Drug Eruption and Hepatitis Induced by Antituberculosis Therapy: A Case Report

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ABSTRACT

Pulmonary tuberculosis remains a global health issue, with one of the challenges being the adverse side effects of anti-tuberculosis drugs that can interfere with the success of therapy. This case reports a 67-year-old man with pulmonary tuberculosis who experienced a rifampicin-induced drug eruption and pyrazinamide-induced hepatitis during first-line antituberculosis combination therapy. After temporarily discontinuing the antituberculosis regimen, the patient was given supportive therapy with corticosteroid and antihistamine for the drug eruption, and stronger neo-minophagen C injections for the hepatitis. After stabilization, the regimen was adjusted to a combination of isoniazid and ethambutol, and streptomycin was added as the third agent; however, due to an allergic reaction, streptomycin was replaced with levofloxacin. The new regimen, isoniazid-ethambutol-levofloxacin, combined with appropriate management of the adverse reactions resulted in favorable clinical outcomes, marked by the disappearance of the itchy red rash on the face and body, improvement in liver function as seen from liver enzymes and bilirubin levels, and a stable general condition. This case report emphasizes the importance of being aware of the adverse side effects of antituberculosis regimens, especially in elderly patients. Regular monitoring of liver function, early detection of drug reactions, and safe and individualized regimen adjustments are important strategies to prevent complications without compromising the success of tuberculosis treatment. This case provides important lessons regarding a cautious, evidence-based clinical approach to addressing serious side effects of antituberculosis drugs.

Keyword : Drug eruption; Hepatitis; Hepatotoxicity; Antituberculosis drugs; Tuberculosis

Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and remains a global public health problem.[1] The incidence of this disease is also significantly influenced by risk factors such as age, socioeconomic status, residence, and smoking status.[2,3] In 2021, a report from the World Health Organization (WHO) estimated that 10.6 million people were infected with tuberculosis and 1.6 million people died in the same year.[4] Meanwhile, in Indonesia, the estimated incidence of tuberculosis increased by 19% with the mortality rate also increasing by 26% based on 2015 and 2023 WHO tuberculosis report.[5] This makes Indonesia the country with the second highest tuberculosis burden worldwide. Therefore, various efforts continue to be made, including treatment using anti-tuberculosis drugs.

The standard antituberculosis treatment recommended as first-line therapy is quadruple therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide for 2 months, followed by rifampicin and isoniazid for 4 months.[6] However, this first-line tuberculosis therapy still has adverse side effects in some patients, and it is even said that around 60% of tuberculosis patients experience these side effects.[7] The most frequently reported side effects include gastrointestinal disturbances, hepatotoxicity or hepatitis, skin reactions/drug eruptions, and neurological and renal disorders.[8] These side effects of antituberculosis therapy pose a significant challenge in tuberculosis management. This is because they can lead to temporary therapy discontinuation and prolong the treatment duration. Therefore, it is crucial to identify these adverse side effects early to prevent progression and determine appropriate strategies or regimen substitutions.

This case reports a 67-year-old man diagnosed with pulmonary tuberculosis and comorbid hypertension who experienced a drug eruption during combination antituberculosis therapy. This situation reflects the complexity of managing tuberculosis patients with cardiovascular comorbidities in elderly patients, where drug interactions, organ decline, and the risk of adverse drug reactions present significant clinical challenges. This case report is expected to provide an overview of a comprehensive and individualized management approach to drug reactions in tuberculosis patients, including the importance of early detection, temporary discontinuation of the offending drug, and safe and effective adjustment of the therapeutic regimen. In addition, this report emphasizes the urgency of

safe and effective therapy, as well as regular monitoring of liver and kidney function during antituberculosis drug therapy as an effort to prevent serious complications and increase the success of pulmonary tuberculosis treatment. The combination of skin reactions and organ dysfunction in patients with comorbidities is rarely reported, so this case provides important learning value for clinical practice and multidisciplinary management of antituberculosis therapy.

Case Illustration

A 67-year-old male patient was admitted to the emergency room of Dr. Soegiri Regional Hospital with complaints of shortness of breath for one month and fever for four days. The patient stated that his shortness of breath was recurring and worsening at the time of his arrival. The patient also experienced nausea and vomiting with each meal, as well as abdominal pain. He had an occasional cough without hemoptysis, and the patient denied any peripheral edema. His previous medical history revealed hypertension, as well as chronic suppurative otitis media with mastoiditis for which surgery was planned. The patient had no history of diabetes mellitus.

