycobacterium tuberculosis*, is the most common cause of death in people living with HIV/AIDS (PLHIV). The World Health Organization (WHO) reports that PLHIV has a 20 times higher risk of developing active TB than people without HIV. Cutaneous adverse drug reaction (CADR) is one of the various side effects that can occur in TB with HIV patients, which makes the

management indeed a challenge. CADR manifestations can include maculopapular rash, urticaria, fixed drug eruption, angioedema, erythema multiforme, toxic epidermal necrolysis, Steven Johnson Syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS). This side effect can occur due to anti-TB drugs (ATD) or other drugs taken by TB HIV patients.[1–5]

Several studies report that PLHIV is at a higher risk of experiencing CADR caused by anti-TB drugs compared to the general population. The etiology of CADR is not yet known, however, it is believed to be related to changes in drug metabolism, drug interactions, a Th2 cytokine profile that triggers IgE synthesis to drugs, oxidative stress, and hyperactivation of the immune response.[1,3,4] CADR can make TB management more difficult because it can delay therapy or treatment regimens.[6,7]

CASE

Mr. NS, 23 years old, was referred from Aceh Jaya Hospital with chief complaints of itching on the body and redness since 3 days ago. The patient was not complaining of a cough, and there was no history of an old cough. However, the patient had a history of coughing up blood 1 month ago, but then there were no more complaints, like coughing up blood, shortness of breath, nausea, or chest pain. The patient had a history of fever fluctuating 1 month ago, but the fever has subsided.

The patient also complained of night sweats, decreased appetite, and weight loss of 10 kg in the last 3 months. Other than that, the patient complained of diarrhea for 1 month. The patient was subjected to a sputum GeneXpert examination and an HIV test, the results of which indicated the absence of *M. tuberculosis* and the presence of HIV, respectively.

Consequently, the patient was diagnosed with clinically confirmed TB and HIV stage 3. The patient was administered anti-TB medications. Three days before the admission, the patient complained of itching and red rashes that felt hot all over the body while taking the anti-TB. Defecation and urination were normal.

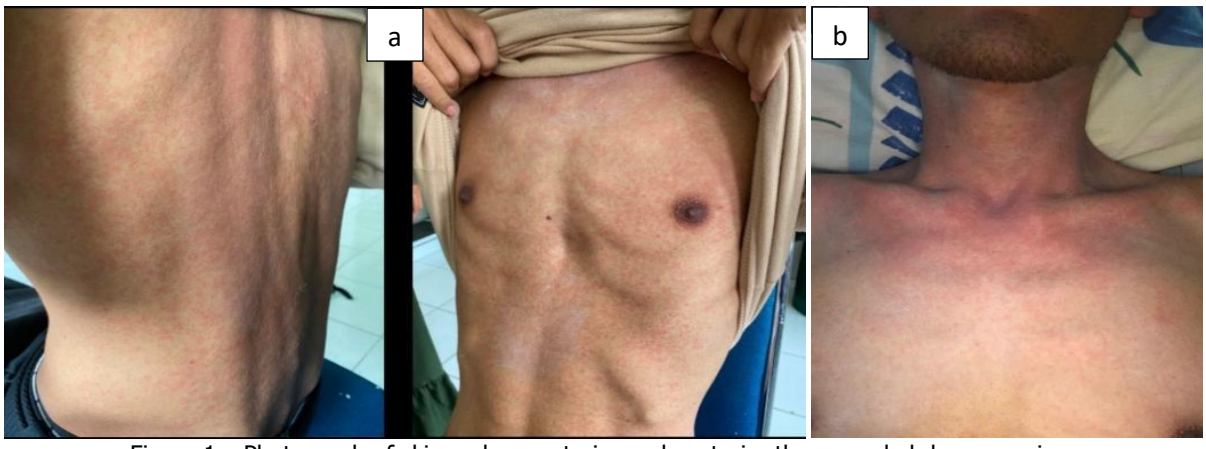

Figure 1a. Photograph of skin rash on anterior and posterior thorax and abdomen region;
1b. on the Colli region after consuming OAT

On the examination, the patient was compos mentis and hemodynamically stable. Physical examination (Figure 1a) revealed a widespread reddish rash on the anterior and posterior thorax and abdomen. Physical examination of the lungs was normal. The X-ray result (Figure 2) also displayed normal lung results.

