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Case Report

Diagnostic and Treatment Challenges of Recurrent Tuberculosis in Patient with Drug-Induced Hepatotoxicity: A Case Report

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ABSTRACT

Introduction: Pulmonary tuberculosis (TB) remains one of the most significant global health challenges, especially complicated by cases with incomplete treatment histories. The recurrence of TB poses diagnostic and therapeutic dilemmas that significantly impact patient outcomes.

Case Presentation: We report a case of a 57-year-old female patient presenting with recurrent pulmonary TB after an incomplete treatment course. The patient's history revealed gaps in adherence to the prescribed TB regimen, leading to multiple relapses. In this study, we found that patients undergoing TB treatment may experience liver damage as a result of the TB medication, also known as DIH. Comprehensive diagnostic procedures, including chest radiography, sputum culture, and molecular testing, confirmed recurrent TB. The patient's clinical manifestations, treatment plan, and response to therapy are detailed.

Conclusion: Recurrent TB is common, particularly in older adults, and is influenced more by environmental factors than occupation. Additionally, ATT poses risks of hepatotoxicity, especially in malnourished patients, underscoring the importance of managing side effects and addressing factors like malnutrition to prevent complications and improve outcomes. This case underscores the importance of complete adherence to TB treatment regimens and highlights the challenges in managing recurrent TB. It emphasizes the need for robust follow-up, patient education strategies, early diagnosis, and prompt intervention to prevent recurrence and enhance patient outcomes.

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INTRODUCTION

Pulmonary tuberculosis (TB), a chronic infectious disease caused by *Mycobacterium tuberculosis*, mainly targets the lungs but can also spread to other organs. Despite ongoing global health initiatives, TB continues to be a major health concern, ranking 13th among leading causes of death and second among deadly infectious diseases, following COVID-19 [1]. Individuals with compromised immune systems, such as those with HIV/AIDS, diabetes, malnutrition, or immunosuppressive medications, are at higher risk of contracting TB. Environmental and social determinants, such as overcrowding, inadequate sanitation, and exposure to tobacco smoke and alcohol, significantly increase the risk [2].

TB symptoms depend on the affected area but commonly include a persistent cough for more than two weeks, sputum that may contain blood, chest pain, shortness of breath, general malaise, weight loss, loss of appetite, fever, and night sweats [3]. Anti-tuberculosis drugs (ATT) are essential for treating TB and play a key

role in preventing the spread of the infection. With proper ATT therapy, pulmonary TB can achieve high cure rates with minimal complications [3].

TB remains a significant global public health challenge, particularly in Indonesia. The WHO Global Tuberculosis Report in 2023 ranks Indonesia as the second-highest country for TB cases, with approximately 824,000 new cases reported in 2022 [4]. In 2022, East Java reported 78,334 TB cases, with 7,177 cases in Surabaya [5]. This data highlights the ongoing high transmission and disease burden despite various control measures [4]. Community health centers, or Puskesmas, play a crucial role in the early detection, diagnosis, treatment, and control of TB. In Surabaya, the Tenggilis Community Health Center has been actively engaged in the TB control program. The center reported an increase in TB cases in 2022, particularly among those of working age, according to the Surabaya City Health Department. This rise in TB cases may be attributed to factors such as high population density, frequent mobility, and access to healthcare.

Recurrent pulmonary TB poses a significant challenge in areas with high prevalence, making diagnosis and treatment more difficult. This case report examines a patient with recurrent pulmonary TB and drug-induced hepatotoxicity (DIH), focusing on the clinical presentation, treatment history, and factors contributing to both the recurrence and liver toxicity. The study aims to improve the understanding and management of such cases to enhance patient outcomes and prevent future recurrences.

CASE PRESENTATION

A 57-year-old woman visited the Tenggilis Community Health Center on February 3, 2024, after being screened during a mass tuberculosis screening in the Tenggilis Mejoyo District, which took place from January 27, 2024, to February 7, 2024. She complained of a persistent cough that had lasted for two weeks. The cough worsened, particularly during the day, and was accompanied by dark brown sputum. The patient also reported mild shortness of breath, which made her easily fatigued, especially when walking or performing daily activities, and she felt more comfortable sleeping or lying on her right side. The patient also complained of a decreased appetite and weight loss from 45 kg to 39 kg.

