Unusual Co-existence of Drug-Susceptible Lung Tuberculosis and Drug-Resistant Pleural Tuberculosis: A Rare Case Presentation of Dual Infection

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ABSTRACT

Tuberculosis (TB) has become one of the global burdens of disease, with increasing morbidity and mortality every year. Tuberculosis can affect not only the lungs but also the extrapulmonary organs. The prevalence of drug-resistant tuberculosis (DR-TB) is rising and has caused a higher mortality rate than drug-susceptible tuberculosis (DS-TB). This article presents a patient with a rare co-infection of pulmonary DS-TB and pleural DR-TB. Pulmonary and pleural TB (pTB) was diagnosed using the Xpert MTB/RIF assay. The patient was treated with an individualized DR-TB regimen and recovered.

Keywords*: drug-susceptible tuberculosis, drug-resistant tuberculosis, extrapulmonary tuberculosis, pulmonary tuberculosis, dual infection*

INTRODUCTION

Tuberculosis (TB) has become a global health problem. The 2022 Global Tuberculosis Report estimated 10.6 million new cases of TB and 1.6 million deaths attributed to TB occurred in 2021.[1] Most TB cases were caused by drug-sensitive *Mycobacterium tuberculosis* (M. tuberculosis), while others were caused by drug-resistant M. tuberculosis. The morbidity and mortality rate of drug-resistant tuberculosis (DR-TB) is higher than drug-susceptible tuberculosis (DS-TB)[2]; therefore, it is always essential to consider DR-TB as a differential diagnosis. The risks for severity and mortality of DR-TB are based on the patient's age, presence of comorbidity, and nutritional status.[2] Tuberculosis infection primarily affects the lungs but sometimes can also involve extrapulmonary organs, which remains a diagnostic challenge for clinicians, especially with extrapulmonary DR-TB. The rare finding of M. tb in extrapulmonary organs is one of the reasons why it is difficult to examine whether there is drug resistance in M. tb.

CASE ILLUSTRATION

A 50-year-old Indonesian male presented to the ER with worsening dyspnea that started one day ago. The symptom has occurred for a week, accompanied by a cough and pleuritic chest pain. The patient experienced weight loss of approximately 9 kilograms within the last three months. Four months before admission, the patient had been diagnosed with DS-TB and was treated with a first-line antituberculosis drug regimen. There was no history of other pulmonary disease, diabetes mellitus, or immunologic

disorder. However, he had smoked 1-2 packs of cigarettes daily for over 30 years.

Physical examination showed alert mental status, with a blood pressure of 90/60 mmHg, heart rate of 71 bpm, respiratory rate of 24x/min, and oxygen saturation of 100% (with nasal cannula 3 L/m). Chest examination revealed hyper-resonant percussion on the periphery of the lungs, dullness on the base of the lung, reduced vesicular breath sound, and bilateral rhonchi. The laboratory results are summarized below (**Table 1**).

Electrocardiography showed sinus rhythm, a heart rate of 64 bpm, and a QT interval of 460 ms, without ST-T changes, and signs of heart block or ventricular hypertrophy. Chest x-ray (**Figure 1**) and a CT scan with contrast (**Figure 2**) demonstrated evidence of hydropneumothorax on the right hemithorax, fibro infiltrate, multiple consolidations and cavities, bronchiectasis on both lungs, and right-sided pleural thickening.

We inserted a chest tube connected to water-sealed drainage and obtained the pleural fluid for analysis, microbiologic culture, and drug-susceptibility testing. The fluid analysis result suggested an exudate with yellowish color and cloudy opacity, a positive Rivalta test, fluid pH of 7.9, cell count of 61,624/mm^3 (PMN 55,556/mm^3; MN 6,068/mm^3), protein fluid/serum 4,2/6,2 (protein ratio 0.68); glucose fluid <5 mg/dl/serum 103 mg/dl; LDH fluid/serum 5,418/237 (LDH ratio 22.86). The pleural fluid cytology showed no malignant tumors, some mesothelial cells, macrophages (foam cells), leucocytes, and necrotic tissue. The Xpert MTB/RIF assay of pleural fluid revealed: "M. tb detected with rifampicin resistance." We also performed the Xpert MTB/RIF assay from the sputum sample and found "M. tb detected with rifampicin sensitive." Repeat Xpert MTB/RIF assay showed identical results. Second-line Line Probe Assay (LPA) was not performed due to limitations in resources.

