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Drug-Induced Liver Injury in Young Female with Primary Tuberculous Lymphadenitis Mimicking Lymphatic Malignancy: A Case Study

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A B S T R A C T

Background: Drug-induced liver injury (DILI) is a side effect that is often found in tuberculosis (TB) treatment and interferes the effectiveness of treatment. Risk factors for DILI during treatment of pulmonary tuberculosis are age, gender, and comorbid conditions such as hepatitis and use of hepatotoxic drugs.

Case Report: A 22-year-old female presented with persistently enlarged, inflamed, painful right-sided neck swelling with purulent discharge for 7 months. The patient reported no history of comorbid diseases and risk factor other than passive smoking at home. Other symptoms are night sweats, loss of appetite, and significant weight loss. Initially, she was diagnosed with lymphatic malignancy, but after tissue sampling, she was diagnosed with tuberculous lymphadenitis without pulmonary TB based on histopathological examination, which revealed necrotizing granulomatous inflammation. GeneExpert was performed on sputum sample showing a negative result. The patient initially started first-line anti-TB therapy consisting of isoniazid, rifampin, pyrazinamide, and ethambutol. After 58 doses, the patient developed complaints of decreased appetite, nausea, and vomiting, without any improvement of the neck lumps. Laboratory results showed significant increase of ALT and AST. We diagnosed the patient with DILI and anti-tuberculosis drugs were stopped temporarily.

Conclusion: We present a unique case of a young woman, without comorbid chronic disease, with TB-lymphadenitis and DILI. DILI is a major side effect in TB treatment, causing therapy failure due to the non-adherence of treatment. A number of cohort studies have shown that the risk factors for DILI in patients receiving TB treatment are age>35 years, male gender, and history of comorbid disease such as hypertension and diabetes.

Keywords: Anti-Tuberculosis Drug; Drug Induced Liver Injury; Lymphadenitis; Risk Factor; Tuberculosis

Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis that primarily affects the lungs, making it the most common infectious lung disease throughout history. However, tuberculosis is a multisystem disease affecting many organs and can progress without symptoms. It may affect extrapulmonary sites such as the central nervous system, gastrointestinal system, lymph nodes, skin, musculoskeletal system, and reproductive system.[1,2] The most common extrapulmonary site of tuberculosis (TB) is lymph nodes. Scrofula (historically known as the "King's Evil") is tuberculous cervical lymphadenitis caused by hematogenous or lymphatic spread of pulmonary tuberculosis or reactivation of latent tuberculosis, or rarely, caused by primary adenoid or tonsil involvement.[3]

Recent guideline of first-line anti-TB therapy is combination of isoniazid, rifampicin, pyrazinamide, and ethambutol.[4,5] However, all of those drugs possessed hepatotoxic effects. Therefore, drug-induced liver injury (DILI) is a serious side effect that occurs during tuberculosis treatment leading to treatment nonadherence, failure, or development of drug resistance. Anti-tuberculous DILI has been reported in 2–28% of patients worldwide with clinical features varying from mild, asymptomatic elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), acute hepatitis, or even liver failure.[6] Successful TB treatment involves the administration of rifampicin, isoniazid, pyrazinamide, and ethambutol, which carry the risk of hepatotoxic side effects. Various risk factors, including BMI, INH metabolic acetylator status, age, gender, metabolic conditions, drug interactions, and alcohol consumption, can help predict the likelihood of hepatotoxicity leading to DILI.[6,7]

This case report presents a unique case of a young immunocompetent female patient with lymph node swelling on the right side of her neck suspicious for lymphatic malignancy. After repeated histopathological examinations, the patient was diagnosed with TB lymphadenitis and underwent TB treatment with FDC, but experienced DILI leading to treatment delay.

Case Description

A 22-year-old female presenting with persistently enlarged, inflamed, painful right-sided neck swelling with purulent discharge for 7 months (Figure 1). The patient reported no history of comorbid diseases and risky behaviour other than passive smoking at home. Other symptoms are night sweats, loss of appetite, and significant weight loss (weight loss of 6 kg (44kg-38kg) in the last 7 months).

