

Drug Induced Liver Injury, Fulminant Hepatic Failure and Tuberculosis on 15 Year Old Girl: A Case Report

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Abstract

Drug Induced Liver Injury (DILI) in children accounts for 1% of all reported drug adverse reactions, and approximately 20% of all cases of acute liver failure in children. Acute decline in liver function without a history of liver disease accompanied by hepatic encephalopathy is defined as Fulminant Hepatic Failure (FHF). Viruses, drugs, toxins, and various conditions such as cardiovascular and metabolic diseases can cause FHF. Hepatotoxicity associated with anti-Tuberculosis (TB) drugs has been reported in 5%-28% of people treated with anti-TB drugs. We present a case of a 15-year old girl with DILI, FHF and TB. Consumption of anti-TB drugs cause hepatocellular DILI which then lead to FHF. Patient was successfully treated and can finished 6 months TB treatment without any complaint after re-challenged.

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INTRODUCTION

Drug Induced Liver Injury (DILI) has high incidence and can be caused by several medicine factors. Discontinuation of the suspecting agent immediately will prevent the development of liver disease.¹ FHF is a rare clinical syndrome, about 2000 cases each year in United States. FHF define as hepatic encephalopathy in a patient with liver disturbance and without any history of liver disease.² Anti-Tuberculosis therapy (ATT)—associated acute

liver failure (ATT-ALF) count as the most frequent ALF caused by drugs especially in South Asia. Mortality rate of ATT-ALF is high (67,1%) and only 32,9% of patients were recovered.³ Tuberculosis is a re-emerging disease and become health problem in developed countries and developing countries including Indonesia.⁴ Data from the World Health Organization (WHO) in 2014 stated that there were 9 million new TB cases, equivalent to 126 cases per 100,000 population where 56% of cases occurred

in Asia and 550,000 cases occurred in children.⁵ Indonesia at 5th position after India, China, Nigeria and Pakistan as the highest TB incidences in the world.⁶ Hepatotoxicity is the most common side effects of TB treatment and needs immediate discontinuation.⁷ In general, hepatotoxicity associated anti-TB drugs reported in 5-28% patients.⁸

CASE REPORT

On July 2019, a 15 year and 4 month old girl referred to dr. Kariadi Hospital Semarang from regional hospital in Kudus because of drug induced hepatitis and peritonitis tuberculosis. Two weeks before hospitalization she was diagnosed as peritonitis tuberculosis based on abdominal pain, ascites and thickening of the intestinal wall from abdomen sonog raphy result, positive tuberculin skin test and suggestive tuberculosis from chest x-ray.



Figure 1. Chest x-ray: suggestive tuberculosis.

She got anti-TB drugs as fixed drugs combination (FDC) intensive phase for adult, 3 tablets each day. Each tablet consist of isoniasid 75 mg, rifampisin 150 mg, pirazinamid 400 mg, and etambutol 275 mg. Liver function test before TB treatment was normal: total bilirubin 0,4 mg/dL, direct bilirubin 0,14 mg/dL, indirect bilirubin 0,26 mg/dL, AST 22 U/L, ALT 11 U/L and HBsAg negative. She has complete immunization. She was studying in the 9th grade Islamic boarding school. From family history, her father and her grandmother received 6 months treatment for tuberculosis when she was 3 year old. Her father already did sputum examination 2 days before her hospitalization and the result was negative. She lived with her parent, sister, and grandmother in a *joglo* type house (Java traditional house). House size is 9 x 13 meters. Every bedroom except grandma's room has one small window. Sunlight enters rooms only through small windows and rooms tend to be dark when the lights are turned off. There are no ventilation above the windows and doors.

She was admitted in regional hospital because of vomiting, lethargic and yellow skin. Laboratory examination revealed AST 1106 U/L, ALT 446 U/L. She got omeprazole and ursodeoxycholic acid tablets. After 3 days of hospitalization she referred to dr. Kariadi Hospital Semarang.