We performed screening tests to obtain the baseline data before starting the therapy, such as routine blood analysis, liver and kidney function

Table 1. Laboratory Results

Hb	**12.9 g/dL**	**PCT**	**0.03 ng/mL**
Ht	38.7%	Albumin	2.90 g/dL
RBC	4.74 x 10^6/µL	Na	141 mEq/L
WBC	7.67 x 10^3/µL	K	3.7 mEq/L
PLT	169 x 10^3/µL	Cl	103.3 mEq/L
SGOT (AST)	29 U/L	P	2.5 mg/dL
SGPT (ALT)	29 U/L	Mg	2.04 mg/dL
Serum creatinine	0.80 mg/dL	Glucose	99 mg/dL
Serum urea	36.4 mg/dL	Anti-HIV	non-reactive

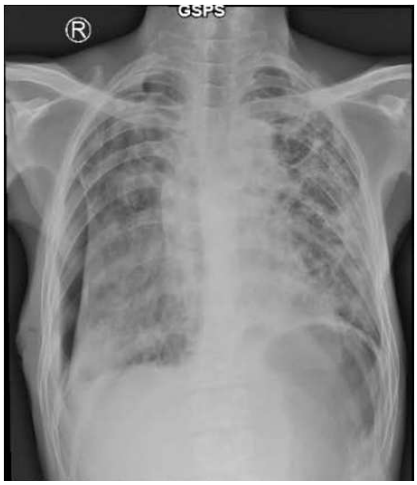

Figure 1. Chest x-ray

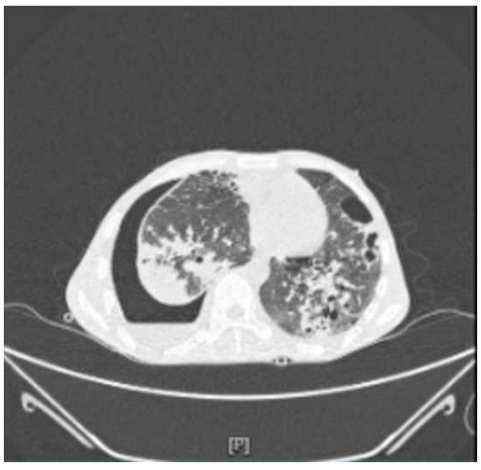

Figure 2. CT Scan of the lungs with contrast

tests, uric acid level, electrolyte level, TSH level, color-blind test and visual field measurement, neurologic examination, psychiatric screening, and ECG. Our patient was diagnosed with extrapulmonary DR-TB and showed multiple lung cavities on radiography; therefore, we decided to give the individualized DR-TB regimen.

The patient was started on drug-resistant antituberculosis individual regimens consisting of bedaquiline 400 mg daily (first two weeks), then 200 mg daily 3x/week, levofloxacin 750 mg daily, linezolid 600 mg daily, clofazimine 100 mg daily, dan cycloserine 500 mg daily. The patient responded well to the treatment, improved clinically, and continued the treatment at home. Later, the microbial culture showed positive M. tuberculosis growth, and drug-susceptibility tests revealed another resistance to isoniazid and pyrazinamide but no resistance against quinolone or linezolid. This result was consistent with the definition of multidrug-resistant TB (MDR-TB), and the antituberculosis treatment was continued.

