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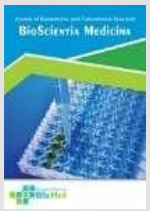

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Management of Pulmonary Tuberculosis in Liver Cirrhosis: A Case Report

Hadya Gorga[1*], Irvan Medison[1], Dewi Wahyu F.[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

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***Corresponding author:**
Hadya Gorga

E-mail address:
hadyahg@gmail.com

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A B S T R A C T

Background: Anti-tuberculosis drugs (OAT) are metabolized in the liver and have a high potential for hepatotoxicity, and will increase the risk of drug-induced liver injury (DILI). This study aimed to describe the management of pulmonary tuberculosis in patients with cirrhosis of the liver. **Case presentation:** 45 years old male patient with cough with phlegm for 5 months, weight loss. The patient is also known to have cirrhosis of the liver. From the results of the bacteriological examination, it was found that TCM mtb was detected as high. The patient has risk factors for low BMI, a history of alcohol, hypo albumin, and comorbid hepatic cirrhosis. This patient was given a hepatoprotection. After liver function improved, the patient was started on anti-tuberculosis drugs with a regimen of 2 hepatotoxic drugs, namely isoniazid, rifampin, and ethambutol, given gradually and planned to be given for 9 months, with regular monitoring of liver function in the first 2 months. **Conclusion:** Effective management of pulmonary tuberculosis infection depends on giving OAT at the appropriate dose and duration. The selection of regimen and duration of therapy can be considered based on the condition of chronic liver disease. Careful assessment and periodic evaluation of liver function are required.

1. Introduction

Pulmonary tuberculosis (TB) is a major health problem in developing countries. In Indonesia, pulmonary TB ranks 4th for morbidity rates, while as a cause of death ranks 5th. TB attacks most of the productive age group of the group socioeconomic weak. Although efforts to eradicate TB have been made, the incidence and prevalence of pulmonary TB in Indonesia have never decreased. With the increase in population, the number of pulmonary TB sufferers also increases.[1,2]

Cirrhosis of the liver is a disease with a wide prevalence leading to immunosuppression and a higher prevalence of TB than in the general population. Cirrhosis of the liver is also a relatively common condition, with autopsy studies showing a prevalence of around 5-10%. Evidence suggests a higher prevalence of TB in patients with cirrhosis compared to the general population. A study conducted in West India showed that the prevalence rate is 15 times higher than that of the general population. Another study from India showed that the prevalence of TB in cirrhotic patients was almost five times higher (8.1%) compared to the general population (1.6%).[1,3]

The high incidence of TB in patients with cirrhosis is mainly due to immune dysfunction with a higher virulence compared to the general population. In a cohort study of cirrhosis in patients from Denmark (1977-1993), the incidence of TB was 168.6 per 100,000. Highest in men aged > 65 years, with an incidence of 246 per 100,000. Furthermore, patients

with cirrhosis who acquire TB have a poor prognosis.[3]

Treatment of tuberculosis in patients with liver disease raises various clinical problems. Treatment of patients with underlying disorders is complicated by poor tolerance, higher incidence of hepatotoxicity, and presence of considerable change significant in the liver, which can affect the pharmacokinetic function of the drug as well as the possibility of TB resistance to a higher multidrug response (MDR). In addition, there is an increased risk of drug-induced liver injury in potentially more serious cirrhosis.[4,5] This study aimed to describe the management of pulmonary tuberculosis in patients with cirrhosis of the liver.

