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CASE REPORT

DECIPHERING DRUG-INDUCED LIVER INJURY POST ANTI-TUBERCULAR TREATMENT: CASE REPORT AND DIAGNOSTIC INSIGHTS

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ABSTRACT

First-line anti-tubercular medications are viable in treating tuberculosis brought about by susceptible strains of Mycobacterium tuberculosis. Most antibacterial medications are known to cause hepatotoxicity, which might keep the microscopic organisms from sticking to the medicine and subsequently cause drug resistance in mycobacteria. Anything from mild, nonspecific alterations to fulminant hepatic failure, cirrhosis, and liver cancer can be caused by drug-induced liver injury. It has been reported that isoniazid plus Rifampicin treatment results in metabolites reaching hepatotoxic levels much faster than isoniazid alone. This is because the two treatments work synergistically rather than requiring further medication. Inducible CYP2E1 by ATT is constitutively expressed in the liver. A female patient, aged 25 years, was brought to the Emergency Room in an unconscious state and reported seven days of bilious non-projectile vomiting, yellowish sclera, anorexia, and pain and discomfort in the abdomen especially on the right side. She was diagnosed with tuberculosis one month ago, and she has been on the first category of anti-tubercular medication ever since. Furthermore, she was additionally recommended corticosteroids 10 days prior. On the CT scan of the chest, areas of decreased density were observed in the posterior segments of the Left Upper lobe. The results of her liver function test indicated that she had hepatitis. After stopping the present hepatotoxic drug and switching to a different regimen, her symptoms were relieved and her laboratory values started to recover to normal. When treating ATT-induced liver injury, second-line anti-tuberculosis medications should be recommended while taking cirrhosis and hepatitis B into account as well as the hepatic resilience of hepatotoxic treatments.

KEY WORDS: Adverse Reactions; Anti-Tubercular Agents; Drug-induced; Drug Metabolism; Hepatitis; Hepatotoxins; Liver Injury.

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INTRODUCTION:

Tuberculosis (TB) continues to pose a major public health issue in India, contributing to roughly 27% of the worldwide TB incidence. A recent systematic review and meta-analysis indicated a pooled incidence rate of 12.6% for anti-tubercular drug-induced liver injury (ATDILI) among patients in India, underscoring the importance of this adverse effect.[1] The conventional treatment protocol for TB includes first-line anti-tubercular drugs (ATDs) such as isoniazid, rifampicin, pyrazinamide, and ethambutol. Although these medications are effective in managing TB, they are not without risks, as they can lead to adverse drug reactions, particularly ATDILI. The reported incidence of ATDILI in India shows considerable variability, with studies documenting rates between 2% and 28%.[2]

ATDILI can manifest through a range of liver injuries, varying from mild, asymptomatic increases in liver enzymes to severe acute liver failure. In India, adverse drug reactions are the leading cause of drug-induced acute liver failure, responsible for 63% of reported cases. Several risk factors contribute to the development of ATDILI, including older age, female sex, malnutrition, pre-existing liver conditions, and genetic variations that influence drug metabolism. Clinically, patients may present with symptoms such as nausea, vomiting, jaundice, and pain in the right upper quadrant of the abdomen. Timely identification

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and intervention in cases of ATDILI are essential to avert the progression to more severe liver damage. It is advisable to monitor liver function tests both before and during treatment to facilitate the early detection of hepatotoxicity.[3] In instances where there is a notable increase in liver enzymes or the presence of symptomatic hepatotoxicity, it is imperative to cease the use of the implicated medication and to implement suitable management strategies.[4]

The timely identification and intervention of ATDILI are essential to avert the advancement to severe hepatic damage. It is advisable to monitor liver function tests both prior to and throughout treatment to swiftly identify any signs of hepatotoxicity. In instances where there is a notable increase in liver enzyme levels or the emergence of symptomatic hepatotoxicity, it is imperative to cease the use of the causative agent and to apply suitable management approaches.[5]

The significant occurrence of tuberculosis (TB) in India, coupled with the potential risk of anti-tuberculosis drug-induced liver injury (ATDILI), necessitates a comprehensive understanding of its incidence, risk factors, and management approaches among healthcare professionals. Such insights are crucial for achieving an effective treatment regimen for TB while simultaneously reducing the likelihood of adverse drug reactions, thereby enhancing overall patient outcomes.

