International Journal of Advances in Medicine
Theodora A et al. Int J Adv Med. 2022 Sep;9(9):946-950
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20222103

Case Report

Cholestatic drug induced liver injury in active pulmonary tuberculosis patient: a case report

Agnes Theodora[1]*, Ketut Suryana[2]

[2]Department of Internal Medicine, Merpati Clinic, HIV and Allergy - Clinical Immunology Services Unit, [1]Wangaya Regional General Hospital, Denpasar, Bali, Indonesia

Received: 18 July 2022
Accepted: 08 August 2022

***Correspondence:**
Agnes Theodora,
E-mail: agnestheodorachan-dra@gmail.com

ABSTRACT

Drug induced liver injury (DILI) has been a long-standing concern in the treatment of tuberculosis. Anti-tuberculosis therapy (ATT) is known to have hepatotoxicity effect. DILI is diagnosed clinically using liver biochemical test, such as alanine transaminase (ALT), alkaline phosphatase (ALP), and total bilirubin. Calculating ratio (R) of ALT over ALP, is useful to classify types of injury pattern in DILI. Roussel Uclaf causality assessment method (RUCAM) scale serves as a method to assess the causality agents for DILI. Here we report a case of 59 years old male who developed cholestatic DILI on fourth weeks of ATT. Patient came in with loss of consciousness, jaundice, nausea, pruritus, and abdominal tenderness. Patient's ALT level was normal, but ALP and total bilirubin was significantly elevated, with R values less than 2, indicating a cholestatic type of injury. Patient sputum was positive for tuberculosis bacteria, showing an active infection. Patient was admitted and ATT was discontinued. Patient showed improvement, but eventually fall into sepsis and developed respiratory distress on sixth day of admission despite adequate treatment and close monitoring. Despite most of the cases resolves spontaneously upon cessation of the toxic agents, in the severe form, it may fall into chronic liver injury, acute liver failure, and eventually death. Preventing DILI is readily important by educating, screening for risk factors, and routine evaluation of liver enzymes in patient under ATT. Early diagnosis and prompt treatment are needed to avoid poor prognosis in the course of the disease.

Keywords: DILI, Tuberculosis, Anti-tuberculosis, Cholestatic, Liver injury

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by gram positive aerobic acid-resistant bacilli bacteria, *Mycobacterium spp*. The primary infection site of TB is the lungs, followed with extrapulmonary sites, such as pleura, lymph nodes, intestine, and bone.[1] TB is a global health burden. Based on World Health Organization (WHO) data, in 2020 there were 9.9 million individuals infected with TB with mortality rate as high as 15 percents.[2] In Indonesia 384.025 new cases were reported with 12 percent case fatality ratio (CFR). In 2021, 443.325 new cases were reported, showing increment from the previous year.[3] Diagnosis of TB is established from isolating the bacteria from the patient's bodily fluid or by using the rapid molecular test to detect the deoxyribonucleic acid (DNA) of *Mycobacterium tuberculosis* in the sputum. Treatment for TB initially started with 4 drug-regimen: isoniazid, rifampin, pyrazinamide, and ethambutol (RHZE) for 2 months, then followed with only rifampicin and isoniazid (RH) for the next 4 months. For patient who developed drug-resistant TB, second line of regiment will be prescribed.[1,4]

Anti TB treatment has adverse effects that affecting adherence and efficacy of the treatment. Hepatotoxicity is one of the serious adverse effects that encountered in TB patient. Drug induced liver injury (DILI) secondary to anti

TB treatment is reported in 2-28% among patients who received the therapy.[5,6] Several risk factors that may associated with this complication include pre-existing chronic liver disease, hepatitis B or C, co-infection with human immunodeficiency virus (HIV), high alcohol intake, older age, and malnutrition.[5] The pattern of liver injury varies from hepatocellular, cholestastic, and mixed. It can progress into chronic liver injury or acute liver failure.[6,7] In this review, we aim to review a case report of a 59 years old male with active pulmonary tuberculosis who developed a severe cholestatic drug induced liver injury during the intensive phase of his therapy.