2. Case Presentation

A 35-year-old male patient came to the pulmonary clinic of Dr. M. Djamil General Hospital, Padang, Indonesia, with complaints of coughing up phlegm for 5 months before entering yellow phlegm, intermittent. There were no complaints of shortness of breath, coughing up blood, or chest pain. Fever intermittent since 1 month before entering the hospital. The fever is not high, and no chills are accompanied by night sweats. Weight loss is there, more or less 12 kg in these 3 months. His appetite has decreased since 1 month ago. There was no previous history of pulmonary TB. Eyes look yellow since 5 months ago. Because of this complaint, the patient has gone to an internal medicine doctor and was diagnosed with cirrhosis of the liver, and routinely goes to the internal medicine polyclinic. There was no history of diabetes mellitus (DM). There was no history of other comorbidities such as liver disease (hepatitis), hypertension, asthma, and malignancy. There is no family history of TB, DM, hypertension, asthma, and malignancy in the family. The patient is a construction worker, a light smoker, does not consume herbs/herbal medicine, and has consumed alcohol for 5 years.

Physical examination found the general condition looked moderately ill, compost mentis awareness, vital signs within normal limits, body mass index 16.4, icteric eye sclera, Physical examination of the lungs symmetrically left and right, left chest movement equal to the right. On palpation of the chest, there is fremitus left and right, on resonant percussion, and from auscultation, bronchovesicular breath sounds. Abdominal examination, no distension, palpation supple, heartburn tenderness present, percussion resonant, and auscultation of normal bowel sounds. Examination of the extremities revealed no edema and clubbing finger.

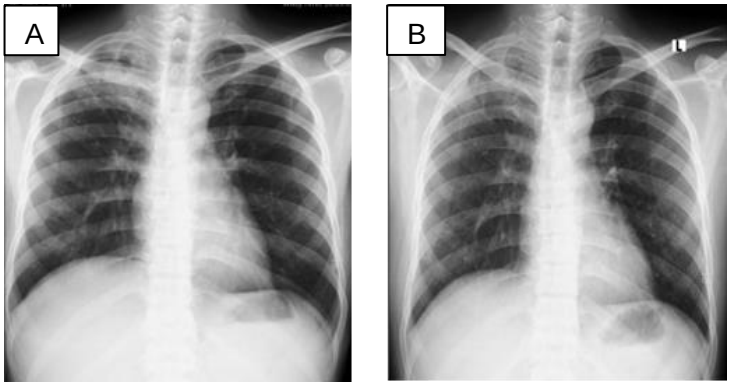

Figure 1. Chest X-ray of the patient. (A) Chest X-ray before treatment; (B) Chest X-ray 2 months after OAT treatment.

Laboratory examination results showed hemoglobin 11.8 g/dL, leukocytes, and platelets within normal limits. Clinical chemistry examination revealed hypo albumin with an albumin level of 2.8 g/dL. In addition, an increase in liver function was found with a total bilirubin value of 5.78 mg/dL, direct bilirubin 4.3 mg/dL, indirect bilirubin 1.4 mg/dL, SGOT 78 u/dL, and SGPT 66 u/dL. Blood sugar checks when 120 mg/dL. Other lab tests, such as kidney function, and electrolytes, are within normal

limits. Based on sputum examination results obtained BTA +2. The rapid molecular test examination with MTB detected high results and rifampicin resistance was not detected. The patient was diagnosed with pulmonary tuberculosis, and a new case confirmed bacteriologically hypoalbuminemia and suspected cirrhosis of the liver.