She denied symptoms such as fever, night sweats, chest pain, or lumps in her neck or armpits. The patient had a history of pulmonary TB in 1999, for which she underwent 9 months of treatment and was declared cured. She then had her second pulmonary tuberculosis in 2012, she underwent 1 year of treatment and was declared cured. The patient first contracted TB from her husband (now lives separately), who was initially diagnosed with TB in 1998 and successfully completed treatment within the same year. In 2023, her husband was diagnosed with a relapse of TB, and also completed treatment within the same year. Additionally, the patient's first child contracted TB during her first year of vocational high school. The treatment history of her child remains unclear, although the patient is convinced that the child received medication and has already been cured. There is no significant history of other illnesses from either the patient or the patient's family. The patient also denies any history of diabetes mellitus or other immunocompromising conditions. The patient is a housewife and a *kader* Posyandu (integrated service post cadre) in Kutisari, while her husband works as a truck driver transporting goods between cities. The patient is currently living in a densely populated area with poor ventilation and lighting in a small, cramped house shared with her three children (Fig.1). The patient is a participant in the BPJS healthcare program. The patient has a selective diet, avoiding red meat, duck, and chicken. She prefers to eat vegetables, tofu, tempeh, seafood, and eggs. The patient claims to exercise regularly once a week and always keeps her house clean. She does not smoke or drink alcohol, and no one in her family smokes. However, a heavy smoker who often smokes in front of her house lives close to the patient.

Investigation

Based on the physical examination, the patient was alert and oriented with Glasgow Coma Scale (GCS) of 15. She appeared skinny. Her Body Mass Index (BMI) was 15.4, which classified as severely underweight. The thoracic examination revealed decreased tactile fremitus in the lower third of the right lung, dullness on percussion in the lower two-thirds of the right lung, and hyperresonance in the apex of the left lung. Vesicular breath sounds were heard in both lung fields but were diminished in the right lung. No abnormalities were found in the examination of other areas from head to toe.

A molecular rapid test conducted on January 31, 2024, showed that *Mycobacterium tuberculosis* (MTB) was detected at very low levels, and rifampicin resistance was negative (Table 1). An immuno-serological test revealed that the anti-HIV test was non-reactive. Based on the results of the molecular rapid test, it was concluded that the patient was diagnosed with bacteriologically confirmed recurrent pulmonary TB.

Treatment

The patient received Category 1 anti-tuberculosis treatment (ATT) with a regimen of 2 months of HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) followed by 4 months of HR3 (Isoniazid and

Figure 1. (a) The interior view of the patient's house, which has limited natural light and poor ventilation. (b) The exterior of the patient's house, which appears overcrowded with unused items and contains numerous stagnant pools of dirty water that could pose health risks.

Rifampicin, three times weekly). The patient was scheduled for follow-up sputum AFB (Acid-Fast Bacillus) examinations in the 2nd, 5th, and 6th months. The patient was advised to wear a mask both indoors and outdoors, practice proper cough etiquette, and maintain distance from household members. The TB prophylaxis medication was also prescribed for the patient's three children.

Outcome and Follow-Up

After one week, the patient was admitted to Jemursari Islamic Hospital on Sunday, February 11, 2024, after receiving ATT from the Tenggilis Community Health Center with complaints of cough, fever, weakness, and vomiting whenever she took the ATT or after every meal. She denied symptoms such as night sweats, chest pain, or lumps in her neck or armpits.

A chest X-ray on February 11, 2024, showed right pleural effusion and suspected old pulmonary TB in the left lung (Fig.2). A laboratory examination was conducted, revealing an increase in lymphocytes to 18.80%, elevated neutrophil count of 72.70%, elevated level of AST (aspartate aminotransferase) to 309 U/L and ALT (alanine aminotransferase) to 79 U/L. Based on the laboratory results, the patient was experiencing side effects from the treatment, indicating hepatotoxicity or liver damage.

The patient's ATT was paused during hospitalization until her condition improved and liver enzyme levels (AST and ALT) decreased. After a week, she was discharged as her symptoms had subsided, and ATT was resumed. Following two months of treatment, her TB symptoms showed significant improvement, and the treatment continued for a total of six months. By the end of the treatment, she was declared fully cured and no longer needed ATT.

DISCUSSION

Mycobacterium tuberculosis (M. tb) is transmitted through aerosol droplets from active TB patients [6]. Once inhaled, the bacteria reach the lungs and are engulfed by macrophages [7]. If not destroyed, the bacteria multiply, leading to the formation of granulomas—immune cell clusters that contain the infection [7,8]. In healthy individuals, granulomas keep the bacteria dormant, leading to latent TB [7]. However, if the immune system is weakened, the bacteria can reactivate, causing the granulomas to liquefy and release the bacteria, leading to active, contagious TB [7,8].

In this case, the patient did not exhibit symptoms of fever or night sweats, indicating that not all TB patients experience classic symptoms of TB. Fever in TB can be caused by various factors, including direct TB complications, hypersensitivity, drug resistance, reactions to medications, and other concurrent diseases like other lung infections, malaria, and amoebic liver abscess [9]. According to Luies & du Preez, tuberculosis can cause the production of toxins and increased secretion of TNF-α, which contributes to fever. The absorption of toxins from bronchial and lung cavity damage may also trigger fever as part of the body's inflammatory response to TB infection [10].

