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Treatment of Pulmonary TB Patients on Antitubercular Medications with Transaminitis

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Abstract: ***Tuberculosis is a disease that caused by Mycobacterium tuberculosis. Tuberculsosis is still a world wide problem. Tuberculosis is the world 13th cause of death. In the 2014 the prevalence of the disease in Indonesia is 254 cases / 100.000. The clinical manifestation of tuberculosis infection in lung are productive cough dan can be accompanied with hemoptoe. Patient can also experience loss of significant body weight, breathless, fatigue, and the symptoms usually worsen at night. Standard treatment of tuberculosis according to World Health Organization are isoniazid, rifampicin, pyrazinamid, etambutol, and streptomycin. The side effect of these drugs are ranged from mild to severe. One of the side effect are transminitis. Monitor the function of liver in the patients that especially have risk factos such as liver disease and other coinfection are recommended. We report a case of transminitis after treatment of antituberculosis drug day 27th. A 59 year old woman complained feeling breathless with pain in epigastric area, nausea, and vomitting. The blood analysis showed increment of SGOT (288 U/L) and SGPT (150 U/L). the antituberculosis treatment was stopped and the patient has received the symptomatic treatment. After 4 days, the patient's condition got better and the liver function in day 5th was SGOT (35 U/L) normal although there was still elevated level of SGPT (72 U/L).***

Keywords: Tuberculosis, Transaminitis, *Antituberculosis Treatment*

1. Introduction

Definition of Pulmonary TB

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis infection. TB infection usually found in lungs, although TB infection can also be found in other parts of the body such as lymph nodes, bones, nervous system and membranes of the brain. TB is a dangerous disease butit can be cured and prevented. TB infection spreads through the air, where patients who have been infected with TB coughing, sneezing or spitting, the Mycobacterium tuberculosis bacteria also come out and are in the air as droplets.

Clinical Symptoms

Symptoms of pulmonary TB are chronic cough that lasts for more than 2 weeks, the cough can be accompanied by sputum or blood, chest pain, feeling tired all the time, night sweats, chills, fever, decreased appetite, and weight loss for no reason.

Epidemiology

TB infection is the 13th leading cause of death and the second most common death caused by infection after COVID-19. In 2020, there are 1.5 million people in the world die from TB infection. In global, TB cases have decreased by about 2% per year. In Indonesia, the prevalence of TB sufferers has decreased where in 2014 there were 297 cases per 100, 000 population and decreased in 2017 to 254 cases per 100, 000 population. Through a survey of tuberculosis in 2013-2014 conducted by the Ministry of Health of the Republic of Indonesia, adults at 65-74 years old have the highest prevalence for TB infection and usually accompanied bylow educational background.

Hepatotoxic TB Drugs

Patients who have been diagnosed with TB must undergo intensive and long-term treatment. The goal of TB treatment is to cure the infection, prevent death, prevent disease recurrence, break the chain of transmission of TB disease and also prevent the occurrence of germ resistance to anti-tuberculosis drugs. There are several types of drugs used in the treatment of TB: Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Streptomycin (S), and Ethambutol (E). Drugs in the treatment of TB have bactericidal properties except ethambutol which has bacteriostatic properties. Treatment of tuberculosis uses a combination of various types of drugs, but in the content of anti-tuberculosis drugs there are drugs that have adverse side effects on the liver (hepatotoxic).

Isoniazid is the first line drug given to TB patients. Isoniazid generally can cause side effects, such as lack of appetite, nausea and abdominal pain and peripheral neuropathy which generally occurs when accompanied by other risk factors such as diabetes mellitus, chronic renal failure, alcoholism, malnutrition or HIV infection.

Rifampicin, always be a part of the treatment regimen unless there are contraindications. In the use of rifampicin, the first 2 months of taking rifampin can cause temporary disturbances in liver function (increased serum transaminases), but can also cause serious liver function disorders, especially in patients who have a history of previous liver disease. Rifampicin induces liver enzymes thereby accelerating drug metabolism. Rifampicin also known to give urine a reddish color.

Pyrazinamide has bactericidal properties and is active against Mycobacterium tuberculosis. Pyrazinamide is also known to be very effective against meningitis TB because of its ability to penetrate into the cerebrospinal fluid. Pyrazinamide can cause mild side effects such as joint pain and is also known to cause liver toxicity although it is rare.