Patients were given curcuma therapy 3x1 tab and hepagard 2x1 tab. The Planned to check the liver physiology check every 3 days and check the hepatitis marker. On the next poly control day, the sclera was still icteric. The results of the hepatitis marker examination showed Anti HAV IgM: negative, HBsAg (ELISA): 0.1, Anti-HCV: 0.1, and Impression: within normal limits. Liver function examination showed improvement in total bilirubin 3.8 mg/dL, direct bilirubin 2.8 mg/dL, indirect bilirubin 1.0 mg/dL, SGOT 38 u/dL, and SGPT 50 u/dL. The patient is then planned to start entering the Anti-tuberculosis Drug by choosing a special regimen. OAT special regimen begins with desensitization rifampicin for 4 days up to a dose of 1 x 600 mg, then proceeds with desensitization additional isoniazid regimen until the 7th day. After 1 week, the hepatic function examination was repeated. The results of the liver function examination found no significant increase in value. Process Desensitization of the drug was continued with the addition of the ethambutol regimen up to a dose of 1 x 1000 mg for 7 days. After 2 weeks of desensitization medication, clinical evaluation and liver function checks were carried out. There were no symptoms of nausea and vomiting from the patient's complaint of jaundice still visible in the eye. Liver function examination results showed total bilirubin 3.4 mg/dL, direct bilirubin 2.3 mg/dL, indirect bilirubin 1.1 mg/dL, SGOT 28 u/dL, and SGPT 30 u/dL. Full doses of special category OAT are started after 2 weeks of processing the desensitization drug. Provision of special categories of OAT is planned to be given for 9 months. The patient was also asked to control the polyclinic 2 weeks later to do a liver function examination.

3. Discussion

Tuberculosis (TB) has been a human disease for centuries. Its frequency is increased severalfold in patients with cirrhosis of the liver. The gold standard for TB management is isoniazid, rifampicin, pyrazinamide, and ethambutol for 6 months. Although good results have been seen with this treatment in general, the management of patients with underlying cirrhosis is a challenge. The suppressed immune response causes changes in many diagnostic tests. Three of four drugs antitubercular First-line drugs are hepatotoxic, and basic liver function is often impaired in patients with underlying cirrhosis.[4,6,7]

Liver disease, especially cirrhosis, can have a significant effect on all the pharmacokinetic processes of a drug: absorption, distribution, metabolism, and elimination. Absorption Drugs can be affected as a result of pathological changes in the GI tract, whereas changes in drug distribution can occur due to changes in plasma and tissue binding and fluid shifts. Drug metabolism, which can affect bioavailability, can be modified as a result of changes in enzyme activity and transporter expression and activity. Lastly, the elimination of drug molecules can be impaired due to decreased hepatic extraction and renal clearance. Ultimately these changes may lead to higher systemic drug concentrations and longer half-lives. Thus, increasing the risk of serious side effects.[7-9]

If there is acute hepatitis (caused by a virus) that is not related to TB disease, treatment should be postponed until the acute condition improves. In patients with severe and unstable hepatic impairment, liver function tests should be performed before treatment starts.[7] Challenges in the treatment of TB in cirrhotic patients arise because of three drugs, anti-tuberculosis first-line potentially hepatotoxic. Administration of these drugs can cause worsening of liver function with decompensated stable cirrhosis and occasionally lead to fulminant liver failure, with high mortality. There is no consensus as to which drug to administer for different degrees of liver damage, although WHO guidelines state that the more unstable or severe the liver disease, the fewer hepatotoxic drugs

should be used. [9,10]

In patients with a history of pre-existing functional impairment, it is important to diagnose the cause and degree of existing liver dysfunction before starting anti-TB drugs. In chronic liver disease, it is necessary to determine the severity of the disease according to Child-Pugh criteria. This degree of severity can then be the basis for considering a modified OAT regimen. In addition, an increase in ALT enzyme levels more than 3 times the normal limit before OAT therapy is given is also one of the considerations for modification of the OAT regimen.

The choice of treatment regimen in patients includes rifampicin, isoniazid, and ethambutol, following the guidelines for TB treatment in liver disease. The consideration used is the value of the child-pugh score in patients who are still in the mild category so that a regimen containing 2 hepatotoxic drugs can be given. Based on the Indonesian TB therapy guide, the regimen of rifampicin and isoniazid can be added to the regimen of ethambutol.

