Case Report

The First Report of Two Cases of Fatal Liver Injury Due to Anti-tuberculosis Drugs in the Presence of Alpha-1 Antitrypsin Deficiency

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Abstract

Tuberculosis (TB) is a major global health problem. Awareness of liver injury due to anti-TB therapy is vital because fulminant hepatic failure is a devastating and often fatal condition without liver transplantation. Here, we report for the first time, two patients of fatal liver injury due to anti-TB drugs in the presence of alpha-1 antitrypsin deficiency. Based on the triad of rapid loss in hepatocyte function, the onset of hepatic encephalopathy, and absence of a prior history of liver disease, the diagnosis of acute liver failure was established. Both patients had low levels of serum alpha-1 antitrypsin, consistent with alpha-1 antitrypsin deficiency. Despite aggressive medical therapy and supportive care, patients developed multi-organ failure and died. It seems measuring the serum levels of alpha 1-antitrypsin before beginning anti-TB therapies is necessary, especially when there is emphysema or bronchiectasis.

Keywords: Alpha1-antitrypsin deficiency, anti-tuberculosis drugs, death, hepatitis

Introduction

Tuberculosis (TB) is a major global health problem. In 2014, there were an estimated 9.6 million new TB cases: 5.4 million among men, 3.2 million among women, and 1.0 million among children.[1] Although most patients with TB are successfully treated, hepatotoxicity is the most severe side-effects leading to drug termination in patients treated with anti-TB drugs. In addition, hepatotoxicity due to first-line anti-TB medications is common among the Asian and African population.[2,3]

Most of the hepatotoxic reactions induced by anti-TB drugs are dose-related; some are, however, caused by drug hypersensitivity. The underlying mechanism of anti-TB drug-induced hepatotoxicity is not clearly understood. The main risk factors for liver toxicity include the older age, female gender, malnutrition, chronic high alcohol intake, human immunodeficiency virus status, concomitant Infection, chronic liver disease, chronic hepatitis B and C infections, severe pulmonary diseases, hypoalbuminemia at the outset of the treatment, acetylator status, and nutritional status.[4-6]

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Here, we report two patients of fatal liver injury due to first-line anti-TB drugs in Iran. Interestingly, both patients had alpha-1 antitrypsin deficiency. To the best of our knowledge, this is the first published report of fatal liver injury due to anti-TB drugs in the presence of alpha-1 antitrypsin deficiency.

Case Reports

Case 1

A 63-year-old male was admitted to our hospital with complaints of cough and dyspnea for the past 3 months. He had been experiencing fever, cough, sputum, exertional dyspnea, night sweats, weight loss of 4 kg, and loss of appetite for 2 months before his admission. The patient had a smoking history of 30 pack-years. On general examination, the patient

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was ill with a blood pressure 120/75 mmHg, respiratory rate 24 breaths/min, pulse rate of 104 beats/min, temperature of 39.1°C, and the oxygen saturation 88%. Respiratory examination revealed bilateral coarse crackles and wheezes. Initial laboratory data are summarized in Table 1.

The chest radiograph showed a loss of volume in the right lung, reticulonodular opacities with honeycombing in the right upper lobe and tracheal shift toward the right side; this observation was considered to be old TB along with pulmonary fibrosis. An echocardiogram revealed evidence of cor pulmonale, including pulmonary hypertension with mild tricuspid regurgitation. His tuberculin skin test had 20 mm of induration at 48 h. Sputum was negative for acid-fast bacilli smear. Since the patient had a fever, dyspnea, and poor general condition, the diagnosis of smear-negative TB was made. Our patient was then treated with anti-TB medication with combination film-coated tablets containing 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol hydrochloride in addition to 40 mg Vitamin B6, Atrovent®, and Seretide® inhalers. The patient's general condition gradually improved within 7 days, and he was no longer dependent on oxygen and was therefore discharged from the hospital.