DISCUSSION

This article presents a unique case where the patient had a dual infection of a drug-susceptible pulmonary TB and drug-resistant pleural (extrapulmonary) TB simultaneously. Concurrent pulmonary and extrapulmonary TB infections have been widely reported, but the report of co-existence between drug-susceptible and drug-resistant M. tuberculosis at the same time is scarce. Many internal and external factors can cause M. tuberculosis resistance. Internal factors include mismatch, mistranslation, or mutation of DNA polymerases, while external factors include inappropriate antituberculosis regimens, inadequate dosing, or irregular drug consumption.[3] Drug resistance is mainly found in patients with a history of TB treatment, failure of previous TB treatment, close contact with other DR-TB patients, and those who do not respond well to DS-TB treatment. Once a patient is suspected of DR-TB, the initial study should obtain an Xpert MTB/RIF assay from the infected organ. In this case report, the patient was diagnosed with pulmonary DS-TB four months prior and had already started with antituberculosis treatment but showed no clinical improvement and subsequently developed hydropneumothorax. The poor response to antituberculosis treatment raised suspicion about the possibility of DR-TB, and the emergence of hydropneumothorax suggested the possibility of bacterial translocation to the pleura.

Pleural tuberculosis (pTB) is one of the most common forms of extrapulmonary TB. It occurs more often in DR-TB than the DS-TB. The process of pleural effusion starts with a caseous focus on subpleural tissue that ruptures into the pleural space.[4] The M. tb enters the pleural space, triggering inflammation and increasing pleural vascular permeability, causing the pleural fluid to accumulate.[5,6] The diagnosis of pTB can be confirmed by finding the acid-fast bacilli in the pleural fluid sample or detecting the M. tb gene using the Xpert MTB/RIF assay of the pleural fluid. The Xpert MTB/RIF assay utilizes polymerase chain reaction (PCR) to amplify and detect the mutation of the rpoB gene, which determines the M. tuberculosis resistance to rifampicin.[7] A review conducted by Cascio et al. revealed that pleural Xpert MTB/RIF has a sensitivity of 38-75% and specificity of 85-99%.[6]

Nowadays, Indonesia's TB policy recommends the usage of Xpert MTB/RIF assay to diagnose extrapulmonary TB only for samples taken from lymph nodes, cerebrospinal fluid, or other suspected infected tissue,[8] but the usage of Xpert MTB/RIF assay on pleural fluid has not been recommended yet due to low sensitivity. Following this case, the authors suggested Xpert MTB/RIF assay on pleural fluid when suspecting any pleural DR-TB.

In this case report, the simultaneous dual infection of DS-TB and DR-TB was speculated due to the spontaneous mutation of the drug-susceptible M. tb to become drug-resistant M. tb during antituberculosis treatment.[9] Multiple lung cavities provide a safe environment for M. tb due to poor penetration of the drugs and the immune system into the necrotic area. The cavity contains a high oxygen concentration, leading to increased bacterial replication speed. The higher replication rate means a higher chance of spontaneous bacterial mutation.[10] Other speculations include a separate but almost

simultaneous infection of DS-TB and DR-TB at the beginning of the disease or a new DR-TB infection following the existing DS-TB disease.

Based on the 2022 consolidated WHO guideline, DR-TB treatment was categorized as a short-term, individualized, and newer regimen of BPAL/M.[11] Most DR-TB cases in Indonesia are still treated with short-term or individualized regimens due to the limited distribution of BPaL/M drugs. According to Indonesia's national guideline for TB, the criteria for giving the short-term regimen include no resistance to fluoroquinolone, no history of contact with pre-XDR/XDR TB, not consuming the second-line antituberculosis for more than a month, no resistance to the short-term regimen of DR-TB antituberculosis (except isoniazid resistance with the mutation of inhA or katG), not being pregnant or breastfeeding, not having severe pulmonary or extrapulmonary TB, co-infection with DR-TB HIV, and children older than six years old. Unless all the criteria are fulfilled, the patient must be treated with the individualized DR-TB regimen.[12]

CONCLUSION

Diagnosing and treating tuberculosis can present challenges. In patients with both pulmonary and extrapulmonary TB, the possibility of dual infection with different drug susceptibility should be considered. Clinicians should take microbial samples from all affected organs for drug-susceptibility testing when a patient does not respond well to antituberculosis treatment.

CONFLICT OF INTERESTS

The authors stated no conflict of interest.

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