# ANTITUBERCULAR DRUG INDUCED HEPATITIS AND NEPHROPATHY: A CASE REPORT

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***Abstract-***

Tuberculosis (TB) is a condition brought by bacteria (Mycobacterium tuberculosis) that most often infects the lungs. About one-quarter of the world's population has been affected with TB infection, which means that they have been infected by TB bacteria but are not infected with the disease and cannot transmit it. Recent guidelines for anti-TB treatment has also recommended ways for managing the common adverse events like GI upset, rash, drug fever, hepatotoxicity and optic neuritis. However, there are no recommendations for the management of acute kidney injury. Incidence of hepatotoxicity resulting from ATT ranges from 2-28%. Rifampin, Isoniazid, Pyrazinamide and Ethambutol are the first line agents used for TB management. We report a case of a 45-year-old male with chief complaints of yellowish discoloration of eyes, urine, breathlessness and cough with sputum for a period of 1 week. He had a past medical history of Pulmonary Tuberculosis and was started on ATT regimen to which he developed jaundice and abnormality in LFT and RFT. Laboratory investigation confirmed the diagnosis as ATT induced Hepatitis and Nephropathy. Using Naranjo Scale, causality assessment was done and the result showed that the reaction occurred is possible. This condition might have been resulted from other co-morbidities (DM) and risk factors (chronic alcoholism) which was successfully managed by providing supportive care and symptomatic treatment.

***Index Terms*** - Tuberculosis, ATT Regimen, Hepatitis, Nephropathy, Renal function test, Liver function test.

## I. INTRODUCTION

Tuberculosis (TB) is a bacterial infection of the lungs caused by the Mycobacterium tuberculosis bacteria. TB infection affects about a quarter of the world's population, which means they have been infected with TB bacteria but are not infected with the disease and cannot transmit it. An aggregate of 1.4 million individuals died from Tuberculosis in the year 2019 (counting 2,08,000 people with HIV). Tuberculosis is one of the top ten causes of death worldwide, and the leading cause of death from a single infectious agent (beyond HIV/AIDS). In 2019, an estimated 10 million people worldwide contracted tuberculosis, with 5.6 million men, 3.2 million women, and 1.2 million children[1]. According to Revised National Tuberculosis Control Program (RNTCP), DOTS is employed as the major algorithm for the management of tuberculosis [2]. Rifampin [R], Isoniazid [H], Pyrazinamide [Z] and Ethambutol [E] are the first line agents used for the management of tuberculosis and will be given for duration of 2 months, then followed by 4 months of Isoniazid and Rifampin. Anti-tubercular drugs have been associated with increased risks of liver and kidney injury. Recent guidelines for anti-TB treatment has also recommended ways for managing the common adverse events like GI upset, rash, drug fever, hepatotoxicity and optic neuritis. However, there are no recommendations for the management of acute kidney injury [3]. Incidence of hepatotoxicity caused by ATT ranges from 2-28% [4]. In the absence of jaundice or other symptoms, an elevated liver enzyme of 5 times the upper limit of normal can be used to confirm ATT-induced hepatitis; in the presence of hyperbilirubinemia symptoms, an elevated liver enzyme of up to 3 times the upper limit of normal can be used to confirm ATT-induced hepatitis [5].

## II. CASE HISTORY:

A 45 year old male patient was admitted to the hospital in-patient department of general medicine with chief complaints of breathlessness, yellowing of eyes and urine, cough with sputum, which was scanty white color in appearance with non-foul smell for a period of 1week. On examination, blood pressure was 130/90 mmHg, pulse rate 96bpm, RR 30cpm, SpO2 96% at RA and GRBS 168mg/dl and on physical examination, patient was found to be pallor and icteric. The patient past history revealed that patient had cough since the last 1 year, which got aggravated, along with fever and breathlessness 20 days back and was diagnosed with pulmonary tuberculosis based on subjective and objective evidence. CBNAAT revealed presence of Mycobacterium tuberculosis and was started on ATT regimen (Isoniazid 75mg+ Rifampin 150mg+ Pyrazinamide 400 mg +Ethambutol 275 mg). He has a past medical history of Type 2 DM in the past 1 year, IHD and is a chronic alcoholic for the past 10 years.