The absence of fever might indicate a lower level of toxin absorption from bronchial or lung damage, or the TB infection may not have progressed to a stage that triggers a strong inflammatory response. Night sweats in TB are often linked to circadian rhythm fluctuations, with body temperature typically lower before dawn and rising in the evening. Reduced cortisol hormone secretion at night may also contribute to TB-related night sweats. Night sweats are closely related to circadian rhythm fluctuations and changes in cortisol

Table 1. Results of The Patient's TCM GeneXpert MTB/RIF Test

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SPC	29.0	171	NA	PASS
IS1081-IS6110	25.1	589	NA	PASS
rpoB1	31.2	295	POS	PASS
rpoB2	30.8	236	POS	PASS
rpoB3	32.7	129	POS	PASS
rpoB4	33.9	104	POS	PASS

* BMI = Body Mass Index
† p-value < 0.05 indicates statistical significance

secretion [10]. The patient's stable circadian rhythm and cortisol levels may prevent the fluctuations that typically cause night sweats in TB, or the TB infection may not be severe enough to disrupt these processes.

Based on the data we obtained, the patient had undergone TB treatment three times, with previous treatments resulting in recovery. It was also noted that the patient lived with her child, who had also been diagnosed with TB but without a clear history of treatment. This situation makes the patient susceptible to relapse. The occurrence of recurrent TB infection itself is not uncommon. A study conducted by Cudahy et al. reported that out of 500 TB patients studied, 333 (79%) successfully completed their TB treatment. Among these 333 patients, 35 (11%) experienced bacteriologically confirmed TB relapse. The recurrence of the patient's condition is suspected to be due to the poor, cramped, and poorly ventilated-environment of their home [11].

A study conducted by Du et al. at a university in Taipei, Taiwan demonstrated that enhancing indoor ventilation to CO2 levels below 1000 ppm was an efficacious strategy for containing a TB outbreak that occurred in an environment with inadequate ventilation. This improvement in ventilation was associated with a 97% reduction in the risk of contacts becoming new active TB cases and was instrumental in halting the TB outbreak at the university [12]. Enhancing living conditions by expanding space, improving airflow, and minimizing overcrowding can decrease the likelihood of TB transmission and recurrence. Keeping indoor CO2 levels under 1000 ppm is especially effective in preventing the spread of TB.

Despite the patient being an integrated service post cadre in Kutisari and adhering rigorously to health protocols, this does not prevent her from contracting infectious diseases such as pulmonary tuberculosis, even experiencing recurrence up to three times. This study aligns with research conducted by Jaya and Mediarti in 2019 at the South Sumatra Pulmonary Hospital, which stated that there is no correlation between occupation and the recurrence of pulmonary TB. This implies that the recurrence of pulmonary TB is not influenced by the level of work activity but may instead be affected by the living environment, such as the humidity of the house, the condition of the windows, and the amount of natural light entering the home [13].

It was stated that the patient contracted pulmonary tuberculosis for the second time at age 45 and for the third time at age 57. This patient's history aligns with data from Dr. Pirngadi Hospital in Medan City, where a statistical analysis revealed a significant relationship between age and the recurrence of pulmonary tuberculosis (p-value <0.05). The study found that the age group most frequently affected by recurrent TB is over 45 years old. Similarly, a study from a health center in North Pontianak identified the 45 – 60-year age group as the most common for TB recurrence, attributed to a weakening immune system, which is crucial for combating *Mycobacterium tuberculosis* infection [14].

Host vulnerability is another key factor associated with relapse, particularly among those who may suffer from stress, poverty, and deprivation. In addition, social risk factors may be a proxy for patients with previous poor adherence to treatment, increasing their chance of relapse [15]. In undeveloped countries, a higher incidence of tuberculosis may cause a higher burden of DIH. Moreover, the incidence of drug-induced hepatitis due to ATT is higher in these countries. So, this issue is not only important for clinical practitioners to manage the patient's illness but also the burden of this complication should be considered within the health service policy and management [16].

