



Drug Induced Hepatotoxicity in Anti-tuberculosis Therapy: A Case Study

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ABSTRACT

The prevalence of Anti-Tuberculosis Therapy (ATT) induced liver injury is increased for the past many years with many preexisting factors and conditions like alcohol abuse, persisting liver injury, female gender etc., Studies already mention Isoniazid (INH), Rifampicin (RIF) and Pyrazinamide (PYZ) to report many cases on liver hepatitis/injury. The present case is on a 53 year old patient who is a known case of Tuberculosis Meningoencephalitis and on therapy with CAT I ATT. After few days of therapy, he produced signs of malaise, epigastric discomfort, episodic vomiting. Withdrawal of the ATT drugs in these signs was not done. Later on the patient was found to produce signs of Jaundice with yellowish appearance of the sclera. On examination and other laboratorial tests results the patient was found to be diagnosed with fulminant liver injury due to ATT. Liver cells regeneration therapy was begun and discontinuation of Isoniazid, Rifampicin was done. Substitution of ATT therapy was with Ethambutol 800mg and Streptomycin 500mg. The patient was educated on maintenance of proper hygienic life and understanding of the Adverse Drug Reactions (ADR) and side effects of each and every drug he takes. Monitoring of liver and renal function test should also be carried out by the health care professional from time to time in order to avoid critical situations.

Keywords: Isoniazid, Rifampicin, Hepatitis, Liver injury, Anti tuberculosis therapy.

INTRODUCTION

The Epidemiology of drug induced liver injury who is treated with ATT is about 2-28%. The clinical manifestation of tuberculosis is characterized by excessive cough, sputum production, unintentional weight loss and loss of appetite, coughing up blood or mucous along with weakness, fatigue, fever, night sweats. It was diagnosed by mantoux skin test, blood test for the presence of *Mycobacterium tuberculi*, X-ray for the presence of white patches within the lungs¹⁻³. Also tuberculosis complications may cause chronic problems and death including lung, kidney, and liver problems that can be more severe. Tuberculosis and anti-tuberculosis drug together cause defects of liver. The tuberculosis-meningitis also includes increased risk factor for Human Immunodeficiency Virus (HIV) infection, Hepatitis B virus infection which is accompanied by poor nutrition. Rarely, total serum bilirubin levels may vary leading to jaundice and Hepatitis infection. The abnormalities in SGOT (Serum Glutamate Oxaloacetate Transaminase), SGPT (Serum Glutamate Pyruvate Transaminase) enzymes may lead to hepatitis or liver injury or hepatotoxicity. Liver hepatitis depends upon the drug dose fashion⁴⁻⁷. The enzymes produced by the liver plays a dynamic role in hepatotoxicity (over or under production). The clinical presentation for liver hepatitis manifest with, lymphadenopathy, fever, rash and hepatocyte injury, commonly called as hepatocyte injury. Histopathological evidence includes, ballooning of liver, degeneration and inflammatory infiltrates. The delayed onset of symptoms may include rash, fever, arthralgia, hypersensitivity and eosinophilia⁸⁻¹¹.

Hepatocytes are the functional and structural unit of liver, whose damage is referred to as liver hepatitis. Tuberculosis Meningoencephalitis is the predominant lesion with focal accumulation of mixed inflammatory cell infiltrate in meninges and brain. It is extra-pulmonary tuberculosis affecting other parts of the body including pulmonary system. Immediate treatment is essential, or else the cause may lead to increased mortality¹²⁻¹⁵. The antimicrobial otherwise anti-tuberculosis (ATT) drugs such as Isoniazid, Rifampicin, Pyrazinamide, Streptomycin, Ethambutol may be some of the local choices. Rifampicin is an antimicrobial drug, also used for Non-Mycobacterial infections. Increased intake of Rifampicin may lead to resistance to antibodies and antimicrobials. Rifampicin and other ATT drugs are metabolized by liver. Intake of these medicaments may produce increased Bilirubin and Serum Aminotransferase levels, which may be detected through signs and symptoms, jaundice, fever, rash, arthralgia, facial edema and eosinophilia otherwise called as extrahepatic manifestations. To be more clear, for metabolizing Rifampicin, Isoniazid the liver produces various enzymes, such as CYP 3A4 and ABC C2 (MRP2). These enzymes may be directly toxic to hepatocytes or induce immunological reactions, through which patients may have a rise in serum bilirubin related with gene defects. Patients having past liver damages, such as liver cirrhosis, may have increased risks in developing complications¹⁶⁻¹⁸.