Following admission, routine investigations were done to assess the condition of the patient. LFT and RFT were deranged, Hemoglobin was 8.5gm%, WBC 16.1 lakh/cumm. Chest X Ray depicted the presence of dense opacity, pleural effusion in the lower left lateral and basal segment of lung. Ultrasonography of abdomen showed mild left pleural effusion, bilateral grade II nephrotic changes.

Antitubercular drug was withdrawn on the 4th day of admission as the clinical and laboratory investigations confirmed the diagnosis as ATT-induced Hepatitis and Nephropathy. Using Naranjo Scale, causality assessment was done and the result showed that the reaction occurred is possible (4). This condition might have been resulted from other co-morbidities (DM) and risk factors (chronic alcoholism). Since it is known well that the use of Antitubercular drugs results in hepatotoxicity and nephrotoxicity, ATT regimen was changed to modified regimen (Ethambutol 200mg) along with a second line anti-TB drug Levofloxacin (LFX). Patient was symptomatically managed using Inj. Ceftriaxone 1g BD, Inj. Lasix 40mg BD, Tab. Ecosprin 75mg OD, Tab. Clopidogrel 75mg OD, Tab. Atorvastatin 40mg OD, Inj. Amiodarone 150mg stat, Inj. Calcium gluconate TID, Tab. Hepamerz BD and Nebulization Asthalin 2nd hrly.

Figure 1: Icterus due to elevated liver enzymes.

## III. DISCUSSION:

ATT-Induced hepatitis is one of the classical adverse events linked with anti-tubercular drugs, with an occurrence of 4.28% to 11.5%. Among them, Isoniazid and Rifampicin have greater chances of causing liver disease. Renal insufficiency resulting from use of ATT is also well documented [6]. With the combination of Isoniazid and Rifampicin the incidence of hepatotoxicity is 2.6% while with Rifampicin monotherapy and Isoniazid monotherapy it is 1.1% and 1.6% respectively [2]. INH-induced hepatotoxicity results either from direct INH toxicity or from an intermediate metabolite, mainly by N-acetyltransferase (NAT). Dosage adjustment for Isoniazid and Rifampicin is not needed in case of renal impairment when compared with Ethambutol and Pyrazinamide. Hepatic dysfunction is an increase in alanine transaminase (ALT) levels of about 1.5 times the upper limit of normal value on at least two occasions within four weeks of treatment. ALT and bilirubin levels fluctuate frequently during ATT and do not necessarily indicate true hepatotoxicity [7]. The various risk factors that contribute to drug-induced hepatitis include geriatrics, female gender, malnutrition, alcoholism, underlying liver disease, extensive pulmonary parenchymal disease, and HIV infection [8].

We are reporting a case of 45 years old male patient who has been diagnosed with Tuberculosis 20 days back when he was admitted to hospital with cough, breathlessness and fever as chief complaints. The patient was started on DOT therapy of ATT to which he developed jaundice and abnormality in LFT's and RFT's, and was again diagnosed with ATT-induced hepatitis and nephropathy. It is well known that ATT causes hepatotoxicity, so ATT regimen was stopped and the patient was managed with hepatoprotective agents such as Tab Hepamerz and second line agent Levofloxacin. When the patient's condition got improved, he was started on modified ATT regimen (Tab Ethambutol).

Considering all the available information, causality assessment of the current medical condition of the patient was analyzed using Naranjo Causality Assessment Algorithm. Naranjo score of 4 was attained which indicates that the use of antitubercular agents and associated risk factors like DM and use of alcohol can be considered as possible sources of hepatotoxicity and nephropathy.

## IV. CONCLUSION:

Anti-tubercular drug remains the mainstay of treatment for pulmonary tuberculosis. Although it is being used widely, most of the patients may experience adverse effects. Adverse events like hepatitis and nephropathy may result in drug resistance and treatment failure. Hence frequent monitoring of LFT and RFTs may be helpful in preventing the morbidity and mortality caused by ATT. Among the first line agents Rifampin is the most common cause of hepatotoxicity and nephrotoxicity. Levofloxacin (2nd line agent) can be used as an alternative drug for minimizing the risk of hepatotoxicity. Clinical Pharmacist should counsel the patients receiving anti tubercular drug regarding hepatotoxicity and should screen the presence of risk factors and monitor the signs and symptoms and laboratory parameter to withhold the medication if needed. It is also important to counsel the patient regarding the lifestyle modifications (alcohol intake) and co-morbidities.

## CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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