She came in somnolence condition, disorientation, nausea, yellowish skin, icteric sclera, abdomen was flat, positive epigastric pain, hepatomegaly 2 cm bellow arcus costalis, no asterixis /hyper-reflex and no tremor. She was diagnosed as suspect hepatic encephalopathy, DILI and Tuberculosis. She got methylprednisolone injection 1 mg/kgBB/day, omeprazole injection and ursodeoxycholic acid tablets, and stop anti-TB drugs. She moved to high care unit. Liver function test revealed AST 2865 U/L, ALT 1045 U/L, ALP 190 U/L, Gamma GT 92 U/L, total bilirubin 6,01 mg/dL, direct bilirubin 4,25 mg/dL, indirect bilirubin 1,76 mg/dL, albumin 3,0 g/dL, lactic acid 2,7 mmol/L, IgM anti HAV negative, anti HCV negative, Plasma Prothrombin Time 2,1 times, Partial Tromboplastin Time 1,66 times. Abdomen sonography showed ascites and mild hepatomegaly. She was diagnosed

as Fulminant Hepatic Failure, and was given vitamin K injection for 3 days. At fourth days of hospitalization she became fully conscious and moved to regular ward. Laboratory examination revealed AST 92 U/L, ALT 518 U/L, Sodium 135 mmol/L, Potassium 3,9 mmol/L; Chloride 97 mmol/L, Calcium 2,0 mmol/L; total bilirubin 3,2 mg/dL; direct bilirubin 2,5 mg/dL; indirect bilirubin 0,7 mg/dL, Plasma Prothrombin Time 0,9 times, Partial Tromboplastin Time 1 times, TB gene expert from sputum was negative. At seventh days of hospitalization methylprednisolone was tapered off to 0,7mg/kgBB/day orally and she was discharged.

In the outpatient clinic after four days she has no complaint, no hepatomegaly. Liver function test revealed AST 56 U/L, ALT 201 U/L, total bilirubin 1 mg/dL, direct bilirubin 0,8 mg/dL, indirect bilirubin 0,2 mg/dL. Anti-TB drugs was started; INH 300mg/day, Rifampicin 450mg/day, vitamin B6 20 mg/day, and methylprednisolone was tapered off to 0,4 mg/kgBB/day for one week then stopped. One week later AST 32 U/L, ALT 74 U/L, then Pirazinamide 1000mg/day was added. After two weeks AST 59 U/L, ALT 62 U/L. Three weeks later ethambutol 800mg/day was added. Five weeks later, AST 43 U/L, ALT 43 U/L, she got fixed drugs combination (FDC) intensive phase for adult, 2 tablets each day and vitamin B6 20 mg/day. At seven weeks AST 44 U/L, ALT 58 U/L, FDC dosage was increased to 3 tablets each day. She received maintenance TB treatment and after 6 months was stopped without any complaint.

DISCUSSION

Children DILI (cDILI) happens less than 10% from all DILI cases and 20% from all acute liver failure in children.⁹ DILI is a diagnosis per-exclusionam so need to exclude other causes like hepatitis virus.¹ Criteria from British Thoracic Society (BTS) for DILI is ALT or AST > 200 IU/L with bilirubin increase.¹⁰ To classify which types of DILI, need to calculate R score. Formula for R score is serum (ALT/ALT ULN) : (Alkali phosphatase/ alkali phosphatase ULN). Hepatocellular DILI if $R \geq 5$. Mixed DILI if $2 < R < 5$. Cholestatic DILI if $R \leq 2$.¹¹ Patient's R score was 12,4

($R \geq 5$) classified as hepatocellular DILI.

Abbara's study showed that 53% of cases appeared within 2 weeks of starting anti-TB drugs like this patient, and 87.6% occurred within 8 weeks, so that all patients receiving anti-TB drugs should have universal liver function monitoring within the first 8 weeks of therapy.¹² Next step is discontinue anti-TB drugs until LFT within normal limit and start re-challenge.

BTS management protocol to re-challenge anti-TB drugs after ALT in normal limit is first give streptomycin and ethambutol (if unwell or sputum is smear-positive within 2 weeks of commencing treatment), then isoniazide (dose titration, every 2-3 days), then rifampicin (dose titration, every 2-3 days), then pyrazinamide (dose titration, every 2-3 days). Daily LFT monitor and stop offending drug, alternative regimen advised by fully trained physician.¹¹ In this patient, anti-TB drugs was started by administering isoniazide 8 mg/kg and rifampicin 12 mg/kg and evaluate AST and ALT every week. No increase in AST and ALT after one week, then pyrazinamide 27 mg/kg was added. AST and ALT was evaluated after one week. Then ethambutol 22 mg/kg was added. After two weeks there was no increase in AST and ALT, so anti-TB drugs became 2 tablets of adult FDC intensive phase per day. Two weeks later there was no increase in AST and ALT, the FDC dose was increased to 3 tablets per day.