Previously, the patient had visited a primary health care center and received standard antibiotic therapy, but there was no clinical improvement. Subsequently, she was referred to the surgery polyclinic at Sragen General Hospital for debridement and biopsy due to suspicion of lymphatic malignancy. The first biopsy results were nonspecific chronic lymphadenitis with suppurative necrosis and lymphoid follicular hyperplasia. After 3 months, the patient returned to the hospital because the lump was getting bigger and painful. Rebiopsy results showed caseous tuberculous lymphadenitis with secondary infection. After the biopsy results came out, the patient immediately underwent GenExpert sputum examination with Mtb not detected results. Looking at the patient's clinical condition, the surgeon collaborated with a pulmonologist for initiating TB treatment. The patient was diagnosed with clinical lymphadenitis TB without pulmonary TB based on histopathological examination without bacteriological examination. The patient was initially started on first-line therapy of combination isoniazid, rifampin, pyrazinamide, and ethambutol.

After about 2 months (58 doses of anti-TB drugs) on TB treatment, the patient came back to the emergency ward with complaints of decreased appetite, nausea and vomiting, without any improvement in neck lumps. There were no complaints of icteric or enlarged abdomen. The patient said that she always routinely took medication as directed and did not take other drugs or over the counter. Physical examination showed underweight nutritional status (BMI 16.9 kg/m2) with a solitary mass in the colli dextra region, size 14x8x4, hyperemic, pus, with a 1.5x1 ulcer with a connective tissue base, solid consistency, and fixed. No hepatomegaly was found. The patient's blood reports revealed a hemoglobin level of 9,2 g/dl, elevated total leukocyte count of 27,110/cu mm and significant increase of ALT and AST. The chest x-ray of the patient was reported as normal (Figure 2). We diagnosed the patient with DILI grade 1 and anti-TB therapy was stopped temporarily. During treatment for about 7 days, we administered the antibiotic azithromycin and re-initiated TB treatment with Ethambutol 1000 mg once daily. Monitoring of clinical conditions is carried out daily by surgeons, pulmonologists, internists and TB-trained nurses (Figure 3). After the patient is assessed as fit enough and her liver enzyme parameter back to normal, the patient is referred to the central hospital for further examination.

Discussion

To enhance the strength and value of this case report, the authors have incorporated a literature review on the risk factors for drug-induced liver injury (DILI) in extrapulmonary tuberculosis (EPTB) cases. The aim was to assess whether the risk factors identified in relevant journals could be applied to the current case report. The literature search was independently conducted by two authors (MID and HAN), across four major journal databases—PubMed, Cochrane Library, Wiley, and Scopus—using

Table 1. Risk Factors for the Occurrence of DILI in EPTB Population Identified from Literatures[15-19]

Author	Year	Design Study	Number of Subject (n)	Risk Factor	OR	Notes
Singanayagam A, et al[15]	2012	Prospective Cohort Study	288	Pregnant or <3 month postpartum	6.83	Risk factor of DILI vs Non-DILI
				Chronic Liver Disease	9.48	
				Abnormal ALT at baseline	4.19	
Naqvi IH, et al[16]	2015	Prospective Cohort Study	278	History of DM	4.53	Risk factor of DILI vs Non-DILI
				Concomitant Hepatotoxic Drugs	5.34	
				EPTB	2.21	
Abbara A, et al[17]	2017	Retrospective Cohort Study	1529	Baseline ALT	2.28	Risk factor of DILI vs Non-DILI
				Baseline ALP	6.67	
				Baseline Bilirubin	1.93	
				Weight	0.97	
				HIV	3.50	
				History of Alcohol	6.00	
Zhao H, et al[18]	2020	Retrospective Cohort Study	140	Female	2.41	Risk factor of DILI grade 1-3 vs DILI grade 4-5
				Re-Challenge of anti-TB therapy	5.82	
Jiang F, et al[19]	2022	Prospective Cohort Study	3155	Age	1.01	Risk factor of DILI vs Non-DILI
				Baseline ALT	1.02	
				Baseline ALP	1.02	
				Baseline Bilirubin	1.02	
				HBsAg positive	1.66	

specific keywords or their synonyms (refer to Appendix 1). Search results were screened to eliminate duplicates, followed by the assessment of abstracts and full-texts based on predefined eligibility criteria for this case report. Inclusion criteria involved observational studies focusing on adults diagnosed with extrapulmonary tuberculosis (EPTB) or scrofula, written in English with full text available. Exclusion criteria included non-research papers and publications not in their final stage.[8] Despite the identification of numerous risk factors through diverse assessment methods, the study chose not to proceed to the meta-analysis stage. All identified risk factors from the literature were discussed with the attending physician (SST) and the patient's responsible doctor (IRO) to determine whether these risk factors were indeed present in the patient, aiding in guiding further management decisions.

