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A Case Report: Tuberculosis Drug Induced Liver Injury

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Abstract. *Tuberculosis is one of the world's health problems, especially in developing countries. Treatment regimen with multiple first-line anti-tuberculosis drugs (ATD) such as Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and Streptomycin remains the most effective for treatment of tuberculosis. Adverse drug reactions (ADRs) to antituberculosis drugs may range from mild gastrointestinal disturbances to serious hepatotoxicity, peripheral neuropathy, and cutaneous adverse effects. We report a 65 year old male patient with a complaint of yellowish discoloration of sclera, nausea and vomiting after three days of initiation of ATD therapy. The patient has been diagnosed with Tuberculosis relapse and has been taking ATD since June 2024. The patient noted epigastric pain. Laboratory examination found an increase in bilirubin level and electrolyte imbalance. The treatment is in the form of discontinuation of ATD, supportive therapy and followed by hepatoprotective supplements. ATD should be discontinued in patients with hepatotoxicity and fixed drug eruption until liver function and clinical symptoms improve. Initiation of ATD administration is carried out by administering one by one regimen. The patient is currently experiencing antituberculosis drug-induced hepatotoxicity, which is managed by providing supportive care and different AT regimens were prescribed.*

Keywords: *Tuberculosis, Drug-Induced Liver Injury, Hepatotoxicity*

1. BACKGROUND

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium Mycobacterium tuberculosis. Most TB germs are often found infecting the lung parenchyma and causing pulmonary TB, but these bacteria also have the ability to infect other body organs (extra-pulmonary TB) such as the pleura, lymph nodes, bones and other extra-pulmonary organs. (Kementerian Kesehatan Republik Indonesia; 2020). In Indonesia itself it was reported in 2019 there were 845.000 (770.000-923.000) new cases of pulmonary TB, 19.000 of the new cases were TB-HIV positive cases. (Perhimpunan Dokter Paru Indonesia. 2021).

2. THEORETICAL STUDY

Symptoms that can arise include coughing for ≥ 2 weeks, coughing up phlegm, coughing up phlegm that can be mixed with blood, can be accompanied by chest pain, shortness of breath, malaise, weight loss, decreased appetite, chills, fever, sweats at night. (Kementerian Kesehatan Republik Indonesia; 2020). To enforce diagnosis, bacteriological examination, radiological examination and several other supports can be carried out. (Perhimpunan Dokter Paru Indonesia. 2021).

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If TB is diagnosed, the patient can start therapy in 2 stages, namely the initial/intensive stage and the advanced stage in the form of 2RHZE/4HR, for 6 months. (Kementerian Kesehatan Republik Indonesia; 2020). Pulmonary TB can achieve cure maximum with few complications in patients with adequate Anti-Tuberculosis Drug (OAT) therapy.

Drug-induced liver injury (DILI) or drug-induced hepatitis is a form of side effect that causes discontinuation of TB treatment or a change in anti-tuberculosis drug regimen. (Ramappa V, Aithal G. 2013). The incidence of DILI is estimated at 14 per 100.000 general population per year worldwide and around 0.7 % to 1.7% of them are inpatients DILI due to OAT occurs within 2 months after administration and the highest incidence occurs in the first 2 weeks. The incidence of DILI is difficult to predict, there are several risk factors for DILI during OAT administration. Several risk factors include body mass index (BMI), isoniazid metabolic acetylator (INH) status, age, gender, metabolic factors, drug interactions, and alcohol consumption. (Soedarsono, Riadi A. 2020).

First-line antituberculosis drugs have the potential to cause hepatotoxicity such as transaminationitis and fulminant liver failure. Liver function test reports of antituberculosis drug-induced hepatotoxicity elicited a threefold increase in the liver enzymes Alanine Transaminase (ALT) and Aspartate transaminase (AST). Clinical manifestations of hepatotoxicity include abdominal pain, nausea, vomiting, and jaundice. (Mahayanti N, Sudarsana I. 2022). In this case report, a male patient with relapsed Tuberculosis with DILI is reported.

3. CASE REPORT

The patient is a 65 year old man with complaints of severe nausea and vomiting since 1 day before admission to the hospital. The patient had a history of going to the pulmonary clinic 3 days ago and was given routine medication. After taking OAT for 3 days the patient complained of nausea and vomiting every time he ate, and headaches. The patient also complained of shortness of breath accompanied by a cough with phlegm. Coughing occurs throughout the day, frequent and worse when lying down. The patient's cough and shortness of breath were not influenced by activity, weather, or dust. The patient sleeps in a sitting position because if he lies down the coughing and shortness of breath gets worse. Denied coughing up blood. The patient has a history of being treated and admitted to the emergency department on 01/06/2024 with complaints of shortness of breath, cough and intermittent fever for the past 3 months. Fever is more common at night, patients complain of frequent chills and cold sweats when they have a fever. The patient admitted that he had experienced weight loss since 3

months ago, from 65 kg to 53 kg due to the patient's decreased appetite. After the patient was treated, the patient underwent routine pulmonary control with relapsed tuberculosis. The patient had a history of previous illnesses in the form of hypertension and Chronic Obstructive Pulmonary Disease (COPD) for 2 years.

The patient's blood pressure is 142/92 mmHg, pulse rate is 96 x/m, temperature is 36 and the patient's respiratory rate is 24 x/m. On physical examination, icteric sclera was found in the right and left eyes and there were no enlarged lymph nodes in the neck area. On chest examination, vesicular breath sounds were found, there were no wheezes and there were crackles throughout the lung fields. The left border of the heart is normal and the heart sounds are normal S1 and S2, there are no murmurs or gallops. The abdomen was found to have epigastric pain and everything else was within normal limits and there was no splenic enlargement. Normal bowel sounds. The extremities feel warm and there is no pitting edema in the pretibia area.

