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Case Report

Coincidence of drug induced liver injury and cholecystitis on human immunodeficiency virus patient with anti-tuberculosis treatment

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ABSTRACT

Tuberculosis (TB) is a serious health problem. Anti-TB treatment has good efficacy, but in some cases side effects can occur that can affect medication adherence and development of drug resistance. One of the serious side effects of anti-TB treatment is drug induced liver injury. We reported the case of a 56 year old male patient with TB-HIV confection who developed symptoms of hepatotoxicity after 3 weeks of intensive phase of anti-TB treatment.

Keywords: Drug induced liver injury, Tuberculosis, HIV, Cholecystitis

INTRODUCTION

Liver is center of metabolism of xenobiotics that enter the gastrointestinal tract and susceptible to the harmful effects of many drugs, herbs or dietary supplements.[1,2] More than 900 drugs, toxins and herbs have been identified to cause liver damage. Approximately 20-40% of all cases of fulminant liver failure are due to drugs and even 75% of idiosyncratic drug reactions are related to liver transplantation or death.[3] Incidence of drug-induced liver injury is estimated at 14 to 19 cases per 100,000 people. Approximately 3% to 5% of patients treated with jaundice are due to drug induced liver injury.[2] In western countries, hepatotoxicity is the leading cause of acute liver failure and was associated with 32% of drug withdrawals from the market between 1975-2007.[1,2]

TB is a serious global health problem because of its high incidence, problem of drug resistance and confection. According to the WHO in 1993, it was estimated that there were 7 million to 8 million new cases of tuberculosis with 1.3-1.6 million deaths each year. Meanwhile, in 2010 it is estimated that new cases of tuberculosis reached 8.8 million cases with a mortality rate of 1.4 million deaths.[4] There are several side effects that can occur during anti-tuberculosis treatment such as hepatotoxicity, skin reactions, gastrointestinal and neurological disorders cause morbidity thereby reducing the effectiveness of therapy.[4]

TB treatment regimens such as a combination of isoniazid, rifampicin, pyrazinamide and ethambutol are often associated with drug-induced liver injury (DILI) thereby promoting treatment non-adherence, treatment failure or the development of drug resistance.[5] DILI associated with anti-tuberculosis treatment is reported to occur in 2% to 28% of patients. Risk factors for DILI on anti-tuberculosis treatment include coinfection with HIV, hepatitis B or hepatitis C, pre-existing chronic liver disease, high alcohol consumption, malnutrition, old age, female sex and slow acetylators.[6]

In this case report, we described HIV-positive patient with pulmonary TB who received anti-TB drugs and showed symptoms of hepatotoxicity.

CASE REPORT

A 56 year old male patient came to the hospital with complaints of general weakness and jaundice since from 3 days ago accompanied with nausea and vomiting. Initially the patient complained of wet cough since from 2 months ago accompanied by night sweats, recurrent fever in the

last 2 months without obvious cause and weight loss about 15 kg (weight loss from 60 kg to 45 kg) in the last 6 months. History of suffering from TB or contact with TB patients was denied. Then the acid-fast bacteria test was carried out at primary health care and the results were positive pulmonary TB so that patient given category 1 anti-TB treatment. History of chronic diarrhoea for the last 3 months, history of suffering from HIV, history of malignancy and history of drug or food allergies was denied. History of consumption of drugs or herbs other than anti-TB drugs in the last 1 month was denied. Physical examination revealed that the patient looked thin with compos mentis consciousness. The patient's weight was 45 kg and the height was 160 cm (BMI=17.58).