CASE REPORT

A 59 years old male was brought into the emergency department due to decrease of consciousness for 1 day ago. Patients had history of progressive abdominal tenderness, discolouration of the eyes, nausea, loss of appetite, pruritus and fatigue that started since a week before admitted to the hospital. Patient also complained of productive coughs and chills from ten days prior. Patient recently had been re-diagnosed with a relapse case of pulmonary tuberculosis after declared cured 8 months ago. Patient was given the 2RHZE/4RH regiment. He had been taking the medication daily for 4 weeks. Patient did not take any other medications or herbal supplemental drugs. Patient had no other history of past illnesses and chronic diseases. He had history of self-medication at home with antacid tablets and cough syrups that he bought on the counter a week prior to admission.

Physical examination shows normoweight with body mass index of 22 kg/m^2. Patient was lethargic, with Glasgow coma score (GCS) of E2M4V4, other vital signs were normal. Each sclera was icteric (Figure 1). Heart examinations were normal. There were rales and increase of bronchial sound in both lungs. Abdominal examination showed palpation tenderness on right upper quadrant and epigastric area. Ascites was absent. Both palms showed slight yellowish discolouration. Sirosis stigmata is absent. Laboratory examination showed normal complete blood count, liver function tests show alanine transaminase (ALT) at 31 U/l and aspartate aminotransferase (AST) at 170 U/l. Total bilirubin was increased at 20.14 mg/dl with conjugated bilirubin at 16.1 mg/dl. Alkaline phosphatase (ALP) was elevated at 300 IU/l. Total protein was at 6.1 g/dl, with decrease of albumin at 2.3 g/dl and slight increase of globulin at 3.8 g/dl. Renal functions show slight increase of serum creatinine at 1.5 mg/dl. Electrolytes panel showed a decrease in potassium levels at 2.7 mmol/l. Gamma-glutamyl transpeptidase (gamma GT) was normal. Serological examination of HbsAg, anti-HCV, and anti-HIV were negative. Gene Xpert sputum test showed MTB detected medium without rifampicin resistant. Chest radiological examination showed infiltrates in both lungs, particularly on the right lobe, with high suspicion towards active pulmonary tuberculosis (Figure 2). Abdominal ultrasound showed parenchymal liver disease with mild fatty liver. There were no signs of obstruction or stones in the biliary structures. Head computed tomography (CT)-scan was performed to exclude neurological events that may contribute to the decrease of consciousness in our patient. It was unremarkable. Patient was diagnosed with cholestatic drug induced liver injury, pulmonary tuberculosis, and hepatic encephalopathy.

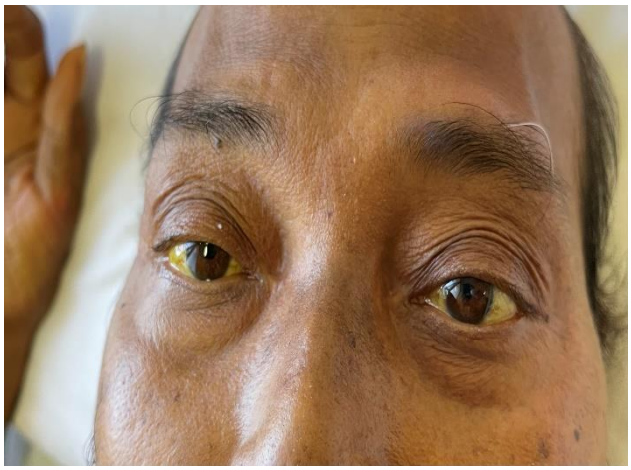

Figure 1: Clinical features showed icteric in both sclera.

Patient was admitted into the ward for monitoring and further therapy. ATT was discontinued. Patient was given hydration, antibiotics, curcuma tablet three times daily, Heparmin tablet three times daily, N-acetyl cysteine 200 mg intravenous once daily, ursodeoxycholic acid (UDCA) three times daily, methylprednisolone 62.5 mg intravenous once daily, citicoline 500 mg intravenous twice daily, lactulose syrup three times daily, and gastro protective agents. Patient regaining his consciousness to alert on second day of admission. Coughs and chest discomfort were not improving.