According to the American Thoracic Society, special dose regimens for liver disorders can be started with rifampicin. After 3-7 days of the administration, and it is proven that there is no increase in SGPT and SGOT, then it can be continued with isoniazid and ethambutol. A regimen for patient treatment, in this case, is in accordance with the ATS guidelines.[7]

Patients were given hepatoprotection, namely curcuma 3 x 1 tablet and hepagard 2 x 1 tablet. Hepatoprotectors are drug compounds that can provide protection to the liver from damage caused by poisons, drugs, and others. Curcuma contains *Curcuma xanthorrhiza* (curcuma) 20 mg. Meanwhile, hepagard contains *Curcuma longa* dried extra 20 mg, silybum marianum dried extra 100 mg and cynaraeschool extra 50 mg. Curcuma and Hepagard contain curcumin which acts as an antioxidant. He will catch the superoxide ion and break the inter-superoxide ion chain (O_2-). In the end, this lipid peroxidation process will prevent liver damage mediated by the antioxidant enzyme superoxide dismutase (SOD). The SOD enzyme will convert O_2- into a less toxic product. In addition to these mechanisms, curcumin also increases glutathione S-transferase (GST) and inhibits several proinflammatory factors such as nuclear factor-kB (NF-kB) and cytokines.[13,14]

Various literature and guidelines suggest not giving PZA to patients with liver cirrhosis, especially decompensated liver cirrhosis. In severe TB conditions and having indications for PZA administration, it is recommended to consider giving a lower dose of 15-30 mg/kg/day, which has a significantly lower risk of hepatotoxicity. Based on this risk, the administration of OAT in TB patients with cirrhosis of the liver requires careful consideration, in which patients with compensated cirrhosis of the liver can consider giving an OAT regimen with 2 hepatotoxic drugs. However, in TB patients with decompensated liver cirrhosis, regimens containing hepatotoxic agents are not recommended.

Each OAT has a different level of hepatotoxicity, as well as the pathogenesis mechanism in causing liver damage. In general, OAT has the potential to cause hepatotoxicity through different mechanisms, including oxidative stress, lipid peroxidation, reduced glutathione levels, and activation of CYP2E1 enzymes. The following describes the mechanism of toxicity caused by INH, rifampin, and pyrazinamide.

Isoniazid can inhibit *Mycobacterium tuberculosis* (MTb) mycolic acid synthesis, which is an important component of the MTb cell wall that determines bacterial survival. This drug is also able to interfere with the synthesis and metabolism of DNA, lipids, carbohydrates, and nicotinamide adenine dinucleotide (NAD). Isoniazid (INH) is the OAT that most often causes DILI. Four studies with large populations have demonstrated a high incidence of DILI due to INH used as monotherapy (in the treatment of latent TB) of 0.1-0.56%.[13] Isoniazid causes hepatotoxic effects through its metabolite, namely mono-acetyl-hydrazine (MAH). MAH triggers the emergence of free oxidants, which are toxic to tissues. In addition, isoniazid also inhibits glutathione peroxidase and catalase, which are useful as antioxidants against free radicals. Thus isoniazid

causes hepatotoxicity by disrupting the oxidant-antioxidant balance.[9] The main metabolism of INH occurs in the liver through the role of the N-acetyltransferase (NAT) enzyme system, which transfers the acetyl group from acetyl-CoA to the nitrogen group of the arylamine substrate and converts INH to acetyl isoniazids which will undergo hydrolation to form isonicotinic acid and mono acetyl-hydrazine.[14,15]

The isonicotinic acid is then conjugated with glycine and excreted out of the body. Meanwhile, mono acetyl-hydrazine will pass through one of the 3 metabolic pathways to form either diacetyl-hydrazine, hydrazone, or oxidized products (hepatotoxins). The first two compounds are capable of excreted exit, but the oxidized product (hepatotoxin) is electrophilic reactive, which can bind covalently to hepatocytes. Furthermore, antigenic macromolecules are formed that stimulate an immune response that will destroy the metabolite-protein complex. This process is likely one of the mechanisms of hepatotoxicity resulting from treatment with INH.[14]