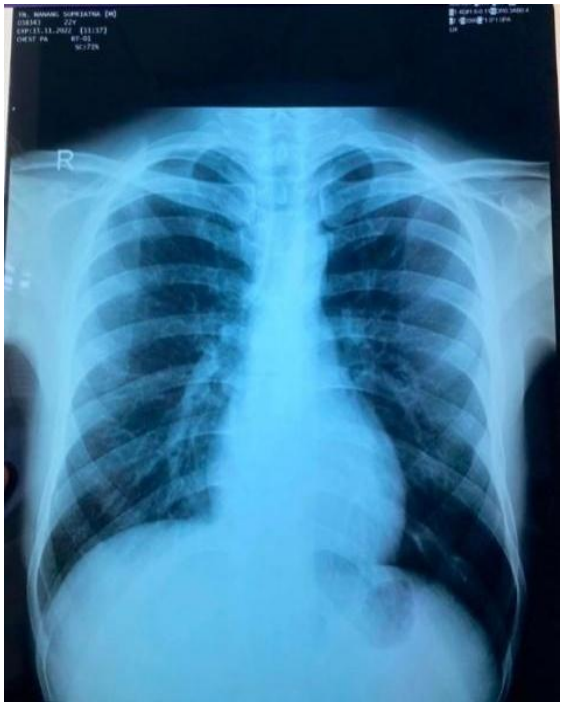

Figure 2. Chest X-ray Results

The working diagnosis of this patient was clinically confirmed pulmonary TB in the first month of the intensive phase, erythroderma et causa allergic to anti-TB drugs, and stage III HIV. A drug challenge was performed on the patient with Isoniazid 1x300 mg, Ethambutol 1x1000 mg, Pyrazinamide 1x1000 mg, and Rifampicin 1x450 mg. During the drug challenge, the patient showed an allergic reaction to Rifampicin and Pyrazinamide. Cetirizine 1x10mg and Methylprednisolone 3x4mg were added to the patient's treatment.

After a drug challenge, we planned to give the anti-TB drugs for 9 months, divided into the intensive phase for 2 months using the regimen 2HEL (Isoniazid, Ethambutol, Levofloxacin), and the continuation phase for 7 months using the regimen of 7HE (Isoniazid and Ethambutol). The patients were also explained about the complications of the disease and the side effects of anti-TB drugs. Periodic evaluation will be carried out on patients with evaluation of clinical, vital signs, laboratory, and drug side effects.

DISCUSSION

Based on the history taking, physical examination, and supporting examinations, the patient exhibited a constellation of symptoms and complaints that led to the suspicion of both TB and HIV. A thorough examination was conducted, encompassing the analysis of sputum for gene Xpert and HIV tests. However, the GeneXpert result showed that the MTB remained undetected, while the HIV test yielded a reactive result. Consequently, the patient was diagnosed with clinically confirmed TB and HIV stage 3. The patient was prescribed a regimen of four fixed-dose combinations (FDC) of anti-TB medications.

After taking the anti-TB drugs, the patient was diagnosed with erythroderma due to an allergy to the anti-TB drugs. In line with the theory from the AAAAI (American Academy of Allergy, Asthma, and Immunology), drug allergies occur due

to drug exposure, which causes an immunological response.[8,9]

In HIV patients, hypersensitivity reactions on the skin are the most common condition (64%). Immune dysfunction in HIV patients causes an increased risk of allergies. In HIV patients, there is an imbalance between T helper (Th) 1 and Th2 cytokines; there is a decrease in Th1 and an increase in Th2 and immunoglobulin (Ig) E. Increased IgE is associated with disease progression. This is thought to be due to viral proteins with allergen-like domains that induce Th2 synthesis. Apart from dysregulation of the immune response, increased CADR in HIV patients is also related to pre-HIV genetic risk, increased oxidative stress, decreased antioxidants, and pharmacological factors, as well as the virus itself.[1–4,10]

Data regarding the incidence of CADR caused by anti-TB drugs in HIV patients is minimal. Widhani et al reported the prevalence of CADR in HIV patients receiving anti-TB drugs is 10.6%, with the most common manifestations of CADR being maculopapular rash (66.7%) and erythema multiforme (14.6%), and only 8.3% experiencing Steven Johnson Syndrome.[1]