Patient also had episodes of intermittent fever during stays, but controlled with supportive therapy such as Ibuprofen 400 mg as needed. On fifth day of admission, patient's laboratory examination was monitored, it showed decreased in total bilirubin levels at 16.5 mg/dl with conjugated bilirubin at 14.1 mg/dl. Liver function test was normal, with ALT was at 44 U/l and AST was at 17 U/l. There was significant increase of leucocytosis at 27×10^9/l and neutrophil lymphocyte ratio was at 48.24%. Renal function test showed increase of serum creatinine levels at 2.3 mg/dl and blood urea nitrogen level increased at 129 mg/dl. Bleeding time and clotting time was within normal range. Patient was then diagnosed with sepsis and moved into intensive care unit. Phlegm was taken for sputum culture test, but it showed unremarkable result. Antibiotics were escalated to meropenem 1 gram three times daily with adequate fluids and other supportive treatments were continued. Unfortunately, despite adequate treatment and close monitoring, our patient developed acute respiratory distress syndrome and passed away on day sixth of admission.

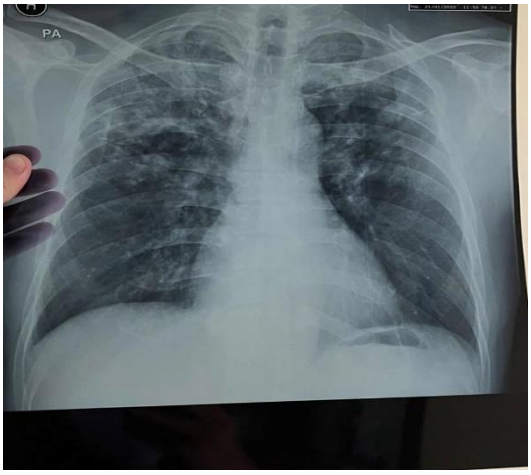

Figure 2: Chest X-ray, showed infiltrates in both lungs, particularly on the right lobe, with high suspicion towards active pulmonary tuberculosis.

DISCUSSION

DILI is defined as a liver injury, that caused by exposure of various medications, herbs, or other non-infectious toxic agents.[5-7] DILI can be classified into intrinsic or idiosyncratic. Intrinsic or direct DILI is a liver injury caused by known predictable agents and is dose related. The onset occurs within short span of time in individual exposed to the agents. Idiosyncratic DILI is unpredictable, not dose related, occurs in small population with longer time interval between exposure and onset.[6]

Acute liver injury is often confirmed by liver biochemical tests. According to European Association for the study of liver (EASL), case definition of DILI is clinically enforced, when one of the following thresholds is met: elevations of more than 5 folds upper limit of normality (ULN) in ALT or elevations of more than 2 folds upper limit of normality (ULN) in ALP in the absence of known pathology disease that caused rise of ALP levels, or elevations of more than 3 folds in ALT and elevations of more than 2 folds ULN in total bilirubin levels. Based on the pattern of the injury, DILI is classified into hepatocellular, cholestatic, and mixed.[6] Differentiating between the type of injury based on the elevation pattern of the liver enzymes. R or ratio of ALT to ALP. Liver injury is classified as hepatocellular, when the value of R is more than equal to 5 or there is a 5-folds of rise above ULN in ALT alone. Cholestatic injury is designated when the value of R is less than equal to 2 or ALP alone is elevated for more than 2 folds above ULN. Mixed pattern is when the value of R is between 2 and 5.[6,7]

Liver injury can be classified into chronic, when there is persistent injury for more than 1 year. Liver imaging in DILI is typically normal, but ultrasound is recommended to be performed in suspected patient. Liver biopsy is performed to support the histological diagnosis of DILI, and useful in the case whereas toxic agents were discontinued but no signs of improvement in the patient.[6]

DILI secondary to ATT is reported in 2-28% of patients with mortality rate up to 22.7%.[5,8] Some risk factors may contribute into the development of DILI in patients under anti tuberculosis therapy, such as advanced age, female sex, co-infection with HIV, chronic hepatitis B or C, pre-existing chronic liver disease, malnutrition and high alcohol intake.[5-9] DILI caused by ATT usually occurs within 2 months after administration or during the intensive phase of the treatment. The highest incidence occurs in the first 2 weeks.[10,11] Our patient starting showing symptoms in week 4 of treatment, however it was not reported, it prolonged until the fifth week when patient was admitted to the hospital. Patient was 59 years old, with dominant signs and symptoms of liver disease consist of jaundice, severe nausea, pruritus, abdominal tenderness, and decrease of consciousness. Patient also had history of coughs and fever due to lung infections. Laboratory result, showed elevation of ALP up to 2.07 folds ULN and total bilirubin is increased to 16 folds ULN. ALT is within normal levels. R value is at 0.10. Based on the clinical laboratory features, patient had a cholestatic type of liver injury. The presence of jaundice is more commonly found in cholestatic patient, and features to worse prognosis with fatality rate as high as 10%, as noted by Hy's law. Particularly, when there is encephalopathy and coagulopathy, indicating an acute liver failure.[6,9,10] Ultrasound was performed picturing a parenchymal liver disease with mild fatty liver. There were no signs of obstruction or damage in the biliary structure, hence excluding other causality for cholestasis. Liver biopsy was not performed. RUCAM scale is used to determine and assess the causality of DILI. Our patient's RUCAM scale towards the ATT reveals scoring at 7, showing a probable result.[9,10]