NAT enzyme deficiency is known to be associated with INH hepatotoxicity. Genetic polymorphisms are thought to affect the synthesis and metabolism of this enzyme which divides individuals into slow, intermediate, and fast acetylator phenotypes.[12] Fast acetylation process can reduce the formation of toxic metabolites. In the slow acetylator phenotype, higher concentrations of INH and acetyl isoniazid are obtained. 14 In this group, INH can undergo hydrolysis to hydrazine which can cause irreversible damage to liver cells. Rifampin can also induce the hydrolysis of INH to hydrazine, and this explains the higher potential for toxicity when the two drugs are combined.[14,15]

Rifampicin is able to bind to bacterial DNA-dependent RNA polymerase enzymes, thereby inhibiting the transcription of DNA into RNA, thereby inhibiting protein synthesis. RIF is primarily metabolized in the liver through the role of microsomal enzymes to convert it to the deacetylated form (RIF).[11] Exact mechanism of hepatotoxicity of rifampin is not yet known clearly because usually rifampicin is always combined. Studies in experimental animals show induced liver damage rifampin associated with oxidative stress on mitochondria, liver cell apoptosis, intrahepatic lipid accumulation, and cholestasis. Most liver toxicity occurs during the administration of rifampin and INH simultaneously. This is expected because rifampicin can induce INH hydrolysis reactions to form hydrazine compounds that are hepatotoxic.[15]

Pyrazinamide causes hepatotoxicity by disturbing the balance of nicotinamide-acetyl dehydrogenase in the liver, which can release oxidant compounds and free radicals. Pyrazinamide has a dose-dependent hepatotoxic effect. The enzymes involved in pyrazinamide metabolism are microsomal deamidase and xanthine oxidase. In the liver, pyrazinamide is metabolized to pyrazinoic acid (POA) by microsomal deamidase enzymes. Furthermore, POA will be converted into acidhydroxypyrazinoate/ hydroxypyrazinoic acid (5-OH-POA) by xanthine oxidase.[11]

Pyrazinamide enters the intracellular environment of bacteria by passive diffusion and is converted to POA by enzymes pyrazinamide bacteria. POA molecules then diffuse passively into the extracellular environment. If the pH of the environment is acidic, a small portion of POA will turn into HPOA and re-enter the TB germs intracellularly. The accumulation of HPOA molecules causes acidification of the intracellular environment, inhibition of vital bacterial enzymes, and synthesis of protein and RNA. An experimental animal study by Shih et al. showed that POA and 5-OH-POA metabolites were more toxic to HepG2 cells. In addition, a relationship was found between an increase in the ratio of 5-OH-POA and POA metabolites with the incidence of liver injury.

This supports the hypothesis that these metabolites are the main cause of hepatotoxicity caused by PZA administration. It is difficult to predict that someone will get DILI when given OAT.[9] The liver is an organ that plays a role in minimizing exposure to toxic chemicals, including OAT. Isoniazid, rifampin,

and pyrazinamide are known to cause toxicity, whereas ethambutol and streptomycin are considered not to cause hepatotoxicity.[15]

This reactive metabolite triggers the formation of excessive reactive oxygen species (ROS), which causes peroxidation of lipids and cell death (apoptosis/ necrosis). The body has endogenous antioxidants (glutathione and enzyme detoxification), which are activated by nuclear factor Erythroid 2-related factor-2 (Nrf2) and small Maf protein (Mafs), while Bach I and small Mafsown opposite activity, namely suppressing the formation of antioxidants. Manganese superoxide dismutase (MnSOD) is a protein found in mitochondria that also plays a role in the detoxification process. Activityactivator and this repressor also affect the occurrence of DILI due to OAT.[9]

4. Conclusion

Effective management of MTb infection depends on giving anti-TB drugs with the appropriate dose and duration. The selection of regimen and duration of therapy can be considered based on the condition of chronic liver disease. Careful assessment and periodic evaluation of liver function are required.

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