Vital signs examination found patient blood pressure 110/70 mmHg, pulse 80 beats per minute, respiratory rate 20 times per minute, temperature 36.5°C and oxygen saturation 98% on room air. Eye examination revealed icteric sclera with no sign of pale conjunctiva. From oral cavity examination, we found oral candidiasis. Examination of the neck, we didn't find enlarged lymph nodes. Physical examination of the lungs revealed vesicular breath sounds without additional breath sounds, while physical examination of the heart was found to be within normal limits. Abdominal examination revealed no tenderness, liver and spleen were not palpable. We didn't find oedema from extremities examination. Complete blood count was within normal limits (haemoglobin 16.4 g/dl, leukocyte count 6.01×103 /µl, platelet count 326×103 /µl). Liver function test revealed elevation of alanine aminotransferase (ALT) 273 mg/dl, aspartate aminotransferase (AST) 216 mg/dl, total bilirubin 22.89 mg/dl, direct bilirubin 16.9 mg/dl, indirect bilirubin 5.99 mg/dl, gamma GT 96 U/l while alkaline phosphatase (ALP) was within normal limits of 85 U/l. Total protein test, revealed a slight decrease 5.4 g/dl (albumin 2.6 g/dl; globulin 2.8 g/dl). We also tried to exclude the possibility of jaundice caused by viral hepatitis with anti-HCV and HBsAg tests both of test show negative result. Examination of renal function revealed blood urea nitrogen 112 and creatinine serum 1.4 mg/dl. Examination of serum electrolytes revealed decreased levels of sodium (117 mmol/l) and chloride (91 mmol/l) while potassium levels increased (5.9 mmol/l).

Examination of blood sugar obtained was 67 mg/dl.

Based on the patient's clinical features such as oral candidiasis, weight loss with pulmonary TB infection, we did an HIV test. The result was HIV positive. A chest X-ray examination revealed the lungs and heart were within normal limits. Abdominal ultrasound examination revealed cholecystitis with other abdominal organs were found within normal limits. Based on the anamnesis and laboratory finding, we suspected this patient have drug induced liver injury related to first line anti-tuberculosis drugs, so we temporarily discontinued the tuberculosis medication.

We administered 3% sodium chloride infusion to treat the patient's hyponatremia. We also gave dextrose 40% infusion, rapid acting insulin (glulisin) 20 IU, calcium gluconate and salbutamol nebulizer to treat patient's hyperkalemia and hypoglycemia. We also provided patient with ursodeoxycholic acid, curcuma, esomeprazole, ondancetron, cefoperazone and n-acetylcysteine. Our evaluation of AST, ALT and bilirubin continued to show significant decrease. On the 12th day of treatment, ALT decreased to 44 mg/dl, AST decreased to 45 mg/dl, total bilirubin decreased to 4.02 mg/dl, direct bilirubin decreased to 3.3 mg/dl and indirect bilirubin decreased to 0.72 mg/dl (Table 1).

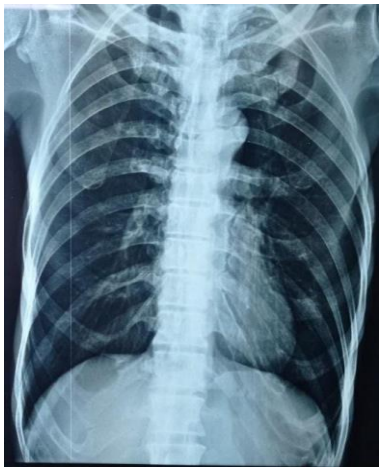

Figure 1: AP chest X-ray, heart and lungs within normal limits.

Table 1: Clinical laboratory data.

Laboratory data	Normal range	September 11th	September 14th	September 17th	September 18th	September 22th
ALT	0-42	273	143	71	-	44
AST	0-37	216	110	53	-	45
Albumin	3.8-5.1	-	-	-	2.6	2.6
Globulin	2.3-3.5	-	-	-	2.8	2.6
Total protein	6.6-8.7	-	-	-	5.4	5.2
Total bilirubin	0.2-1	22.89	17.0	10.44	-	4.02
Direct bilirubin	0.1-0.4	16.9	12.80	8.4	-	3.3
Indirect bilirubin	-	5.99	4.20	2.04	-	0.72

Continued.