The general mechanism of hepatotoxicity is explained by several mechanisms, such as direct toxicity from the free radicals that directly damaging the liver tissues, genetic susceptibility, slow induction of the liver enzymes in metabolic pathway, and adaptive immune response due to exposure to the agent's reactive metabolite.[10,11] The mechanism of liver injury that caused by rifampicin originate from oxidative stress on mitochondria, cholestasis, and accumulation of fat cells in the liver. Rifampicin also known to interfere with the bilirubin excretion by inhibiting the bile salt exporter pump (BSEP). Isoniazid may initiate pathological process such as bridging and multi-lobular necrosis in the liver through metabolites called acetylhydrazine.[11,12] Despite the importance and widely usage of pyrazinamide, little is known about its mechanism of hepatotoxicity. It is both dose dependent and idiosyncratic.[12,13] Signs and symptoms of liver disease may occur in 15% of patients that given pyrazinamide, with jaundice in 2-3% of the patients, and death caused by severe liver necrosis in some cases reported.[11,13]

The most important step for treating DILI, is to withdraw the implicated agents or offending medications. Most cases of DILI spontaneously resolved with discontinuation

the causative agents, however in some cases due to the severity in liver injury, patient still worsening despite the discontinuation.[6,7,14] Patient's with concomitant jaundice should be kept under surveillance, and patients with signs or indication of acute liver failure, such as encephalopathy and coagulopathy should be hospitalized.[6] In our patient, jaundice was detected with loss of consciousness, indicating a encephalopathy. Coagulopathy was not detected. Patient immediately admitted and ATT was stopped. Several therapies are given in patient with DILI, such as N-acetylcysteine (NAC) to reduce the severity in liver injury and may improve survival in early acute liver failure. It has the effect of preventing progression to severe encephalopathy. Steroids are commonly prescribed, although there is still not enough randomized controlled trials to evaluate the efficacy and benefit of the therapy, as it demonstrated limited benefit.[6,7,12] UDCA are often used in cholestasis liver injury, but the benefits are still not well documented.[6,7] There is also limited data for the efficacy of hepatoprotective agents but it is often given as it believed to be beneficial.[6,15] In the case of drug-induced acute liver failure, liver transplantation should be taken into consideration as a definite therapy.[6] Aside from supportive therapy, our patient received all the recommended medication and also broad spectrum antibiotics for the lung infections. Regarding the liver injury, clinically patient showed improvement and there was notably decrease of ALP and total bilirubin levels. Unfortunately, patient fell into sepsis due to worsening of the lung infections that progressed into acute respiratory distress syndrome (ARDS) and ultimately death.

Overall, the prognosis of cholestatic injury tends to be better compared to hepatocellular injury, despite the cholestatic DILI is more likely to develop into chronic injury.[6,15] The cause of poor prognosis of this patient is multifactorial. The damage of the liver was severe as supported with the evidence of concomitant jaundice with significant elevations of ALP and bilirubin levels. They are contributing as factors that associated with poorer prognosis. Despite withdrawal of the medications and supportive treatment, the recovery rate of the liver injury was not able to exceed the lung infections rate that is happening simultaneously. The presence of lung infections acts as a burden in our patients' physique, creating a strain in the immune system and eventually failed. The presence of cholestasis also known to induce sepsis in several reported cases due to hypoxic hepatitis and impairment of bile transport, hence worsening the condition of the patient.[16] Due to the history of relapse case and slow recovery rate despite receiving ATT for 4 weeks, we suspected the possibility of drug resistant tuberculosis in our patient. Drug susceptibility test was negative but not eliminating the possibility of false negative. Sputum culture is still a superior method in this regard, unfortunately our isolate did not give remarkable result.