The results of the patient's initial examination showed blood pressure of 160/90 mmHg, pulse 92 beats per minute, respiration 26 times per minute, body temperature 37.5 °C, oxygen saturation (SpO2) 90%, and the patient was in compos mentis consciousness or GCS E4V5M6. The patient was then given an infusion of 1000 cc/24 hours of lactated Ringer's solution, 4 liters of oxygen per minute, and empirical therapy in the form of ceftriaxone injection, infimycin infusion, and acetylcysteine infusion, accompanied by symptomatic therapy in the form of metamizole and ranitidine injection for gastrointestinal complaints.

Initial supporting examinations included molecular rapid tests, Gram stain, and KOH. The molecular rapid test results were positive for pulmonary tuberculosis. The Gram stain identified Gram-positive cocci and Gram-negative bacilli, and the KOH test revealed positive spores and hyphae. In addition, the results of the thoracic radiology examination showed diffuse opacity and a closed right costophrenic sinus (**Figure 1**). In the clinical laboratory test results, the levels of liver enzymes SGOT and SGPT were within normal limits, namely 36 U/L and 21 U/L, respectively, and direct bilirubin and total bilirubin were 0.18 mg% and 0.39 mg/dL, respectively. The patient was also consulted with the cardiologist, and showed hypertension and cardiomegaly which confirmed the diagnosis of concomitant hypertensive heart disease.

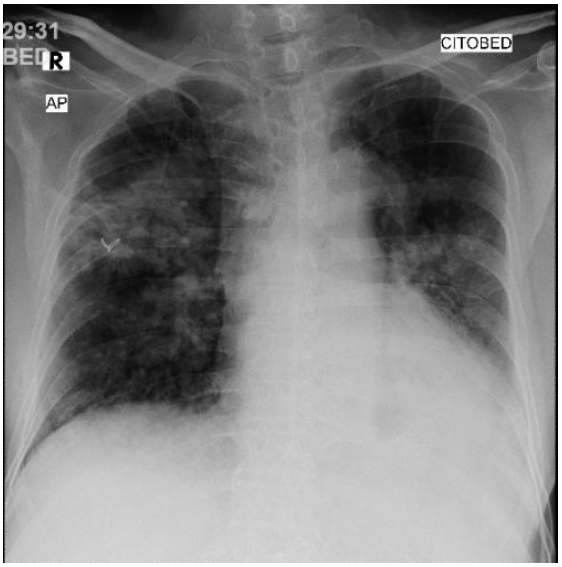

Figure 1. Chest X-ray image

Based on these examination findings, the patient was subsequently diagnosed with pulmonary tuberculosis with comorbidities of hypertensive heart disease and pneumonia. After initial stabilization, combination antituberculosis therapy with rifampicin, isoniazid, pyrazinamide, and ethambutol, along with vitamin B6, was initiated. Additional therapy included cardiovascular medications such as furosemide, captopril, digoxin, spironolactone, and isosorbide dinitrate, with the drug regimen adjusted several times during treatment according to the patient's blood pressure response and cardiac function. On the other hand, patient was also given regular nebulization with salbutamol and budesonide to reduce shortness of breath, as well as oxygen administration to increase their oxygen saturation.

Within one week of treatment, the patient's respiratory symptoms showed improvement, but complaints of nausea and vomiting still appeared occasionally. Further evaluation revealed elevated liver enzymes (SGOT 463 U/L and SGPT 63 U/L), direct bilirubin (0.58 mg%) and total bilirubin (0.80 mg/dL). These findings indicate liver dysfunction suspected to be related to the hepatotoxic effects of the antituberculosis drug regimen. In this case, the patient was diagnosed with pyrazinamide-induced hepatitis. Patient was then given an injection of norphagen or stronger neo-minophagen C (SNMC), which contains glycyrrhizin acid, glycine, and L-cysteine. Pyrazinamide was then discontinued, and the therapy regimen was adjusted to a combination of rifampicin, isoniazid, and ethambutol.

On the 10th day, the patient again experienced shortness of breath accompanied by chest pain, nausea, vomiting, and a burning sensation. Examination revealed an increase in blood pressure of 180/100 mmHg, a pulse rate of 123 beats per minute, and an SpO2 of 94%

using supplemental oxygen. A hypertensive emergency was suspected, so antituberculosis medication was temporarily discontinued and the patient received a nicardipine pump infusion with close monitoring of vital signs, including blood pressure. After antihypertensive therapy was administered, blood pressure decreased and shortness of breath gradually improved.