Forty-two days after discharge, the patient went to the emergency room and was readmitted with complaints of nausea, icterus, and loss of appetite. On admission, physical examination revealed that he was febrile and had bilateral coarse crackles and wheezes at the lungs. Laboratory investigations are summarized in Table 1. The serum alpha-1 antitrypsin concentration was 74 mg/dL (reference values: 109–261), consistent with alpha-1 antitrypsin deficiency. A computed tomography (CT) scan of the chest demonstrated evidence of pulmonary fibrosis in the right upper lobe and bilateral lower-lobe-predominant emphysema. His abdominal ultrasound showed mild ascites. Thirty-one days later, he developed hepatic encephalopathy.

Based on the triad of the rapid loss in hepatocyte function (jaundice, coagulopathy, and ascites), onset of hepatic encephalopathy, and absence of a prior history of liver disease, the diagnosis of acute liver failure (ALF) was established. All his medications were promptly discontinued and the supportive treatment was started with lactulose syrup at a dose of 30 mL orally every 3 h, fresh frozen plasma (FFP) transfusion as needed, empiric antimicrobial coverage (imipenem/cilastatin 500 mg intravenously every 6 h), nutritional support (a low-fat

Table 1: The results of para-clinical manifestations at the time of admission

Para-clinical findings	Normal ranges	First case	Second case
WBC (/μL)	4500-10,000	11,800	14,300
Hemoglobin (g/dL)	13.5-17.5	16.5	14.4
Platelet count (/μL)	150,000-450,000	198,000	517,000
ESR (mm/h)	0-22	12	5
ALT (IU/L)	7-56	1341	615
AST (IU/L)	10-40	1217	1299
ALP (IU/L)	44-147	523	432
GGT (U/L)	0-45	60	135
LDH (IU/L)	140-280	1278	1546
Amylase (U/L)	23-85	52	47
Fasting plasma glucose (mg/dL)	<100	97	110
Total bilirubin (mg/dL)	0.3-1.9	28.9	11.2
Direct bilirubin (mg/dL)	0-0.3	19.8	7.2
Uric acid (mg/dL)	3.4-7.0	3.8	9.6
PT (s)	11-13.5	31	30
INR	0.8-1.1	5.9	6
Creatinine (mg/dL)	0.6-1.2	0.5	0.4
Sodium (mEq/L)	135-145	132	131
Potassium (mEq/L)	3.5-5	3.4	3.5
Albumin (g/dL)	3.5-5.5	2.8	2.6
TSH (uU/mL)	0.5-6	3.1	6.9
HBsAg	Negative	Negative	Negative
HBcAb	Negative	Negative	Negative
HCV antibody	Negative	Negative	Negative
Hepatitis A IgM antibody	Negative	Negative	Negative
HIV-1/HIV-2 antibody	Negative	Negative	Negative
Serum alpha 1-antitrypsin (mg/dL)	109-261	74	65.1

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transpeptidase, LDH: Lactic acid dehydrogenase, PT: Prothrombin time, INR: International normalized ratio, TSH: Thyroid-stimulating hormone, HBsAg: Hepatitis B surface antigen, HBcAb: Hepatitis B core antibody, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

and low-protein diet), and serum glucose control (5% dextrose solution). Given his severe cor pulmonale and oxygen dependence, he was managed medically as he was not the candidate for liver transplantation. Despite aggressive medical therapy and supportive care, patient developed multi-organ failure and died.

Case 2

A 33-year-old male was hospitalized with complaints of nausea, vomiting, icterus, and fever in the past week. His medical history indicated that he had been diagnosed with diabetes insipidus for 10 years ago and asthma for 5 years ago. Forty-five days before his hospitalization, the patient received four-drug anti-TB therapy with combination film-coated tablets, due to smear-positive TB. On physical examination, the temperature was 38.6°C, the blood pressure 100/65 mm Hg, the pulse 98 beats/min, the respiratory rate 22 breaths/min, and the oxygen saturation 94%.

