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MILIARY TUBERCULOSIS AND ELEVATED TRANSAMINASE ENZYMES IN AN UNTREATED HUMAN IMMUNIDEFICIENCY VIRUS (HIV) PATIENT: A CASE REPORT

To Identify and Treat It Comprehensively

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ABSTRAK

Pendahuluan: Tuberkulosis (TB) berkaitan erat dengan Human Immunodeficiency Virus (HIV) dan menyebabkan 25% kematian pada pasien HIV. TB Milier adalah komplikasi dari fokus infeksi tuberkulosis yang menyebar secara hematogen, berupa bercak-bercak halus yang umumnya merata di seluruh bidang paru. Pemberian Obat Anti Tuberkulosis dapat menimbulkan efek samping pada beberapa pasien TB termasuk hepatitis akibat obat, oleh karena itu perlu dilakukan pemeriksaan fungsi hati. Pemeriksaan SGOT dan SGPT sebagai marker fungsi hati yang meningkat dapat menunjukkan terjadinya kerusakan atau peradangan pada jaringan hati. Pada kasus HIV, sangat dianjurkan untuk melakukan pemeriksaan fungsi hati setiap bulan
Ilustrasi Kasus : Seorang laki-laki berusia 28 tahun terdiagnosis TB milier dan HIV mengalami peningkatan enzim transaminase pada awal diagnosis dengan keluhan utama batuk berdahak, demam yang berfluktuasi, berkeringat pada malam hari, lemas, mual, muntah, dan berat badan turun 0,14 kg sejak tiga bulan sebelum masuk rumah sakit. Pasien tampak sakit sedang dengan kesadaran composmentis, suhu 38,8C, saturasi oksigen 98%, BB kurang (13,4 kg.m2), konjungtiva anemis dan sklera tidak ikterik. Hasil laboratorium menunjukkan peningkatan enzim transaminase (SGOT: 398U/L SGPT: 90U/L), hipoalbuminemia (2,17g/dL, Sputum BTA I/II/II: +1/+2/+2, Gen Xpert: MTB terdeteksi, resistensi Rifampisin tidak terdeteksi. Tes HIV reaktif, CD4: 26 sel/UL. Pemeriksaan Ro Thorax menunjukkan opasitas nodular tidak homogen pada kedua bidang paru serta USG menunjukkan penyakit hati kronis. Pasien menerima kombinasi OAT Levofloxacin, ethambutol dan streptomisin, kemudian diberikan ARV TDF + 3TC + EFV setelah satu bulan pemberian OAT kombinasi. Setelah diberikan terapi anti tuberkulosis dan antiretroviral yang dimodifikasi, terjadi perbaikan klinis dan laboratorium.
Simpulan: Pemantauan fungsi hati berperan dalam terapi OAT pada pasien HIV. Bila terjadi peningkatan enzim hati, perlunya evaluasi lebih lanjut mengenai obat yang terduga sebagai hepatotoksik dan memungkinkan untuk memberikan terapi OAT kombinasi menyesuaikan dengan pasien tersebut.

Kata Kunci: AIDS, HIV, Peningkatan Enzim Transaminase, Tuberkulosis

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ABSTRACT

Introduction Tuberculosis (TB) is a significant cause of HIV-related deaths, accounting for 25% of cases. Miliary TB is a complication of hematogenous infection, causing fine patches in the lung. Anti-TB drugs can cause side effects, including drug-induced hepatitis. Monitoring liver function is crucial, with elevated SGOT and SGPT markers indicating liver damage or inflammation. In HIV cases, monthly liver function tests are highly recommended.
Case illustration A 28-year-old man with miliary TB and HIV was diagnosed with elevated transaminase enzymes and symptoms such as cough, fever, night sweats, weakness, nausea, vomiting, and weight loss. He was moderately ill with a temperature of 38.8C, oxygen saturation of 98%, and underweight. Laboratory tests revealed elevated transaminase enzymes, hypoalbuminemia, and MTB-related resistance. The patient was diagnosed with chronic liver disease and a chronic TB infection. He was treated with an OAT combination of Levofloxacin, ethambutol, and streptomycin, followed by ARV TDF + 3TC + EFV. After receiving modified anti-tuberculosis and antiretroviral therapy, he experienced clinical and laboratory improvement.
Conclusion Liver function monitoring plays a role in OAT therapy in HIV patients. If there is an increase in liver enzymes, further evaluation of the suspected hepatotoxic drug is needed and it is possible to provide combination OAT therapy tailored to the patient.