A balance must be maintained between unnecessary cessation of ATT and responding to true Drug Induced Liver Injury (DILI) where the mortality of TB DILI could be up to 27%. The primary role of the liver is in metabolizing foreign chemicals and elimination of them from the body. Metabolism of drug in the body is a complex pathway



which would also affect the therapeutic efficacy of a drug administered with it. Knowledge related to problematic drug interactions with proper identification and understanding the pathways which they follow is to be developed. Any drug induced toxicity thus has many chances of becoming a liver injury/ toxicity in its most cases. Inhibition of liver enzymes by a drug or its metabolite would result in the accumulation of that particular drug in the body and also affects the normal function of the liver. Thus a liver injury/ toxicity could be presented as Hepatitis/ cholelithiasis / Cirrhosis etc. once the drug is withdrawn by the patient the recovery begins in case of mild injury. Severe cases may require an organ transplant if possible¹⁹⁻²¹.

All this is a tedious process indeed and may sometimes require “pathway analysis software”. Individualized and personalized therapies are now-a-days gaining success rates which hold a primary role in the eradication of drug-induced, organ damage or specific eradications.

CASE STUDY

A 53 year old male patient who was a known case of Tuberculosis Meningoencephalitis recently started up on ATT and steroids for the past 15 days, suddenly came to the hospital with chief complaints of altered sensorium for 1 day, history of grade IV breathlessness, history of decreased responsiveness to surroundings, history of abdominal distension for the past 2 days. On his previous

diagnosis with Tuberculosis Meningoencephalitis his therapy was initiated with CAT I ATT (Isoniazid 300mg, Rifampicin 450mg and Ethambutol 800mg). After few days of continuous therapy with ATT he had symptoms of malaise, epigastric pain with pale skin. Without recognizing the symptoms he carried on further with his ATT therapy.

He was a chain smoker and occasional alcoholic. On admission to the hospital with worsening symptoms, he was still on ATT therapy when his condition extended to episodic vomiting, malaise, epigastric discomfort. After 2-3 days the patient was observed to produce signs of Jaundice with yellowish appearance of sclera. The continued examinations of liver parameters were as follows given in table 1. The CT scan of the chest revealed pleural thickening on the right side, cardiomegaly, and patchy air space opacity noted in apical, posterior and anterior segments of the right lobe, basal segments of right lower lobe and basal segment of the left lower lobe. Ground glass opacity was noted in superior segment of the right lower lobe and left upper lobe (Figure 4). CT scan of the brain indicated the ventricles to be normal, cerebral edema; opening of the basal blister was visible with normal brain parenchyma (Figure 1). MRI of the brain showed infract in right thalamus, temporal lobe, left ends of pons, meningeal enlargement in right side, multiple enhancing foci B/L (Figure 3). His blood and urine culture showed the presence of *Candida albicans** 10³ grown (Figure 2).

Table 1: Laboratorial investigation of patient during hospitalization: Table turn into day 1, day 2 likewise

| Parameters | Normal values | Date of Admission | | | | | | |
|---------------------------|---------------|-------------------|------|------|------|-------|-------|-------|
| | | 1/05 | 3/05 | 5/05 | 7/05 | 10/05 | 12/05 | 15/05 |
| AST (U/L) | 15-17 | 30 | 1580 | 1900 | 1865 | 1890 | 1720 | 1253 |
| ALT (U/L) | 30-65 | 20 | 1219 | 1275 | 1400 | 1300 | 1002 | 1485 |
| ALP (U/L) | 50-136 | 70 | 135 | 120 | 106 | 97 | 77 | 79 |
| T. Bilirubin (µmol/L) | 0.1-1.0 | 19 | 239 | 221 | 241 | 273 | 290 | 380 |
| T. Protein (g/L) | 6.4-8.2 | 82 | 85 | 73 | 71 | 63 | 62 | - |
| S. Albumin (g/L) | 3.4-5.0 | 35 | 33 | 23 | 25 | 23 | 21 | - |
| INR | 2.0-3.0 | 1.1 | 1.4 | 2.1 | 3.7 | 4.1 | 2.1 | 4.5 |
| Ammonia (µmol/L) | 11-32 | 119 | - | 117 | - | 110 | - | - |
| Hb % (g/dL) | 12-17 | 13.2 | 11.3 | 11.4 | 10.5 | 10.9 | 9.8 | - |
| WBC (/µL) | 4000-11000 | 9500 | 6700 | 5300 | 6600 | 4400 | 5900 | - |
| PLT (*10 ⁹ /L) | 1.5-4.0 | 219 | 239 | 198 | 143 | 147 | 137 | 148 |