Supporting examination, chest x-ray showed the impression of long-term active pulmonary TB with laboratory results of total bilirubin increasing to 1.5 mg/dl and sodium levels decreasing to 127 mg/dl. Liver function examination showed AST levels of 32 U/L and ALT 33 U/L. The patient's initial assessment was drug-induced hepatitis and relapsed tuberculosis. The patient's OAT treatment was temporarily stopped and symptomatic drugs were given to treat the patient's gastrointestinal symptoms, such as 20 mg omeprazole injection and 4 mg ondansetron injection. The patient was treated with hepatoprotective supplements in the form of Curcuma tablets (Curcuma xanthorrhiza 20 mg) three times a day. After 3 days of treatment, the patient's complaints of nausea and vomiting began to decrease, so he began administering removable OAT therapy by means of desensitization. The patient was tested with Ethambutol 500 mg, Isoniazid 200 mg and Rifampicin 450 mg for 6 days. The patient's gastrointestinal symptoms were no longer present and the sclera was not icteric, the patient was allowed to go home and then the patient was checked into the clinic to continue treatment for relapsed tuberculosis.

4. RESULTS AND DISCUSSION

Pulmonary tuberculosis treatment has side effects in the form of liver damage, known as Drug-Induced Liver Injury (DILI). OAT-induced DILI is reported in 2–28% globally, hepatotoxicity is rare in patients under 20 years of age, complications occur in 0.3% of patients aged 20 to 34 years, and the incidence increases to 1.2% in people aged 35 to 49 years and 2.3% in people over 50 years old. As many as 12% of patients who received isoniazid showed

an increase in AST and ALT values. (Kumar PS, Vidya R, Tabassum, Jageer M. 2020). Low body mass index (BMI) in Tuberculosis patients due to malnutrition increases the risk of DILI. Weight loss, low albumin values, and poor nutritional status are associated with an increased risk of drug-induced hepatotoxicity. A study conducted at RSUD Dr. Soetomo found a significant correlation between BMI and the incidence of DILI in general. In this study, a significant correlation was found between low BMI and an increased risk of DILI. Acute DILI reactions to alcohol consumption occur in patients taking methotrexate and isoniazid. Hepatotoxicity due to alcohol consumption is most likely caused by alcohol inducing CYP2E1 which causes toxic metabolites in the liver. A study in Pakistan found that alcohol consumption increased the risk of DILI. (Kumar PS, Vidya R, Tabassum, Jageer M. 2020).

Some DILI are idiosyncratic processes. This mechanism can affect a single liver cell or several different types of liver cells, such as: hepatocytes, bile gland cells, sinusoidal epithelial cells, stellate and Kupffer cells. A study shows that the hepatotoxicity process of rifampicin can originate from oxidative stress in mitochondria, cholestasis, and accumulation of fat cells in the liver.6 Rifampicin activates CYP3A4 which causes an increase in isoniazid metabolism, producing toxic metabolites. and induce hepatotoxicity. Rifampicin also induces isoniazid hydrolase, leading to increased hydrazine production thereby increasing toxicity when combined with isoniazid. (Yew WW, Chang KC, Chan DP. 2018).

The clinical symptoms of TB DILI are the same as those of acute and chronic hepatobiliary disease, with the dominant symptoms being icteric in acute hepatitis or cholestatic liver disease. Jaundice in acute hepatitis is accompanied by an increase in serum transaminases and a minimal increase in serum alkaline phosphatase. (Kumar PS, Vidya R, Tabassum, Jageer M. 2020). The principle of DILI treatment is to immediately stop OAT and administer symptomatic drugs to treat the patient's complaints. After OAT is stopped, monitor the clinic and laboratory. If the clinical and laboratory conditions improve, restart OAT, starting with INH with a desensitization dose starting with 25 mg and increasing to 2 times the previous dose every 3 days (25-50-100-200-300-400 mg). During this time, pay attention to the clinic and check the laboratory at full dose of INH, if the clinic and laboratory are normal, add rifampicin, desensitize with a dose of 75 mg (first day 75 mg, 4th day 75 mg, 7th day 150 mg, 10th day 150 mg, 13th day 450 mg, 16th day 450 mg, 19th day 600 mg). So the drug combination becomes RHES. Pyrazinamide should not be reused. (Wesnawa M, Kusmiati T. 2019)

To prevent hepatotoxicity, several clinics and hospitals in Indonesia have introduced the use of hepatoprotective supplements from herbal ingredients, such as Curcuma xanthorriza, Silymarin and Echinacea extract. (Herlianto B. dkk, 2014). Research by Basir et al in 2020 shows that in severe cases, temporarily stopping OAT and administering supplements herbs to patients appeared effective in improving hepatotoxicity in two out of four patients. In accordance with previous studies, it has been shown that Curcuma supplements are able to reduce the incidence and severity of hepatotoxicity, as shown by a significant reduction in ALT and AST values in tuberculosis patients after 4 weeks of treatment. (Basir N, Yusrini Djabir Y, Santoso A. 2021).

5. CONCLUSIONS AND RECOMMENDATIONS

In cases where patients experience hepatotoxicity induced by anti-tuberculosis drugs, it is managed by providing supportive care accompanied by temporary cessation of OAT therapy and desensitization of the OAT regimen one by one. In this case, patient education is needed regarding the side effects of tuberculosis treatment.

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PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6