Keywords: *AIDS, HIV, Increased Transaminase Enzymes, TB*

INTRODUCTION

Miliary tuberculosis is a type of tuberculosis that varies from a slowly progressive infection to an acute fulminant disease, which is caused by hematogenous or lymphogenous spread from infected cases into the bloodstream and involves multiple organs. Miliary tuberculosis is a form of tuberculosis characterized by widespread spread to the human body with small (1-5 mm) lesions.[1]

The American Association for the Study of Liver Disease (AASLD) in 2011 recommended that an increase in alanine aminotransferase (ALT) levels more than three times upper limit of normal and an increase in total bilirubin more than twice the upper limit of normal can be used as criteria to determine the presence or absence of significant abnormalities in liver laboratory parameters. Elevated levels of liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and

alkaline phosphatase (ALP) were considered as indicators of liver injury, whereas elevated total and conjugated bilirubin were parameters to assess overall liver function. Assessment of the pattern of liver injury is very important because certain drugs tend to cause injury with a characteristic pattern as well. [2.3.4]

Drug-induced liver injury (DILI) is a form of side effect that causes the cessation of TB treatment or regimen changes due to treatment or regimen changed due to treatment failure, relaps, and drug resistance.Drug-induced hepatitis is managed by stopping the drug that causes liver damage, along with monitoring the clinical condition and laboratory tests that are indicators of liver damage. [5.6.7.8] In this case report, we report a case of miliary TB and HIV with drug liver injury and treated with modified anti-tuberculosis and clinical and laboratory improvement after treatment.

1. CASE ILLUSTRATION

A 28-year-old male came to Hospital with complaints of cough with phlegm, fluctuating fever, night sweats, weakness and weight loss of 14 kg for three months before being admitted to the hospital. The patient also complained of weakness, 2x liquid stools a day, decreased appetite since 1 month. Nausea and vomiting experienced since 3 days before admission to the hospital. There were no complaints of headaches and limb weakness. The frequency of urination is within normal limits. The patient is not married, works as a receptionist in a hotel and has free sex with both men and women. IVDU use and alcohol consumption were denied. There is no history of contact with TB patients.

On physical examination, the patients appeared moderately ill with Full Alert consciousness, blood pressure 120/82 mmHg, pulse rate 72 beats per minute, breathing rate 20 times per minute, axillary temperature 38.8C, and oxygen saturation 98% with oxygen 3 liters per minute nasal cannula. Body mass index (BMI) impression of underweight (13.4 kg.m2). Anemic conjunctiva and sclera are not icteric. Examination of the neck revealed no enlarged lymph nodes. Lung examination found bilateral coarse wet crackles without wheezing and the heart was within normal limits. Abdomen bowel sounds were normal, there was no enlargement of intra-abdominal organs and there was no epigastric tenderness. Extremities seem normal.

Laboratory examination showed anemia (Hb 9,8g/dl, Hematocrit 28,3%, leukocytes 2470/uL, platelets 157000/uL MCV 87 fl, MCH 28,7pg, MCHC 33,0g/dL) peripheral blood morphology anemia left shift hypochromic microcytic with thrombocytopenia. There is an increase in transaminase enzymes, namely SGOT:398 U/L SGPT: 90 U/L and hypoalbuminemia (Albumin:2,17g/dL), normal kidney function, Sodium:124 Potassium:3,0 Chloride:100,3 HbsAg and Anti HCV: non reactive, Anti CMV IgG: reactive and Anti CMV IgM non reactive. Rapid Plasma Reagent (RPR) and Treponema pallidum haemagglutination assay (TPHA) examination for syphilis. AFB examination I/II/II: +1/+2/+2, Gene Xpert: MTB not detected Rifampicin

resistance was not detected. Chest X-ray revealed right pleural effusion, partially nodular inhomogeneous opacity in both lung fields and no radiological abnormalities were seen in heart (Figure 1). Chest CT scan was found (Figure 2). Ultrasound examination revealed chronic liver disease. After administration of anti-tuberculosis drugs and titration of pyrazinamide and isoniazid there was an increase in the transaminase enzyme, namely SGOT:550 U/L SGPT: 252 U/L

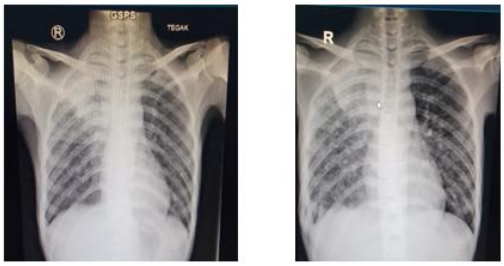

Figure 1. Chest Xray showed Non-Homogen Nodular Opacities.