Further study and research are needed to support the definite guideline regarding DILI in the presence of active tuberculosis lung infections. Strategic and intensive therapy are required to tackle the complicated progression in this incidence. Nevertheless, preventing DILI is certainly readily than treating it. Prevention includes educating patients into the risk of such adverse events before and during taking the ATT. Patients should be warned about signs and symptoms that associated with hepatic injury. Screening for risk factors and routine liver test monitoring are steps that important to be taken among physicians. Early diagnosis and prompt treatment will result into better prognosis.

CONCLUSION

Anti-tuberculosis drug induced hepatotoxicity is a serious adverse effect and continue to contribute in mortality and morbidity of tuberculosis patient. Rifampicin, isoniazid, and pyrazinamide are known to have hepatotoxicity effect by producing reactive metabolites and modulating liver enzyme activity. DILI frequently occurs within the first 2 weeks to 8 weeks of treatment. It is important to screen for risk factors that may contribute in developing DILI in tuberculosis patient. RUCAM scale is helpful to assessing the causality of DILI. Identifying type of liver injury and recognizing signs of liver failure will aid in therapeutic strategy and predicting the prognosis of DILI. The presence of active infection will serve as a burden in the course of the disease, complicating the therapy and resulting in poorer prognosis. Education, close monitoring, and screening for risk factors are several preventive strategies that must be implied by physician towards tuberculosis patient. Early diagnosis, immediate withdrawal, and prompt treatment will result in better outcome of the disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64:e1.
2. World Health Organization. Global tuberculosis report 2021. Available at: https://www.who.int/tb/publications/global_report/en/. Accessed on 28 October 2019.
3. Kemenkes RI. Pedoman Nasional Pengendalian Tuberkulosis. Indonesia. 2021.
4. Gilpin C, Korobitsyn A, Migliori GB, Raviglione MC, Weyer K. The World Health Organization standards for tuberculosis care and management. Eur Respir J. 2018;51:1800098.
5. Abbara A, Chitty S, Roe JK, Ghani R, Collin SM, Ritchie A, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from

a large TB centre in the UK. BMC Infect Dis. 2017;17(1):231.
6. European Association for the Study of the Liver. Clinical Practice Guideline Panel: Chair. EASL Governing Board representative: EASL Clinical Practice Guidelines. Drug-induced liver injury. J Hepatol. 2019;70(6):1222-61.
7. Chalasani NP, Maddur H, Russo M, Wong RJ, Reddy KR. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol. 2021;116(5):878-98.
8. Devarbhavi H, Singh R, Patil M, Sheth K, Adarsh CK, Balaraju G. Outcome and determinants of mortality in 269 patients with combination anti-tuberculosis drug-induced liver injury. J Gastroenterol Hepatol. 2013;28(1):161-7.
9. Danan G, Teschke R. Roussel Uclaf Causality Assessment Method for Drug-Induced Liver Injury: Present and Future. Front Pharmacol. 2019;10:853.
10. Suk KT, Kim DJ. Drug-induced liver injury: present and future. Clin Mol Hepatol. 2012;18(3):249-57.
11. Soedarsono S, Riadi ARW. Tuberculosis Drug-Induced Liver Injury. Jurnal Respirasi. 2020;6(2):49-54.
12. Zhao H, Wang Y, Zhang T, Wang Q, Xie W. Drug-Induced Liver Injury from Anti-Tuberculosis Treatment: A Retrospective Cohort Study. Med Sci Monit. 2020;26:e920350.
13. Hassan A, Fontana RJ. The diagnosis and management of idiosyncratic drug-induced liver injury. Liver Int. 2019;39(1):31-41.
14. Ramappa V, Aithal GP. Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. J Clin Exp Hepatol. 2013;3(1):37-49.
15. Chang KC, Leung CC, Yew WW, Lau TY, Tam CM. Hepatotoxicity of pyrazinamide: cohort and case-control analyses. Am J Respir Crit Care Med. 2008;177(12):1391-6.
16. Ghenu MI, Dragoş D, Manea MM, Ionescu D, Negreanu L. Pathophysiology of sepsis-induced cholestasis: A review. JGH Open. 2022;6(6):378-87.

Cite this article as: Theodora A, Suryana K. Cholestatic drug induced liver injury in active pulmonary tuberculosis patient: a case report. Int J Adv Med 2022;9:946-50.