Three successive samples of sputum were positive for *Mycobacterium tuberculosis*. The serum alpha-1 antitrypsin concentration was 65.1 mg/dL (reference values: 109-261), consistent with alpha-1 antitrypsin deficiency. Chest CT scanning revealed the spread of paraseptal emphysema and destruction of the left lung as well as the numerous cavities in the apex of the left lung. Based on the criteria of sudden loss of hepatic function, altered metal status, and absence of preexisting liver disease, the diagnosis of ALF was confirmed.

The patient underwent supportive treatment with lactulose syrup, FFP transfusion as needed, empiric antibiotic, nutritional support, and serum glucose control. Due to active TB, liver transplantation was not given priority. Six days later, despite the reduced serum levels of liver enzymes, the patient gradually developed massive hemoptysis and was therefore intubated. He was taken to the Intensive Care Unit (ICU), where he died on the 10th day with the clinical presentation of hemorrhage along with hypernatremia.

Discussion

ALF is a rare clinical entity marked by the rapid loss in of hepatic function and with the onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of preexisting liver disease.[7] Drug-induced liver injury is a potential complication of drugs that might progress to ALF. According to the analysis of the United Network for Organ Sharing database, the leading drug groups causing liver transplantation due to drug-induced ALF in the United States were acetaminophen (40%), anti-TB drugs (8%), antiepileptics (7%), and antibiotics (6%).[8]

Awareness of liver injury due to anti-TB therapy is vital because fulminant hepatic failure is a devastating and often fatal condition without liver transplantation. Given the nature of fatal liver injury due to anti-TB therapy, it requires that the guidelines from both the British Thoracic Society and the American Thoracic Society be reviewed. We suggest that liver function should be tested before anti-TB therapy and monthly thereafter.

Approximately 50% of cases of severe acute hepatitis secondary to anti-TB therapy, the discontinuation of hepatotoxic medication allows for improvement of liver function. After liver transplantation, treatment options remain difficult once the standard anti-TB therapy can no longer be used. However, one possible anti-TB regimen after liver transplantation could be isoniazid (as long as it is not implicated in initial hepatitis), ethambutol, and moxifloxacin with or without amikacin. Rifampicin should be avoided because it can interfere with immunosuppressants and lead to acute rejection, and also pyrazinamide should not be prescribed due to its hepatotoxicity.[9]

Alpha 1-antitrypsin deficiency is an inherited metabolic disorder with a suspected worldwide prevalence of 3.4 million people that predisposes the affected individual to chronic obstructive pulmonary disease, in addition to liver disease. Available evidence suggests that alpha 1-antitrypsin deficiency is frequently misdiagnosed by clinicians. The following settings should prompt suspicion by physicians that their patient may be more likely to have alpha 1-antitrypsin deficiency: (1) Symptomatic adults with emphysema, chronic obstructive pulmonary disease, or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators; (2) unexplained liver disease; (3) asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors; (4) necrotizing panniculitis; (5) early-onset emphysema (age of 45 years or less); and (6) bronchiectasis without evident etiology.[10]

In two patients reported, there was evidence of pulmonary failure at the time of making the pulmonary TB diagnosis, acting as a major indicator of the possibility of an underlying pulmonary disease. Both patients quickly developed liver failure due to drugs. All the case investigations were negative in terms of possible underlying liver diseases, and only alpha 1-antitrypsin levels were found to have been low.

In conclusion, with regard to the potential loss of crucial parts of the liver function during the period of affliction with alpha 1-antitrypsin deficiency, measuring the serum levels of alpha 1-antitrypsin prior to beginning anti-TB therapies appears necessary, especially in cases where the TB patient is in his thirties or forties and when his lung radiographs show severe basal emphysema or premature emphysema, chronic obstructive pulmonary disease and even upper lobe emphysema and bronchiectasis.

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Conflicts of interest

There are no conflicts of interest.

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