Laboratory data	Normal range	September 11th	September 14th	September 17th	September 18th	September 22th
ALP	53-128	-	-	-	85	95
Gamma GT	11-61	-	-	-	96	96

DISCUSSION

TB is a chronic infection caused by the bacterium *Mycobacterium tuberculosis*. Tuberculosis bacteria most often infect the lungs, but other organs such as the kidneys, spine, and brain, skin can also be infected.[7] TB is one of the highest contributors to death from curable infectious diseases. In 2004 there were 9 million new cases of TB and caused 1.7 million people died.[8]

The first line TB treatment regimen consisted of 2 phases, an intensive phase for 2 months with a combination of isoniazid, rifampicin, pyrazinamide and ethambutol followed by continuation phase for 4 months with a combination of isoniazid and rifampicin.[7] The most common side effects in anti-TB treatment are hepatotoxicity, skin reactions, gastrointestinal and neurological disorders. Hepatotoxicity is the most serious side effect. Hepatotoxicity can be fatal if not recognized early and therapy was not discontinued in time.[8] Isoniazid, rifampicin and pyrazinamide are known to have hepatotoxicity effect, but pyrazinamide has a higher percentage of drug-induced liver toxicity than other drugs.[7]

DILI is an exclusion diagnosis based on history, laboratory examination, hepatobiliary imaging and liver biopsy. From the anamnesis, it was necessary to obtain a history of chronic ethanol consumption, a history of viral hepatitis, a history of previous liver disease, a history of pregnancy or postpartum in the last 3 months, a history of using hepatotoxic drugs, a history of ALT or previous abnormal bilirubin. Symptoms like nausea, vomiting, abdominal pain, jaundice and unexplained fatigue needed to be explored to determine the possibility of hepatotoxicity.[9,10]

DILI classified into intrinsic and idiosyncratic. Intrinsic DILI is usually dose related, occurred in most individuals exposed to the drug and had a short onset of time (hours to days). Idiosyncratic DILI was usually not dose related (remaining need dose threshold 50-100 mg/day), occurred in only a small proportion of exposed individuals and had longer onset (days to weeks). Anti-TB drugs such as isoniazid and pyrazinamide were often associated with the development of idiosyncratic DILI.[9,11] Below we presented type of drug induced liver injury according to European association for the study of the liver (EASL) and American college of gastroenterology (Table 2).

Based on the American college of gastroenterology criteria of DILI, patient in this case had R value of 9.6 which indicated hepatocellular DILI. Based on EASL criteria, the ALT was found to be 273 mg/dl, meaning that there was an elevation of ALT more than 5 times from the upper limit of the normal value, thus supporting the diagnosis of hepatocellular DILI. Abdominal ultrasound examination we found cholecystitis. Based on laboratory finding and imaging test we diagnosed the patient as DILI hepatocellular type coincidence with cholecystitis.

Approximately 11.5% of patients with TB and HIV coinfection who received anti-TB treatment had hepatotoxicity. Most of the incidence of hepatotoxicity occurred on the intensive phase of treatment. The first eight weeks of anti-TB treatment was a critical period that required careful monitoring for signs of hepatotoxicity. Disseminated pulmonary tuberculosis and low BMI were known to be independent predictors of anti-TB drug-induced hepatotoxicity.[10] How TB and HIV coinfected patients have an increased risk of hepatotoxicity due to anti-TB drugs was still a matter of debate. However, it was known that HIV/AIDS patients with acute illness had oxidative pathway activity which increased the risk of anti-TB drug-induced hepatotoxicity.[8]

The most important step in the management of DILI was discontinuing the precipitating agent. Usually, resolution of DILI occurred within days to weeks after discontinued exposure of causative agent. However in some case, improvement may not occur immediately and worsening of liver injury persisted even after the offending agent was discontinued can occur.[1]

Isoniazid and rifampicin had good efficacy in the treatment of latent TB infection and active TB infection. However, the combination both of drugs carried a risk of triggering DILI. Tuberculosis patients with hepatic impairment (serum alanine aminotransferase more than 3 times the normal value) should consider treatment modification. The more severe the liver damage, the less hepatotoxic anti-TB drug regimens that can be used (Table 3).[5]

Table 2: Type of drug induced liver injury.

Type of injury	Descrption
European Association for the study of the liver	Elevation of ALT ≥5 times from ULN
	Elevation of ALP ≥2 times from ULN (especially if accompanied by an increase in gamma-glutamyltransferase (GGT) in the absence of a cause for bone pathology)
	Elevation of ALT ≥3 times ULN and a simultaneous increase in the total bilirubin concentration exceeding 2 times ULN

Continued.