However, starting on the 15th day or 6 days after the antituberculosis regimen was adjusted to rifampicin, isoniazid, and ethambutol only, the patient again showed new complaints in the form of redness on the face which then spread to the entire body accompanied by itching all over the body. A clinical examination revealed a rash on the face, chest, and abdomen. The patient also experienced persistent diarrhea accompanied by nausea and vomiting. The patient was diagnosed with a drug eruption, most likely due to a reaction to one of the antituberculosis drugs. All antituberculosis medication regimens were temporarily discontinued. The patient then received therapy consisting of the injectable corticosteroid dexamethasone and the antihistamine diphenhydramine to manage the skin reaction. Vitamin K and tranexamic acid were also administered as additional supportive therapy. On the 21st day, the redness and itching lesions on the patient's body began to decrease, followed by an improvement in the patient's general condition.

The patient was subsequently given antituberculosis drugs consisting only of isoniazid and ethambutol, along with additional streptomycin. However, one day after starting this regimen, the patient developed an allergic reaction to streptomycin. Therefore, the streptomycin was replaced with levofloxacin. By the third week of treatment, shortness of breath and coughing had reduced to almost nonexistent, and the redness and itching had completely disappeared. Finally, the patient was diagnosed with pulmonary tuberculosis with rifampicin-induced drug eruption and pyrazinamide-induced hepatitis. Therefore, antituberculosis medication was resumed with a regimen without rifampicin and pyrazinamide, including isoniazid, ethambutol, and levofloxacin. The patient was discharged in stable clinical condition after 23 days of treatment with an outpatient treatment plan and regular monitoring.

At a follow-up visit after discharge, laboratory results showed that SGOT levels had decreased to 74 U/L, SGPT to 73 U/L, direct bilirubin to 0.57 mg% (still high), and total bilirubin to 0.33 mg/dL, indicating a relatively good recovery of liver function. Meanwhile, direct bilirubin levels showed a significant decrease at the next follow-up, dropping to 0.26 mg%. The course of major clinical events in this patient is depicted chronologically in **Figure 2**. The authors have obtained verbal informed consent, both from the patient and the

patient's family, to use the patient's data anonymously for the purposes of publishing this case report.