In this case, the patient was reported to be allergic to rifampicin and pyrazinamide after 3 days of taking anti-TB drugs. Rifampicin is the most common anti-TB drug reported to cause CADR in HIV TB patients. Widhani et al reported that CADR due to rifampin occurred in 41.7% of TB patients with HIV, followed by ethambutol (16.7%) and pyrazinamide (14.6%). The onset of the emergence of CADR varies from several studies conducted. Generally, it occurs in less than 15 days after starting anti-TB drugs. Tan et al reported that 97% of CADR occurred within 2 months of anti-TB therapy. If CADR occurs after the intensive phase, we need to think about the possibility of other drugs as the cause of CADR.[11,12] Similar results were also reported by Lehloenya et al. Different results were found from research by Tan et al, which mentioned the most common cause of CADR was pyrazinamide, subsequently streptomycin and ethambutol.[13]

This is an important point in considering the order of anti-TB drugs that will be carried out for provocation tests. The anti-TB drugs that are most frequent or most likely to result in CADR should be placed in the last order. The CD4 count should also be an assessment of TB patients with HIV who are at risk for CADR. Severe immunodeficiency conditions, namely a CD4+ count of less than 200 cells/mm^3, can be considered a higher possibility of increasing drug reactions.

The management of patients with anti-TB allergies is divided into two groups: with or without rash.[14] It is recommended for symptomatic treatment to use antihistamines like cetirizine 5-10 mg or diphenhydramine 25-50 mg in patients without rash who complain of itching with no other cause before anti-TB drugs and adding the skin moisturizers for patients with dry skin. If there is no improvement with antihistamines, corticosteroid ointment or oral steroids, such as

prednisolone (10-20 mg daily), can be given. Anti-TB drugs can be continued under close supervision. Side effects usually fade within a few weeks.[15]

In cases of anti-TB allergies with manifestations in the form of skin rashes, the patient must be immediately referred to a referral health facility, and all anti-TB drugs must be stopped immediately. Give intravenous fluids shortly if there is a severe skin reaction involving the mucosa, hypotension, or shock manifestations.[16]

A drug challenge at the referral health facilities can be done to determine the anti-TB drug that may cause the allergic reaction. This helps in determining further management, considering the need for complete treatment in TB patients. After the allergic reaction is under control, the anti-TB drugs are given back gradually, starting with drugs that tend to cause reactions at low doses (H or R), for example, isoniazid 50 mg. The dose is increased slowly over 3 days. We will add one more type of anti-TB the next day if there is no response. Reaction after administering certain anti-TB drugs indicates which drug is causing the allergy. If the anti-TB drug causing the allergy is known, TB treatment can be continued by adjusting the anti-TB drugs.[17]

Anti-TB drugs that cause allergic reactions from the lowest possible risk are Isoniazid, Rifampicin, Pyrazinamide, Ethionamide, Cycloserine, Ethambutol, Para-aminosalicylic acid (PAS), and Streptomycin, with the highest risk. Desensitization can be done sequentially.[18–20]

After the drug challenge was carried out, the patient was found to be allergic to rifampicin and pyrazinamide. The choice of anti-TB regimen for patients with allergic reactions accompanied by rashes is similar to cases of liver disorder due to anti-TB. If the patient is allergic to rifampicin, a regimen with two months of isoniazid, ethambutol, and pyrazinamide without rifampicin is recommended, followed by a continuation phase for 10 months of isoniazid and ethambutol.[17]

If pyrazinamide is discontinued due to an allergic reaction before the intensive phase is completed, the total course of isoniazid and rifampicin is lengthened to 9 months. If there is an allergy to isoniazid and this drug cannot be used, the regimen that can be given is rifampicin, ethambutol, and pyrazinamide for 6-9 months. Lastly, if isoniazid and rifampicin cannot be given simultaneously, streptomycin, ethambutol, and fluoroquinolones can be an option and given for 18-24 months.[17]

The limitation of this study was that the patient was not compared photographically during and after the drug challenge, which shows how the drug challenge affects the skin rash.

CONCLUSION

Tuberculosis patients accompanied by HIV infection are at very high risk of developing CADR. Clinical manifestations of CADR can range from mild to severe, which carries a risk of death. Immune dysregulation is a factor causing CADR in TB patients with HIV. Stopping anti-TB

drugs as soon as possible and identifying the culprit are the keys to managing CADR in TB-HIV patients. It should also be accompanied by the administration of antihistamines and corticosteroids. Anti-TB drug provocation tests for each drug and a gradual dose increase are carried out if the clinical CADR has disappeared or improved.

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