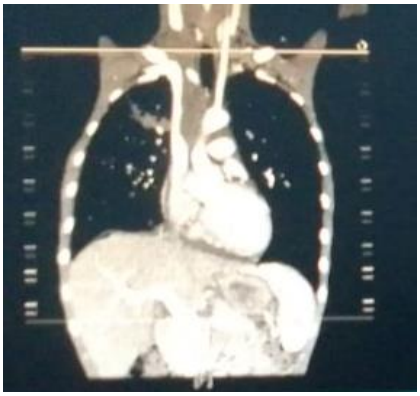

Figure 2. CT Scan Thorax

This patient was diagnosed with miliary TB, smear positive on LES modified OAT (Levofloxacin, Ethambutol, Streptomycin), AIDS not on antiretroviral drugs, normochromic normocytic anemia, Elevated transaminase enzyme, Hypoosmolar euvolemic hyponatremia, Chronic liver disease, Malnutrition with high risk refeeding syndrome.

Patient Managed with normal saline infusion, high-calorie and high-protein diet. Treating miliary TB with increased transaminase enzymes with Anti Tuberculosis Drugs, namely Levofloxacin, Ethambutol, Streptomycin for 2 months. After improvement of liver function and normal transaminase enzymes, Rifampicin titration was carried out and followed by Isoniazid titration. Transaminase enzyme monitoring was carried out every two weeks but the patient's clinical deterioration occurred, namely patients with fever, tingling and an increase in the transaminase enzyme 3 times normal, then discontinuation of Rifampicin and Isoniazid therapy. Administration of anti-tuberculosis drugs with modifications namely levofloxacin, ethambutol and streptomycin, and there was improvement in the transaminase enzyme, namely SGOT: 23 U/L SGPT: 23 U/L treatment with streptomycin was given for 2 months. After the patient was clinically stable for 2 months, a fixed dose combination antiretroviral was administered starting after one month of anti-tuberculosis treatment with the Tenofovir Disoproxil Fumarete (TDF) + Lamivudine (3TC) + Efavirenz (EFV) regimen. Also administered cotrimoxazole 960 mg once a day. On outpatient examination there was improvement in clinical and laboratory. The patient is still on cotrimoxazole, anti-tuberculosis and antiretroviral treatment.

DISCUSSION

Drug-induced Liver Injury is liver damage associated with impaired liver function caused by

drug exposure. One of the causes of drug-induced liver injury is the use of anti-tuberculosis drugs, for example, isoniazid-induced liver injury, isoniazid hepatotoxicity is increasing due to the use of rifampicin, pyrazinamide and alcohol. Tajri et al reported that hepatotoxicity induced by isoniazid and combined anti-tuberculosis therapy including isoniazid was more likely in patients with chronic hepatitis B. Effective treatment of tuberculosis (TB) requires a combination of bactericidal and/or bacteriostatic. This combination is the standard regimen recommended by WHO consisting of 5 first-line anti-TB drugs (isoniazid, rifampicin, ethambutol and streptomycin). The treatment can cause side effects, one of which is discontinuation of treatment with the effect of not achieving cure and even drug resistance. Drug induced liver injury is a form of side effect that causes discontinuation of TB treatment or a change in regimen. About 7% of the side effects of TB treatment are DILI. The highest incidence of DILI in TB treatment occurs within the first 2 weeks of treatment and can also occur within 2 months after administration of anti-tuberculosis drugs.[9.10]

Drug-induced liver injury (DILI) is classified into intrinsic and idiosyncratic DILI. Intrinsic DILI usually occurs in drug-exposed individuals (predictable), is dose related, and has a short onset of time (hours to days) whereas idiosyncratic DILI is not dose related although the dose threshold of 50-100 mg/day is only occurs in a small proportion of exposed individuals (unpredictable) and shows variable lethality with onset of days to weeks. The pathogenesis of these two DILIs has several similarities and differences including drug type, drug characteristics, especially lipophilicity and drug biotransformation. Covalent exposure to the liver can bind to proteins, induce oxidative stress, and activate signal transduction pathways such as mitogen-activated protein (MAP) and cause stress on organelles such as mitochondria or endoplasmic reticulum, which interferes with bile acid transport resulting in necrosis or apoptosis. can also trigger adaptive immune response in individuals genetically. In idiosyncratic DILI, the adaptive immune system has an important role related to Human Leukocyte Antigen (HLA) metabolic factors, drug interactions, and alcohol consumption.[11.12]