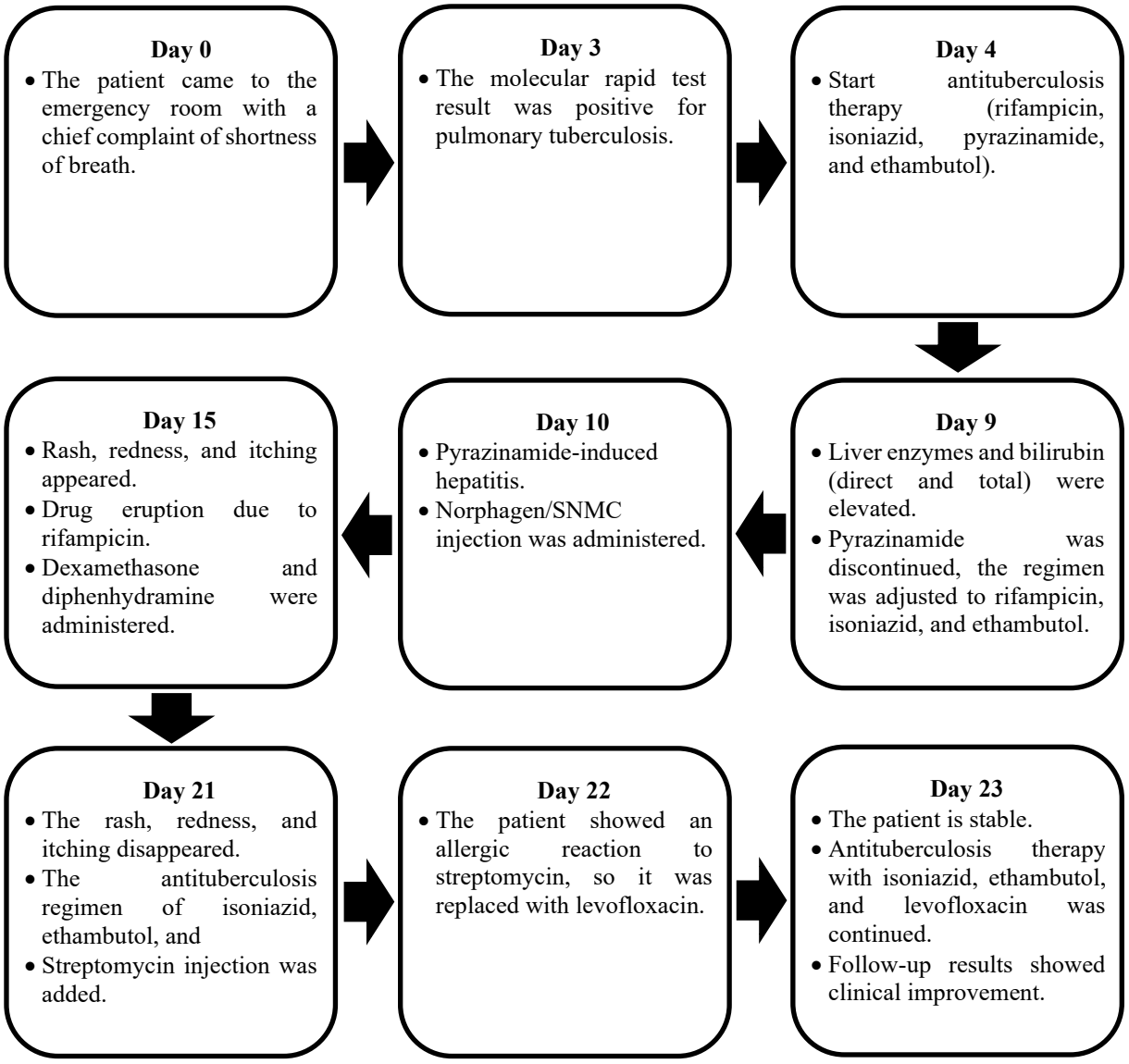

Figure 2. Timeline of the patient's clinical course of events

Discussion

This study reports a case of an elderly male patient with a confirmed diagnosis of tuberculosis through molecular rapid test, who subsequently experienced side effects during antituberculosis therapy in the form of a rifampicin-induced drug eruption and pyrazinamide-induced hepatitis. Drug eruption in this patient appeared as a red, itchy rash on the face, chest, and abdomen. Hepatitis, meanwhile, appeared as an increase in liver enzymes after several days of antituberculosis treatment. Evidence suggests that these side effects and adverse reactions are more frequently reported in elderly tuberculosis patients

than in younger patients.[9] Another study [10] stated that pyrazinamide was the drug that caused the most serious side effects, with the most frequent being hepatotoxicity followed by gastrointestinal intolerance. Increasing age or older patients are risk factors for increased incidence of these side effects. In contrast, although rifampicin is considered safe and rarely causes adverse side effects, a study supports this case report, where it was found that 0.8% of patients receiving rifampicin experienced grade 1-4 rash with 64% of incidents occurring before one month of therapy.[11] Therefore, side effects such as drug eruption and hepatitis induced by antituberculosis drugs remain a significant challenge in the successful treatment of tuberculosis, especially in elderly patients.

The patient in this case experienced a drug eruption in the form of a reddish, itchy rash that spread over the face and body, and appeared 10 days after anti-tuberculosis therapy. Drug eruption itself is defined as a type IV or delayed type hypersensitivity reaction mediated by T cells, with one of the causes being drugs, including antituberculosis drugs.[12] Rifampicin was identified as the drug responsible for the side effects in this patient. This reaction can occur within days through the formation of immune complexes and activation of T cells that target keratinocytes, resulting in a skin rash. Furthermore, several cytokines and chemokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-6, IL-8, IL-15, IL-36, and granulocyte-macrophage colony-stimulating factor (GM-CSF), also contribute to the hypersensitivity immune reaction caused by this drug.[13] However, a study revealed that rifampicin rarely causes hepatotoxicity, but can actually cause adverse reactions. The most common reactions are rashes, a form of hypersensitivity reaction, and gastrointestinal disturbances, particularly in the first month of therapy, which is what occurred in the patient in this case.[14] This suggests that drug eruption reaction to rifampicin in this patient is a relatively rare but important event to identify.

Antituberculosis therapy should be temporarily discontinued in patients experiencing a drug eruption. Research suggests that discontinuing the antituberculosis drug regimen may be followed by administration of antihistamines alone, steroids alone, or a combination of both, depending on the patient's clinical condition.[15] Although the administration of corticosteroids in cases of drug eruption in tuberculosis patients is still controversial [16], in this case report, the administration of a combination of corticosteroids in the form of dexamethasone and antihistamine in the form of diphenhydramine provided significant benefits in this patient. In accordance with previous study [17] which stated that the combination of the two drugs can reduce the symptoms of itchy red rashes in patients with drug reactions.