The patient underwent Category 1 ATT, which consisted of 2 months of HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) followed by 4 months of HR3 (Isoniazid and Rifampicin, administered three times per week). This regimen aligns with the current standard treatment for drug-susceptible tuberculosis (DS-TB), which involves a six-month course of these

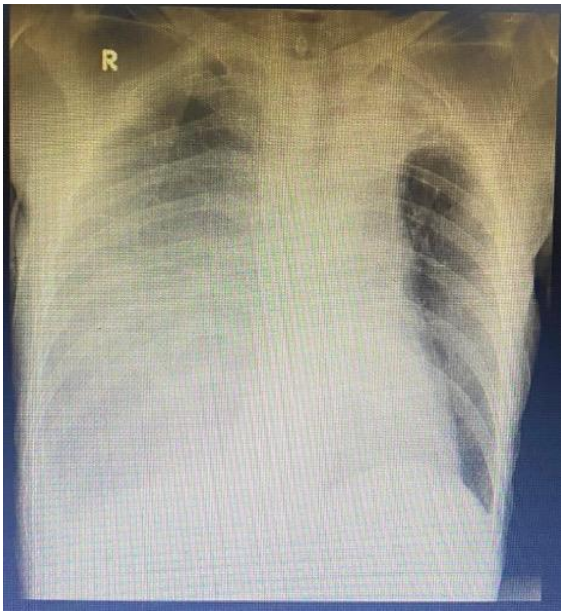

Figure 2. Chest X-ray of The Patient Showed Right Pleural Effusion and Suspected Old Pulmonary TB in The Left Lung

four antibiotics [7]. Even after nearly 60 years, this combination remains fundamental to TB treatment because of its established effectiveness [7]. However, despite their efficacy, these drugs can cause serious side effects, including liver dysfunction and neuropathy. These adverse effects, combined with the prolonged treatment duration and high pill burden, can result in poor patient adherence and contribute to the emergence of drug-resistant TB strains [7,17]. ATT, which includes first-line and second-line drugs like isoniazid, rifampicin, and pyrazinamide, are known for their hepatotoxicity and can cause liver damage [18]. Among these ATT, pyrazinamide is the most hepatotoxic and should be avoided in individuals with chronic liver disease [18]. In undeveloped countries, higher incidence of tuberculosis may cause a higher burden of DIH. Moreover, the incidence of drug-induced hepatitis due to ATT is higher in these countries. So, this issue is not only important for clinical practitioners to manage the patient's illness but also the burden of this complication should be considered within the health service policy and management [19].

Another factor that may contribute to the development of ATT toxicity is gender. This phenomenon can be attributed to the heightened activity of cytochrome P450 3a in women, as well as pharmacokinetic variations, including slower acetylation patterns and lower BMI. Malnutrition and hypoalbuminemia can also serve to elevate the risk of DIH. The dearth of glutathione in malnourished patients results in a diminished capacity to eliminate toxic metabolites, rendering them more vulnerable to oxidative stress that causes hepatotoxicity [20].

Similarly, Wesnawa and Kusmiati have documented cases of DIH in malnourished women. This illustrates the parallels observed in our study, wherein the patient exhibited pronounced malnutrition, as evidenced by a BMI below the normal range and an abdominal examination that described a scaphoid abdomen. Long et al. have highlighted that malnutrition represents a significant risk factor for TB infection, with individuals experiencing malnutrition at a 12-fold elevated risk of developing active TB and 2- to 3-fold increased odds of progressing from latent TB to active TB. Malnutrition and tuberculosis have a tendency to interact with one another. Malnutrition, or undernutrition, is a prevalent issue among individuals diagnosed with tuberculosis (TB). The risk of mortality is elevated among individuals who have experienced a relapse of tuberculosis (TB). A number of studies have indicated the prevalence of malnutrition in patients with tuberculosis. The prevalence of malnutrition in patients is relatively high, with a prevalence rate of approximately 20% [21].

Considering the severity of DIH, the patient exhibited nonspecific symptoms such as fever, weakness, and vomiting, without any evidence of jaundice. Laboratory results indicated elevated AST levels at 309 U/L and ALT levels at 79 U/L. While liver enzyme elevations alone do not adequately reflect the severity of liver injury, it is well-established that when aminotransferase elevations occur alongside jaundice, there is a heightened risk of severe outcomes. In

evaluating severity, it is also crucial to consider analytical tests, including total and conjugated bilirubin, coagulation tests (INR, Factor V, prothrombin time), and hypoalbuminemia, with INR being particularly significant [22]. Given the nonspecific symptoms in this case, the severity of DIH is categorized as mild.

The patient continued with the existing ATT regimen without changes after the AST and ALT levels normalized and decreased. Another reason for maintaining the regimen was that the sputum test confirmed the Mycobacterium tuberculosis strain was still sensitive to rifampicin.

CONCLUSION

Recurrent TB is common, particularly in older adults, and is influenced more by environmental factors than occupation. Additionally, ATT poses risks of hepatotoxicity, especially in malnourished patients, underscoring the importance of managing side effects and addressing factors like malnutrition to prevent complications and improve outcomes. This case underscores the importance of complete adherence to ATT regimens and highlights the challenges in managing recurrent TB. It emphasizes the need for robust follow-up, patient education strategies, early diagnosis, and prompt intervention to prevent recurrence and enhance patient outcomes.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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