The clinical symptoms of DILI caused by the use of antituberculosis drugs are the same as those of acute and chronic hepatobiliary disease, with predominant symptoms such as jaundice in acute hepatitis or cholestatic liver disease. Jaundice in acute hepatitis is more dangerous and has a mortality rate of 10% regardless ofthe type that causes DILI. Cholestasis in hepatitis is characterized by jaundice, pruritus, and elevated serum alkaline phosphatase, with a slight increase in serum alanine transferase (ALT). Elevated ALT and alkaline phosphatase indicate atypical hepatitis or granulomatous hepatitis. Clinical symptoms in acute liver failure are usually non-specific, such as loss of appetite, fatigue, abdominal pain, fever, and jaundice. It is necessary to take a history of infection, drug use, family history of liver disease, and travel history to endemic areas. On physical examination, jaundice, changes in

mental status and signs of coagulopathy may be found The diagnostic approach for DILI is according to the presentation of liver injury. [12]

Prior to starting TB treatment, it should be monitored every 2 weeks for the initial two months in at-risk groups such as patients with pre-existing liver disorders, alcoholics, the elderly and undernourished. This is not only the responsibility of health professionals but this health education must be charged to all patients undergoing TB treatment in detail not only regarding adherence and benefits of OAT but also side effects. Patients should be alert and report immediately if symptoms suggestive of hepatitis such as loss of appetite, nausea, vomiting, jaundice occur during treatment. Furthermore, the clinical condition of the patient should be assessed not only in terms of disease control but also in the symptoms and signs of hepatitis in the patient being followed. [5,6]

The most important treatment for DILI is to stop the drug that causes DILI and provide supportive therapy. In most patients DILI recovers spontaneously but has different variability.There is no specific therapy for the management of DILI. In this patient, initially given modified OAT, namely Ethambutol 750 mg, Streptomycin 750 mg and Levofloxacin 500 mg, six weeks after being given modified OAT therapy, liver function improved and Rifampicin was titrated to a dose of 450 mg, liver function was still normal, then continued with Isoniazid titration, when titration was performed. isoniazid liver function increases, the patient experiences weakness, fever and tingling, discontinuation of Rifampicin and Isoniazid therapy.[13]

Guidelines for the initiation of antiretroviral administration are carried out by clinical assessment and supporting examinations to determine the stage of HIV. The main routine investigations before starting ARV are complete peripheral blood tests, clinical chemistry, hepatitis B and C screening, and screening for sexually transmitted infections such as VDRL and TPHA. CD4 T-lymphocyte counts are also needed as important data before starting antiretroviral therapy in determining the administration of cotrimoxazole therapy for the prophylaxis of other opportunistic infections. According to WHO guidelines, cotrimoxazole prophylaxis is part of the management of HIV. Many studies have shown that the effectiveness of cotrimoxazole preventive treatment can reduce mortality and morbidity rates in HIV patients so that prophylactic therapy is given to HIV patients with WHO stage 3 or 4 and/or CD4 levels <350 cells/mm[3]. In this case, all supporting examinations based on the recommendations and guidelines of the Ministry of Health of the Republic of Indonesia have been carried out and the patient's CD4 examination obtained a result of 26 cells/mm^3 so that cotrimoxazole therapy as prophylactic therapy for other opportunistic infections was also given and this therapy could be discontinued if the CD4 levels were more than 200 cells/mm [3,11,12,13]

According to WHO guidelines, antiretroviral therapy should have fewer side effects, be more convenient, and be simpler. ARV

therapy should also be used in conjunction with other drugs used to treat various opportunistic infections commonly found in HIV patients. The once-daily fixed-dose combination of ARV TDF+3TC (or emtricitabine (FTC))+EFV rarely causes severe side effects and shows a better therapeutic and virological response than once- or twice-daily non-nucleoside reverse transcriptase inhibitors (NNRTIs)). Other options of the first-line ARV are azidothymidine (AZT)+3TC+EFV, AZT+3TC+nevirapine (NVP), or TDF+3TC(or (FTC)+NVP (Ministry of Health., 2019; PAHO., 2020).This patient was given a fixed-dose combination of ARV TDF+3TC+EFV once a day and side effects from drug administration were minimized.[13,14]

CONCLUSIONS

Drug Induced Liver Injury due to the use of anti-tuberculosis drugs can occur within 2 months of giving anti-tuberculosis drugs and the highest incidence is in the first 2 weeks. TB treatment that can cause DILI is INH, Rifampicin and Pyrazinamide. If it occurs during TB treatment then the treatment is discontinued until the clinical disappearance for 2 weeks and liver function returns to normal. Tuberculosis is one of the opportunistic infections that can be found in HIV patients, if the diagnosis can be made quickly and accurately, it can reduce morbidity and mortality.

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