Hepatitis was also reported in this patient as a pyrazinamide-induced side effect, with elevated liver enzymes and direct and total bilirubin levels reported after antituberculosis therapy. Drug-induced hepatitis is a serious adverse reaction characterized by liver damage caused by metabolites or drug-like substances. Elderly patients with cardiovascular and cerebrovascular disease are at higher risk for drug-induced hepatitis, which is consistent with the patient in this case report who had cardiovascular comorbidities.[18] Pyrazinamide is a type of antituberculosis drug that often causes drug-induced hepatitis. One study [19] found that pyrazinamide increased lipid peroxidation and apoptosis, and inhibited the phosphorylation of phosphatidylinositol 3-kinase (PI3K) and AKT. Another study [20] added that pyrazinamide is metabolized through a pathway involving xanthine oxidase, which subsequently increases the production of superoxide radicals, which trigger reactive oxygen species (ROS) in the liver. This results in redox imbalance and lipid peroxidation. Overall, these mechanisms lead to elevated liver enzymes and hepatotoxicity.

Pyrazinamide-induced hepatitis in this patient was managed by discontinuing all antituberculosis therapy before liver damage became irreversible. Subsequently, norphagen injection, or SNMC, was administered to the patient in this case report. This drug selection was based on evidence demonstrating SNMC's significant benefits in normalizing liver enzyme levels, reducing liver inflammation, stabilizing mitochondria to reduce cytochrome-C release, and enhancing hepatocyte regeneration. Thus, this drug is believed to help prevent the progression to irreversible liver failure in patients with hepatitis.[21,22] After temporary discontinuation of the antituberculosis regimen and subsequent administration of SNMC, the patient's condition in this report gradually improved, as indicated by improvements in liver enzymes and direct and total bilirubin.

After stabilization of the patient's hepatotoxicity, only isoniazid and ethambutol remained as tolerable first-line agents. Because two active drugs are insufficient to reliably treat tuberculosis, the clinical team elected to add an injectable aminoglycoside as a temporary third agent while arranging for an adequate oral regimen. Ideally, agents from WHO Group A and Group B are prioritized when composing a replacement regimen; Group C agents are used only when a regimen cannot be composed from Group A and B alone. In our setting amikacin, the preferred aminoglycoside, was not available at our facility on that day and an all-oral regimen could be constituted immediately, therefore streptomycin was administered as an injectable substitute for rifampicin and pyrazinamide. Unfortunately, an allergic reaction occurred within one day of streptomycin and the drug was promptly discontinued. The choice of streptomycin is in accordance with WHO recommendations,

where aminoglycoside antibiotics are the second-line treatment for tuberculosis if the patient cannot receive the first-line drug (**Table 1**).

Table 1. Current approved first-, second-, and third-line medication recommended for tuberculosis treatment.[23,24]

Disease indication	Drug	Administration route
Drug susceptible tuberculosis	Isoniazid	Oral
	Pyrazinamide	Oral
	Rifampicin	Oral
	Ethambutol	Oral
	Rifapentine	Oral
Multidrug resistant tuberculosis	Fluoroquinolones (levofloxacin, moxifloxacin)	Oral
	Aminoglycoside (amikacin, streptomycin)	Injectable
	Rifabutin	Oral
	Capreomycin	Injectable
	Pyrazinamide	Oral
	Ethambutol	Oral
	Thioamides (ethionamide, prothionamide)	Oral
	Para-amino-salicylate	Oral
	Cycloserine	Oral
	Bedaquiline	Oral
	Nitroimidazole delamanid	Oral
Extensively drug resistant tuberculosis	Nitroimidazole pretomanid	Oral
	Clofazimine	Oral
	Linezolid	Oral
	Multidrug-resistant-tuberculosis drugs as appropriate based on drug susceptibility profile	

Amikacin, an aminoglycoside, can be given as the first choice, but if it is unavailable, injectable streptomycin is the next option.[23,24] In this case, patient was given streptomycin. Streptomycin works by binding to the 30S ribosomal subunit and has a bactericidal effect against *M. tuberculosis*.[25] However, this drug also has a risk of hypersensitivity reactions and ototoxicity.[26,27], which in this patient was seen through the appearance of an allergic reaction within one day of therapy. Therefore, after the appearance of an allergy to streptomycin, its administration was stopped and subsequently replaced with levofloxacin.