Ethambutol is commonly used in treatment especially if resistance is suspected. Ethambutol has side effects such as decreased vision, color blindness or narrowing of the visual

field. It is known that the side effects of ethambutol generally occur in patients who receive excessive doses or have other underlying diseases such as kidney disorders.

Relationship between Antitubercular Medications and Transaminitis

In the Decree of the Minister of Health of the Republic of Indonesia number 364/MENKES/SK/V/2009 regarding guidelines for controlling tuberculosis (TB), it is stated that if there is an increase in Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) more than three times, the anti-tuberculosis drugs must be stopped. Several other known risk factors include body mass index, coinfection with Human Immunodeficiency Virus (HIV), high alcohol consumption, malnutrition, old age, and female. TB patients are recommended to do liver function tests before starting the treatment, especially if there is a suspicion of liver function disorders or other risk factors. Some experts even recommend biochemical test monitoring in patients older than 35 years old. Almost all types of anti-tuberculosis drugs can cause confusion and vomiting where it occurs as the beginning of problems in the liver which can also be accompanied by jaundice.

Rifampicin, as one of the given drugs can cause an increase in aminotransferase serum in 10 to 20% of patients with long-term use. The mechanism by which rifampin can increase aminotransferases serum is not well known, but rifampin is metabolized in the liver and induces an increase in liver enzymes including CYP 3A4 and ABC C2 (MRP2). The decrease in liver function is thought to be caused by an idiosyncratic reaction of various metabolic products that are hepatotoxic or cause immunological reactions. An increase in both total and direct bilirubin is also associated with a defect in the MRP2 gene (ABC C2), which carries bilirubin glucuronide to hepatocytes. This can be seen in Dubin-Johnson syndrome. Patients suspected of having a previous liver disorder or cirrhosis are at higher risk for developing jaundice due to rifampicin.

Isoniazid can cause hepatotoxicity due to metabolism by two main pathways, which are N-acetyltransferase 2 (NAT2) and microsomal enzyme cytochrome P4502E1 (CYP2E1). NAT2 is responsible for metabolizing isoniazid to acetylisoniazid, which will then be hydrolyzed to acetyl hydrazine. Furthermore, CYP2E1 will oxidize these substances to N-hydroxy-acetyl hydrazine which will then undergo a dehydration process to become acetyl diazine. Acetyl diazine is a metabolite that is hepatotoxic and can remodel reactive substances such as acetylonium ions, acetyl radicals and ketenes that bind to macromolecules from the liver that cause damage to hepatocyte cells. Isoniazid metabolism via this pathway may be increased, especially when taken with rifampicin. The interaction between isoniazid and rifampicin is known to cause symptomatic hepatitis in 2.55% patients treated with latent TB infection or active TB infection.

Pyrazinamide is a nicotinic acid derivative. These substances can turn into pyrazinoic acid which then undergoes an oxidation process to 5-hydroxypyrazinoc acid. Pyrazinamide is known to inhibit CYP450 and NAD activity therefore increasing free radicals that cause liver damage. The toxicity of pyrazinamide is known to be dose dependent where doses exceeding 40-50 mg/kgBW are associated with a number of hepatotoxicity events. However, this dose exceeds the standard dose that can be used in therapy (25-35 mg/kgBW). Fluoroquinolones are usually used in second-line drugs, especially in suspicion of multi-drug resistant TB (MDR-TB) and the presence of hepatotoxicity due to first-line drugs. Fluoroquinolone treatment has rarely been reported to have hepatotoxicity. There are several cases of hepatotoxicity due to ciprofloxacin, levofloxacin, gatifloxacin treatment due to a hypersensitivity reaction followed by peripheral eosinophilia and fever. However, this reaction is limited to certain people and has not been shown to increase the effect of hepatotoxicity in patients who already have hepatitis due to first-line anti-tuberculosis drugs.