Indonesia is a tuberculosis-endemic country with an estimated 969,000 infected people in 2021. However, there are no data to support the number of extrapulm-

Figure 1. Patient's Clinical Condition - Swelling on Right Side of Neck (March 24th 2023)

onary tuberculosis cases in Indonesia.[9,10] Globally, extrapulmonary tuberculosis (EPTB) occurs in approximately 15-20% of all tuberculosis cases. The incidence and prevalence of tuberculous cervical lymphadenopathy vary between developing and developed countries. It frequently occurs in travelers from endemic areas, particularly immigrants and immunocompromised patients, in Europe and developed (non-endemic) as well as developing countries.[1] Global prevalence estimates are complicated by inaccurate diagnostic criteria and reporting systems, with extrapulmonary tuberculosis accounting for 15% of the 6.3 million cases in 2016, according to the World Health Organization.[1,11]

Lymphadenitis TB is commonly present in the cervical lymph nodes, and many benign and malignant diseases (e.g., nonspecific hyperplasia, nontuberculous mycobacterial disease, sarcoidosis, metastatic carcinoma, malignant lymphoma) mimic this disease.[12] Therefore, it can present a diagnostic challenge for clinicians. This is an unusual symptom of tuberculosis. Systemic symptoms such as fever, malaise, weight loss, and night sweats are often rare or absent, and the clinical findings are usually indistinguishable from lymphadenitis caused by other disorders. Patients with long-standing lymphadenopathy, with or without constitutional symptoms, especially those with a high incidence of tuberculosis, should be screened for lymphadenitis TB.[13]

Anti-tuberculosis drug-induced liver injury (ATDILI) remains one of the most serious side effects and can lead to liver failure and death. DILI is the most common side effect leading to treatment switching or discontinuation of treatment for more than a few days, resulting in poor treatment efficacy or treatment noncompliance.[2,6] Accurate and timely detection of DILI is critical to prevent serious consequences.[6] Several risk factors have been reported to be associated with the development of

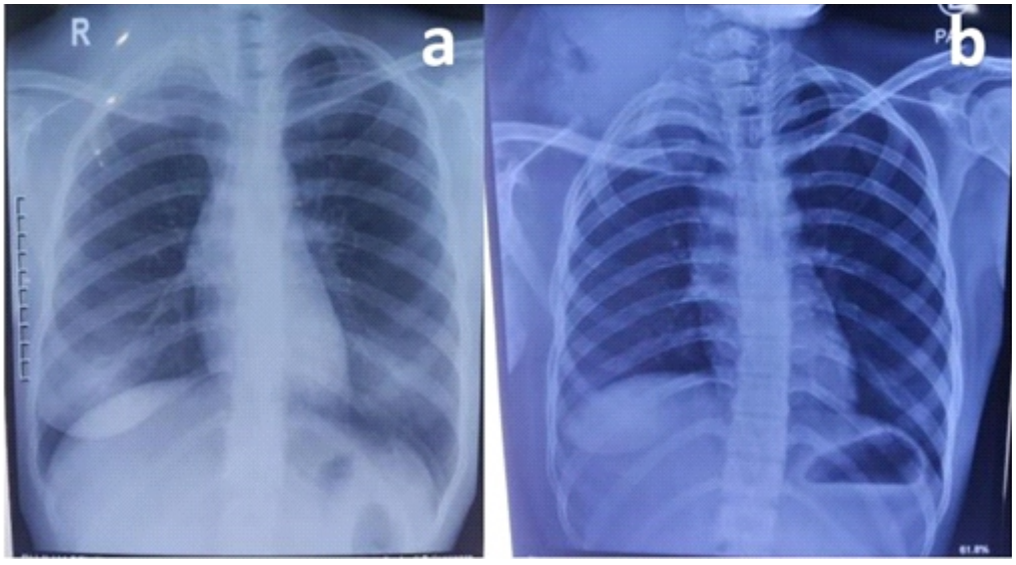

Figure 2. Patient's Clinical Condition - Serial Chest Radiograph (a) Jan 17th 2023 and (b) Mar 26th 2023)