Type of injury	Descrption
There are three types of idiosyncratic DILI: hepatocellular, cholestatic and mixed type.	Hepatocellular liver injury: elevation of ALT alone 5 times or higher or when the ratio of serum activity of ALT to ALP is 5 or more
	Cholestatic liver injury: elevation of ALP alone 2 times or higher or when the ratio of serum activity of ALT to ALP is 2 or less
	Mixed liver injury: ratio of the serum activity of ALT to ALP is between 2 and 5
ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury	The R value was defined as serum alanine aminotransferase/upper limit of normal (ULN) divided by serum alkaline phosphatase/ULN
	R value ≥5 (hepatocellular)
	2<R value <5 (mixed)
	R value ≤2 (cholestatic)

Table 3: Anti-TB drug regimen for liver injury case

Anti-TB regimen
Two hepatotoxic drug regimens
9 months isoniazid and rifampicin, plus ethambutol
2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin
6-9 months rifampicin, pyrazinamide and ethambutol.
One hepatotoxic drug regimen
2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.
No hepatotoxic drug regimen (example in patients with advanced cirrhosis or portosystemic encephalopathy)
18-24 months of treatment with a combination of ethambutol, fluoroquinolones, cycloserine and capreomycin or an aminoglycoside

Apart from discontinuing exposure to the triggering agent, there were several specific drugs intended for the treatment of DILI. Cholestyramine in cases of DILI due to leflunomide and terbinafine, N-acetylcysteine used in cases of acetaminophen overdose, l-carnitine used in cases of DILI due to valproic acid, corticosteroids used in drug-induced autoimmune hepatitis.[12]

A prospective pilot study to evaluate the hepatoprotective efficacy of oral UDCA in patients with TB and drug-induced liver injury concluded that UDCA administered orally in TB patients may reduce hepatotoxicity effect induced by first-line anti-TB drugs.[13] Liver had an important role in glucose homeostasis. There were three processes of circulating glucose in the body. Absorption in the gastrointestinal tract, glycogenolysis and gluconeogenesis. The liver played a role in regulating blood glucose levels through the processes of glycogenolysis and gluconeogenesis. Extensive damage to the liver (more than 80% of the liver mass) can lead to glucopenia, especially fasting hypoglycemia.[14]

In general, there were 2 types mechanism of hypoglycemia. The first mechanism was hypoglycemia hyperinsulinemia and the second was hypoglycemia hyperinsulinemia. Hypoglycemia hyperinsulinemia occurred with administration oral hypoglycemic agents or excessive use of insulin. In this mechanism, hypoglycemia was caused by over-acting insulin. Meanwhile, hypoglycemia hypoinsulinemia was caused by a decrease in glycogenolysis and gluconeogenesis so that blood glucose levels tend to be low. In severe malnutrition patients, there was failure of gluconeogenesis due to low hepatic glycogen stores.[15] Hypoglycemia in this case appeared to be associated with patient's low BMI.

Clinical presentations of DILI were typically indistinguishable from acute biliary events such as cholelithiasis, acute cholecystitis and cholangitis. Acute biliary event developed in 0.12% of patient who received anti-TB treatment. Incorrect diagnosis of acute biliary event may delay anti-TB treatment or lead to complications, such as sepsis, acute pancreatitis or perforation.[16]

Patients with acute biliary event during anti-TB treatment may have asymptomatic cholelithiasis before treatment. Anti-tuberculosis drug such as isoniazid and rifampicin can inhibit the bile salt export pump and cause accelerate the formation of cholesterol stone.[16]

CONCLUSION

This case report discusses a 56 year old male patient with HIV/TB coinfection in the lungs. After 3 weeks of receiving anti-TB treatment category 1 intensive phase the patient showed symptoms of hepatotoxicity. From abdominal ultrasound we find cholecystitis. Based on the patient's clinical presentation, we diagnosed hepatocellular type DILI coincidence with cholecystitis. We discontinued administration of first line of anti-TB drugs and administer antibiotic and UDCA. After 12 days of treatment ALT, AST, bilirubin decreased significantly. Based on these findings, co-infected patients with TB/HIV with low BMI should be closely monitored for possible liver injury induced by anti-TB drugs. Ursodeoxycholic acid may have

the effect of improving liver function in DILI induced by first line anti-TB treatment.

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