2. Case Report

On January 29, 59-years-old woman was brought by her family to the ER with complaints of shortness of breath. The patient complained of shortness of breath since one week and worsened since morning. In addition, the patient also complained of heartburn, nausea, and vomiting. Nausea and vomiting are felt almost every time the patient eating and drinking, so that eating and drinking is reduced and the patient feels weak. The patient also complained of cough for a long time of unknown origin and weight loss was noticed. The patient is currently on TB treatment which was started 27 days ago. There is no family history of illness. The patient also had no history of smoking. On examination, consciousness according to the Glasgow Coma Scale is 15 (E4V5M6), and vital signs examinations showed blood pressure 130/80 mmHg, pulse 112 times per minute, temperature 36.2^{o}C, respiration rate 28 times per minute and 88% saturation with room air. Physical examination of the lungs revealed vesicular breath sounds in both lung fields. Physical examination of the abdomen revealed epigastric tenderness. Blood examination revealed an increase in SGOT (288U/L) and SGPT (150U/L) followed by an increase in BUN (45mg/dL). The patient was treated in the TB isolation room. Initial therapy was given oxygen at 10 lpm using a non-rebreathing mask, IVFD RL fluid 20 drops per minute, discontinuation of anti-TB drugs, Ondansetron 3x4mg, Esomeprazole 1x1 IV, Vitamin B Complex 3x1 tablet, Cefotaxime 3x1 gram, Salbutamol 3x1 tablet, NAC 3x1 tablets.

After being hospitalized for 4 days (02/02) the patient said that the shortness of breath and cough had started to decrease and he had no more nausea and vomiting. The patient complains of bloody stools and weakness. Previously, the patient said that he had difficulty defecating. The results of the blood examination on February 2nd, 2022 showed an increase in NLR (14.12) and an increase in SGOT (109U/L) and SGPT (146 U/L). A decrease in albumin was found to be 2.4 g/dL.

Two days later the patient said that the shortness of breath was reduced and the bloody stools were gone. Physical examination showed BP 130/90 mmHg, pulse 80 beats per minute, temperature 36 degrees Celsius, and respiratory rate

20 breaths per minute with 91% oxygen saturation. Blood examination on February 4, 2022 revealed leukocytosis (12.2 x 103/uL) with neutrophilia (71.6%) and lymphocytopenia (21.5%). Qualitative HBsAg and anti-HCV qualitative tests were non-reactive. Ultrasound examination of the abdomen showed that the liver echoparenchyma was increased and the intensity of free fluid echo was seen in the peritoneal cavity and both pleural cavities (bilateral ascites and pleural effusion).

On February 7th, 2022, the patient said he was still experiencing shortness of breath with blood pressure examination of 110/70 mmHg, pulse 105 times per minute, and respiration rate of 23 times per minute with an oxygen saturation of 86%. The results of the patient's blood examination showed that there was no leukocytosis. SGOT results showed normal values (35 U/L) and there was still an increase in SGPT (72 U/L), and a decrease in albumin (2.8 g/dL).

On February 14th, 2022, the patient said that the shortness of breath had begun to decrease. Vital sign examinations showed blood pressure 120/80 mmHg, pulse 89 times per minute, temperature 36.5 degrees Celsius, respiratory rate 24 times per minute, and oxygen saturation of 92%.

The patient was also subjected to radiological examinations such as abdominal ultrasound and chest X-ray as shown in Figure 1 and Figure 2. The results of the radiological examination of the patient showed an increased impression of hepatic echoparenchyma, the intensity of free fluid echo in the peritoneal cavity and both pleural cavities (ascites + bilateral pleural effusions). The results of the chest X-ray that were performed suggested an active pulmonary TB infection.