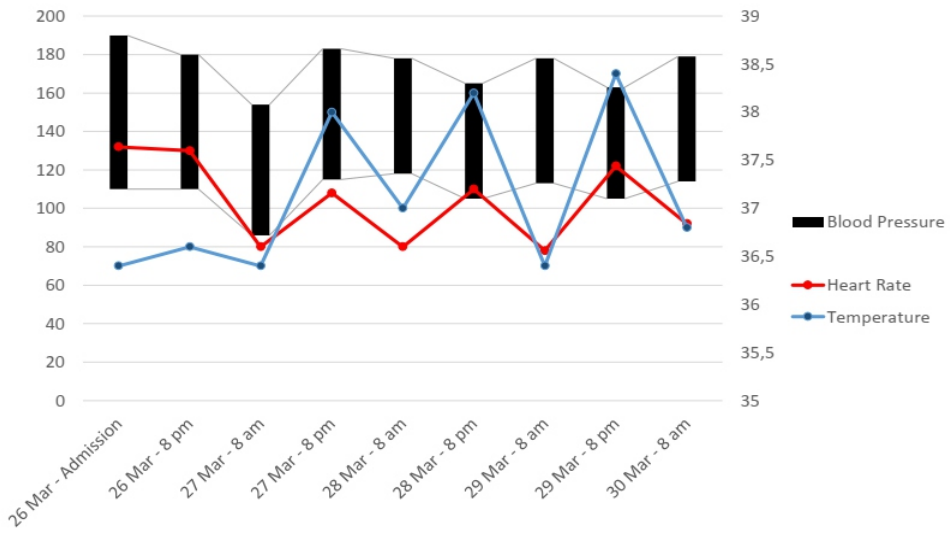

Figure 3. Patient's Clinical Condition - Daily Vital Sign Monitoring During Hospitalization

ATDILI, but various risk factors for tuberculosis DILI include older age, female sex, heavy alcohol consumption, enzyme inducers and other hepatotoxic agents A history of chronic viral liver disease (HBV and HCV) and human immunodeficiency virus (HIV) infection are also known risk factors for tuberculosis DILI.[14] Here, we have summarized all published studies focusing on DILI risk factors.[15-19]

Here we present a case of TB cervical lymphadenitis in a 22-year-old woman with no previous history of pulmonary TB. Even though Indonesia is a TB endemic country and health workers are familiar with the symptoms of TB,[20,21] diagnosing this patient is quite challenging because the initial examination only leads to chronic lymphadenitis without pulmonary involvement. On the first biopsy, the source or pathogen causing the infection could not be identified. Only after repeat biopsy was it known that the possible cause of lymphadenitis was Mtb. After undergoing TB treatment for 58 days, the patient experienced gastrointestinal complaints and required hospitalization in the TB isolation ward. There was no improvement in the patient's chief complaint. A possible risk factor for TB treatment failure in our patient is the presence of superinfection in lymphadenitis. Suspicion of DILI was raised because of the relatively short duration (<90 days) from initiation of TB therapy and elevated liver enzymes (>3 ULN). However, we have not been able to identify risk factors for DILI in these patients. This further hampers the treatment process and increases the risk of therapy failure.

Immediately discontinuing all non-essential drugs is a necessary step once suspected idiosyncratic DILI arises. This action alone has a positive impact on liver enzyme function. In most cases, complete recovery from liver damage is achieved, but in some other cases, the recovery process may take longer. In the worst-case scenario, this can lead to chronic DILI, liver transplantation, or even death. Therefore, evidence-based pharmacotherapy is essential. Various types of drugs, including conventional medications, phytochemicals from herbal medicines, or other chemical compounds, are being studied for their potential use in treating patients with DILI.[22] In our case, the suspicion of DILI made us decide to discontinue TB treatment. Considering the complexity of the cases, we decided to refer the patient to a central hospital with an infectious pulmonologist.

Conclusion

Tuberculous cervical lymphadenopathy, a common EPTB manifestation, complicates diagnosis due to its resemblance to other diseases, presenting a challenge for clinicians. Drug-induced liver injury (DILI) from anti-TB drugs is a severe side effect, with risk factors including older age, female sex, and concomitant use of hepatotoxic agents. This case report presents a case of a 22-year-old woman with TB cervical lymphadenitis in Indonesia, highlighting diagnostic complexities and the emergence of gastrointestinal complaints during TB treatment, raising suspicions of DILI. Despite the short treatment duration and elevated liver enzymes, specific risk factors for DILI remain unidentified, complicating the treatment process. The case's complexity leads to a decision to refer the patient to a central hospital with an infection pulmonologist, emphasizing the need for thorough management and monitoring in intricate TB cases.

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