The prognosis of cDILI is controversial. In the United States the cure rate for cDILI is high and the mortality rate is only 4%, but a high mortality rate of 31% is found in India. Hepatocellular type is dominant in cDILI, which is the same type with this patient.¹³

Fulminant Hepatic Failure (FHF) is defined as hepatic encephalopathy with acute liver damage without a history of liver disease. Viruses, drugs, toxins, and various conditions such as cardiovascular and metabolic diseases are the main causes of FHF.¹⁴ Three classification of FHF are hyper-acute liver failure, acute liver failure, and sub-acute liver failure. Hyper-acute liver failure if hepatic encephalopathy appeared in 7 days after onset of icterus. Acute liver failure (ALF) if hepatic encephalopathy appeared

in 8 until 28 days. Sub-acute liver failure if hepatic encephalopathy appeared in 5 until 12 weeks after onset of icterus. These definition is not always suitable for children because difficulty of defining the onset of hepatic encephalopathy especially for babies. So, Pediatric Acute Liver Failure Study Group (PALFSG) consensus defined ALF in children as biochemical evidence of liver damage and no history of chronic liver disease, coagulopathy not corrected by vitamin K administration, and International Normalized Ratio (INR) greater than 1.5 if the patient has encephalopathy, or greater than 2.0 if the patient does not have encephalopathy. The patient has hepatic encephalopathy and INR level 2,1. There are four levels of hepatic encephalopathy. She came with somnolence condition, disorientation, no asterixis / hyper-reflex and no tremor; categorized as first level hepatic encephalopathy.

Survival rate of ALF patients correlate with level of encephalopathy. Survival rate is 60% for first level of encephalopathy and became 5-25% for fourth level of encephalopathy. Cerebral edema frequently happens in FHF patient, with incidence rate 45%. Cerebral edema become major factor for morbidity and mortality. Papilledema is usually absent in patients with FHF and cerebral edema, in contrary to cerebral edema from other causes.¹⁵ Eye examination on July 28th, 2019 revealed no papilledema. She did not undergo a head MSCT. The most important management for FHF patient is supportive treatment like respiratory stabilization, fluid, electrolyte, glucose, and intracranial pressure to prevent respiratory distress, hypoglycemia, seizure. Liver transplantation can be considered for better outcome and increase 5 years survival rate.¹⁵

Diagnosis of tuberculosis is difficult in children. The clinical manifestations generally resemble other diseases and sometimes are not specific. The definite diagnosis of TB is by finding the Mycobacterium tuberculosis. TB in children is pauci-bacillary and low production of sputum. The Indonesia National TB eradication program offered a scoring system to diagnose TB in children in limited facilities.^{16,17,18} TB scoring system consist of; contact history, tuberculin

skin test, nutritional state, fever ≥ 2 weeks, cough ≥ 2 weeks, lymphadenopathy, swollen in bone/joint, and chest x-ray. Diagnosis of TB if total scores ≥ 6 . In the better health facilities, microbiology examination of *acid fast bacilli (AFB) in sputum should be done*.¹⁹ This patient has history of unexplained fever ≥ 2 weeks. The result of sputum smear staining was negative. Result of the gene expert MTB was not detected. Total TB scoring is seven; has contacts with TB AFB (-) / unclear AFB (2), positive tuberculin test (3), good nutritional status (0), history of unexplained fever ≥ 2 weeks (1), no history of cough (0), no enlarged lymph nodes (0), no joint swelling (0) and chest X-ray results are suggestive of TB (1). The diagnosis for this patient is clinical TB. She also diagnosed as peritonitis tuberculosis based on abdominal pain, ascites and thickening of the intestinal wall from abdomen sonography result. She got anti-TB drugs for 6 months after re-challenged, and so far no DILI was found.

CONCLUSION

A 15 year old girl with Drug Induced Liver Injury related to anti-TB drugs, and Fulminant Hepatic Failure was successfully treated and can finished 6 months TB treatment after re-challenged.

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