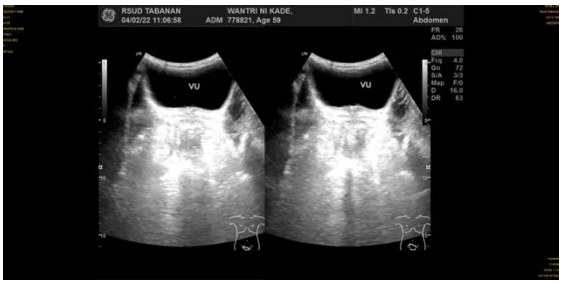

Figure 1: Abdominal Ultrasound

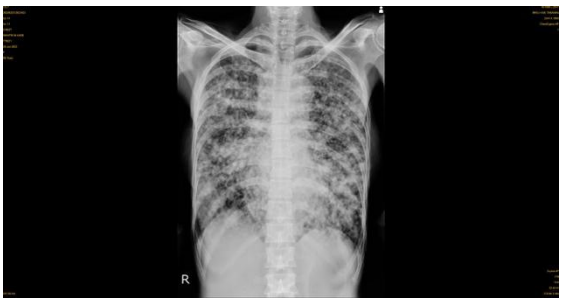

Figure 2: Thorax X-Ray

3. Discussion

In various literatures, there are various TB drugs associated with the incidence of transaminitis. The standard first-line drugs in the management of TB according to WHO are isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. The drugs associated with those effects are mainly the isoniazid and pyrazinamide types. If there is liver damage due to hepatotoxicity, it can increase the risk of changing the therapeutic regimen or decreasing the dose. Liver damage due to anti-tuberculosis drugs can occur 2 months after administration and the highest incidence occurs in the first 2 weeks of treatment. This incidence is very difficult to predict and there are several risk factors such as high body mass index, co-infection with Human Immunodeficiency Virus (HIV), high alcohol consumption, malnutrition, old age, and female gender. In the Decree of the Minister of Health of the Republic of Indonesia number 364/MENKES/SK/V/2009 regarding guidelines for tuberculosis (TB) control, it is stated that if there is an increase in SGOT and SGPT more than three times, anti-tuberculosis drugs must be stopped.

The patient is a 59-years-old woman who was brought by her family to the ER with complaints of shortness of breath. The tightness has been felt since a week and has worsened since morning. In addition, the patient also complained of heartburn, nausea, and vomiting. The patient is on TB treatment which started 27 days ago. On examination, he was conscious, with vital signs showed blood pressure 130/80 mmHg, pulse 112 beats per minute, temperature 36.2^{o}C, respiration rate 28 times per minute and 88% saturation with room air. Physical examination of the abdomen revealed epigastric tenderness. Blood examination revealed an increase in SGOT (288U/L) and SGPT (150U/L) followed by an increase in BUN (45mg/dL). Because of the increase in SGOT and SGPT values three times, it is recommended to stop anti-tuberculosis drugs temporarily. Other therapies given to treat the patient's symptoms are oxygen 10lpm using a non-rebreathing mask, IVFD RL fluid 20 drops per minute, Ondansetron 3x4mg, Esomeprazole 1x1 IV, Vitamin B Complex 3x1 tablet, Cefotaxime 3x1 gram, Salbutamol 3x1 tablet, NAC 3x1 tablet.

After being hospitalized for 4 days (02/02), the patient said that the shortness of breath and cough had started to decrease and he had no more nausea and vomiting. The patient complains of bloody stools and weakness. The results of a blood test on February 2nd, 2022 showed an increase in NLR (14.12) and an increase in SGOT (109U/L) and SGPT (146 U/L). A decrease in albumin was found to be 2.4 g/dL. On February 4th, the patient's complaints improved even though he was still experiencing shortness of breath with a saturation of 91%. Blood examination revealed leukocytosis with neutrophilia and lymphocytopenia. Qualitative HBsAg and anti-HCV qualitative tests were non-reactive. Ultrasound examination of the abdomen showed that the liver echoparenchyma was increased and the intensity of free fluid echo was seen in the peritoneal cavity and both pleural cavities (bilateral ascites and pleural effusion). On February 7th, 2022, the patient said he was still experiencing shortness of breath with an oxygen saturation of 86%. The results of the patient's blood examination showed that there was no leukocytosis. SGOT results showed normal values (35 U/L) and there was still an increase in SGPT (72 U/L), and a decrease in albumin (2.8

g/dL). It can be seen that with the temporary discontinuation of anti-tuberculosis drugs, there is a significant improvement of liver function which is characterized by a decrease in SGOT and SGPT values.

The treatment guidelines for patients with liver damage are 2RHES/6RH or 2HES/10HE. In patients with acute hepatitis or clinically jaundice, anti-tuberculosis drugs should be postponed until the acute phase has healed. If there are no other options, then streptomycin and ethambutol can be given for a maximum of 3 months until the hepatitis is cured and then continued with 6RH.

4. Conclusion

Tuberculosis is a disease caused by infection of Mycobacterium tuberculosis. Generally, TB infection attacks the lungs, although it can attack other organs of the body and cause clinical manifestations. Symptoms of pulmonary TB can be a persistent cough that lasts for more than 2 weeks, cough can be accompanied by phlegm mixed with blood, night sweats, and weight loss. Treatment with WHO standard'santi-tuberculosis drugs has various side effects, both mild and severe. One of the side effects that can occur is liver damage. Liver damage is associated primarily with isoniazid and pyrazinamide treatment. If the SGOT and SGPT levels increase more than three times then it is recommended to temporarily discontinue first-line treatment. Regular monitoring of patients with certain risk factors is needed for early detection and prevent worsening of the patient's condition.

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