CASE DETAILS

Upon arrival at the emergency ward of Trust Multispeciality Hospitals, Kakinada, an unconscious 25-year-old female patient was admitted for treatment. Her main complaints were of altered sensory organs two days prior, bilious non-projectile vomiting, yellowish sclera, anorexia, and pain for seven days that was related to abdominal discomfort, especially on the right side. She was put on an AKT-4 kit and given a Tuberculous meningitis diagnosis a month ago. She used ATT while taking corticosteroids for ten days before stopping the medication. When questioned, she said that she had been feeling drowsy for the past two days, that she had been admitted to a private hospital, and that she had then been sent here. Upon examination, the patient's right atrium was found to have a SpO2 of 97%, a GRBS of 198 mg/dL, an elevated temperature, a pulse of 117 beats per minute, and a respiratory rate of 17 cycles per minute. Examining arterial blood gas analysis, the PO_2 is 166 mmHg and the PCO2 is 29.3 mmHg, which is somewhat lower. The patient had a Prothrombin time of 120 seconds and an INR of 7.18, which are indicative of hepatic encephalopathy, according to the coagulation profile. Severe liver injury is indicated by liver function tests that show total bilirubin 20.6 mg/dL, SGPT 474 IU/L, SGOT 165 IU/L, total protein 5.1 g/dL, and albumin 2.3 g/dL. On the CT scan of the brain, there was evidence of diffuse cerebral edema, while the CT scan of the chest revealed hypodense areas in the posterior segments of the left upper lobe and the posterior basal segments of the left lower lobe of the lung. Hepatitis, cholecystitis, and a calcified granuloma in liver segment VII were all shown on the USG abdomen. A dilated portal vein was present. The patient was given a Tab prescription and had their ATT stopped. 500 mg of Levofloxacin, Tab, once daily. 500 mg of amikacin intravenously once daily. Tericoplanin IV 400 mg once daily, Inj. 10 mg IV OD, tab of vitamin K., 600 mg of ursodeoxycholic acid BD, given intravenously through a Ryles tube. 6 Ampoules Hepamerz with 2.5 ml/h, Inj. Ondansetron IV B, 4 mg. C. and Inj. IV QID mannitol 150 ml for 7 days. 1. The patient was discharged from the hospital on the eighth day after admission, receiving a prescription for 500 mg of Levofloxacin tablet to be taken once daily, along with 800 mg of Ethambutol orally and Nebulized Salbutamol 5 mg three times a day. This decision was made based on positive laboratory results and the patient's improved symptoms, indicating a positive change in her health status.

DISCUSSION

In this instance, the patient experienced hepatotoxicity while undergoing first-line treatment for tuberculosis, indicated by a significant increase in liver transaminase levels that surpassed three times the upper limit of normal (ULN). Following established clinical guidelines, the immediate discontinuation of all drugs that could potentially harm the liver was implemented.[6]

Following a short duration of drug withdrawal and clinical monitoring, treatment was reinstated following a systematic re-challenge protocol that aligns with the guidelines set forth by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). The sequence for reintroducing the medications commenced with rifampicin, which was subsequently followed by isoniazid and then pyrazinamide, with each drug being added only after the stabilization of liver function indicators was confirmed.[7,10] Ethambutol was maintained throughout the process due to its low risk of hepatotoxicity.

Temporary replacement with non-hepatotoxic anti-tubercular medications, such as streptomycin and fluoroquinolones like levofloxacin or moxifloxacin, was utilized as a bridging therapy while the liver was recovering.[8] Once the liver enzyme levels normalized, the initial first-line treatment was resumed unchanged, and no instances of hepatotoxicity were observed during subsequent follow-up.[9]

This clinical perspective underscores the necessity of achieving a balance between therapeutic effectiveness and safety in the context of anti-tubercular treatment. While certain guidelines recommend starting therapy with less hepatotoxic agents in cases of liver impairment, it is essential that clinical decisions are tailored to the individual, taking into account the

severity of the condition, bacteriological findings, and the patient's ability to tolerate treatment. The positive recovery and outcomes observed in this scenario demonstrate that well-organized reintroduction protocols, informed by ongoing liver function assessments, can facilitate the safe and effective management of anti-tubercular drug-induced liver injury (ATDILI).

CONCLUSION

Hepatotoxicity stands out as the most common and perilous adverse reaction linked to anti-tuberculosis drugs, despite the presence of numerous other unfavorable drug reactions. It can also be fatal if left untreated. Drug-induced morbidity and mortality from tuberculosis can be reduced with early diagnosis, treatment, and monitoring.

To avoid adverse effects, the drug's concentration in the serum needs to be monitored. While first-line anti-tuberculosis medications are successful, they can cause liver toxicity, which can result in stopping the medication, which can then cause MDR-TB to develop.

Drug-induced liver injury is still primarily excluded as a diagnosis thanks to careful history-taking, prudent use of Hepatobiliary imaging, blood tests, and liver biopsies. Anti-tuberculosis medications should be stopped and treatment should be restarted to manage anti-tuberculosis DILI. Liver tolerance and the stage of the disease should be taken into consideration when administering anti-tuberculosis medications.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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Conception or Design:	PKY, PB
Acquisition, Analysis or Interpretation of Data:	PKY, PB, HRG, SP
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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.