Levofloxacin is a fluoroquinolone antibiotic chosen as a substitute for streptomycin in this case. Evidence and WHO guidelines on tuberculosis therapy indicate that fluoroquinolones are the priority agents in first-line tuberculosis cases with drug intolerance due to their potent bactericidal activity and relatively good safety profile.[23,28] Currently, there

are two fluoroquinolone alternatives to antituberculosis drugs: moxifloxacin and levofloxacin. However, although both drugs have shown equivalent efficacy, levofloxacin is more commonly prescribed due to its higher potential for cardiotoxicity.[29] A recent network meta-analysis reported evidence that the combination of levofloxacin with conventional tuberculosis therapy demonstrated superior efficacy compared with conventional regimens, and was safer from adverse side effects than the combination of moxifloxacin and conventional regimens.[30] Thus, levofloxacin was appropriately chosen because it provides strong bactericidal activity as well as a better safety profile compared to other alternatives.

Finally, the patient in this case was given an alternative antituberculosis regimen in the form of a combination of isoniazid, ethambutol, and levofloxacin, without the administration of rifampicin and pyrazinamide because both caused adverse side effects in this patient. A study reports evidence that isoniazid and pyrazinamide provide a synergistic effect in the treatment of pulmonary tuberculosis, where both work through transcriptional repression of the inhA gene, which is the isoniazid target gene that encodes the enoyl-acyl reductase carrier protein of the fatty acid synthase system required for bacterial cell wall integrity. Furthermore, ethambutol will induce EtbR-mediated repression of inhA to enhance the mycobactericidal effect of isoniazid.[31] The addition of levofloxacin as a fluoroquinolone provides an additional broad-spectrum bactericidal effect that targets the DNA gyrase and topoisomerase IV enzymes, thereby inhibiting DNA replication and DNA helix activity in *M. tuberculosis*.[32,33] From the follow-up results with this regimen, the patient showed favorable clinical improvement, marked by improvement in liver enzymes and the disappearance of the red rash on the face and body.

This case report provides important insights for clinical practitioners, particularly in the management of tuberculosis patients experiencing severe drug side effects. The combination of rifampicin-induced drug eruption and pyrazinamide-induced hepatitis, as occurred in this patient, emphasizes the need for high vigilance and regular monitoring of organ function from the start of therapy. Early detection of signs of adverse reactions, accompanied by temporary discontinuation of the suspected drug and adjustment of the regimen to a safer one, has been shown to prevent serious complications without compromising the efficacy of therapy. Several risk factors have been reported to increase the likelihood of adverse reactions to antituberculosis drugs, including drug eruption and hepatitis. These include alcohol consumption, advanced age, genetic susceptibility, pre-existing liver disease, history of drug allergy or atopic conditions, HIV infection,

malnutrition or low serum albumin levels, and concomitant use of other hepatotoxic medications. Some studies have also suggested possible associations with sex-related differences and comorbidities such as diabetes, although these findings are not always consistent.[34–37] Based on these considerations, the patient in this case had one clear risk factor, namely advanced age above 60 years.

This case report emphasizes the importance of a multidisciplinary approach involving pulmonologists, internists, and laboratory technicians to ensure appropriate individualized management. In addition to patient education regarding potential side effects and early symptom reporting, several preventive measures should be undertaken by clinicians. These include thorough baseline assessment before initiating therapy such as liver function tests and history of liver disease, alcohol use, and prior drug allergies, regular laboratory and clinical monitoring during treatment, and early risk stratification to identify patients requiring closer follow-up. Prompt recognition and immediate discontinuation of suspected drugs when adverse reaction occur are also critical to prevent progression to severe toxicity. Such proactive strategies can reduce morbidity and improve the safety of antituberculosis therapy in daily clinical practice.

Conclusion

This case report illustrates that although first-line antituberculosis therapy is effective, this regimen can cause serious side effects in the form of drug eruption and hepatitis. Temporary discontinuation of antituberculosis drugs, administration of appropriate supportive therapy, and adjustment of the antituberculosis regimen without rifampicin and pyrazinamide have been shown to provide good clinical outcomes with improvements in liver function and skin symptoms. The case in this report emphasizes the importance of regular liver function monitoring, early detection of drug reactions, and careful and individualized therapeutic decision-making. A rational and evidence-based approach to similar cases in the future is expected to improve the success of tuberculosis treatment while minimizing the risk of complications caused by antituberculosis drugs.

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