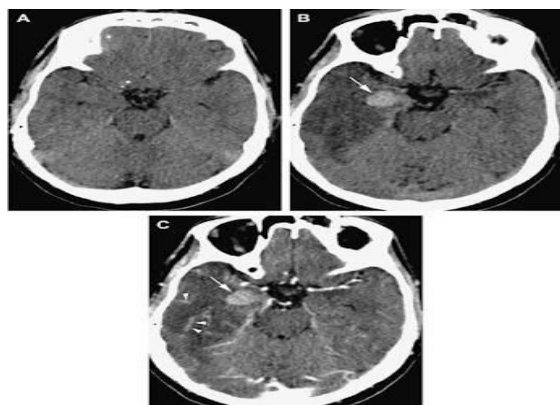


Figure 1: CT scan of the Brain

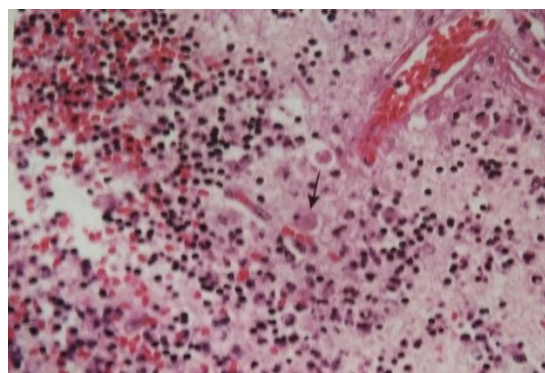


Figure 2: HPE of *Candida Albicans* in Meningoencephalitis from blood culture

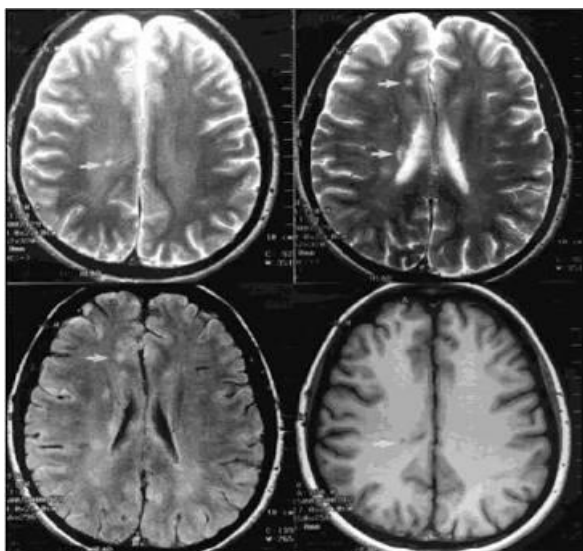


Figure 3: MRI of the Brain



Figure 4: CT of the chest

On examination the patient was unconscious, opening of eyes in response to painful stimuli, drowsy, hiccups. Abdominal examination revealed epigastric tenderness. Serological examinations for Hepatitis A, B, C, E viruses, HIV, Epstein-Barr virus, Herpes simplex virus were negative. Ultrasound examination of the abdomen was found to be normal. The patient was initially treated with Inj. Mannitol 25%, Inj. Dexamethasone 8mg IM, Inj. Phenytoin 15mg/kg IV, Inj. Deriphylline, Inj. Ceftriazone 2g IV, Intravenous fluids and a hepatic diet. The patient was diagnosed with fulminant hepatitis due to ATT. There was marked elevations of prolonged pro-thrombin time, hyperbilirubinemia, increased hepatocellular enzymes, hyperammonemia. He was supplemented with plasma substitutes and vitamin K in order to correct prolonged International Normalized ratio (INR). Discontinuation of Isoniazid and Rifampicin was done and Ethambutol 800mg, Streptomycin was substituted in order to treat the Meningoencephalitis condition. Laboratorial examinations after two days showed slight improvement in his hepatic function with resolving symptoms.

DISCUSSION

INH and RIF are the common drugs made use of in the treatment of tuberculosis of any parts of the body. The effectiveness of therapy with these drugs is about 25-92%. Minimum duration for INH therapy is for 9 months and some strategies follow a 4-month therapy with INH and 2 month RIF therapy. Other alternatives include RIF therapy for 4 months and RIF or PYZ therapy for 2 months. In all these cases the adverse effects and resistance towards these drugs are very much higher. Hence recent studies suggest a combined therapy with INH-RIF for about 3-4 months producing excellent therapeutic activity.

The rate of hepatotoxicity by INH-RIF therapy is about 2.6% while it is low with its individual therapy, 1.1% and 1.6% respectively. Isoniazid and Rifampicin when given together acts upon the P450 enzymes, INH induces the formation of acetyl hydrazine which covalently binds with liver proteins. Hepatotoxicity with ATT drugs increases as concomitant other hepatotoxic drugs are administered, female gender, age, alcohol abuse, preexisting liver disease etc. In the present condition the patient was an occasional alcoholic, chain smoker till the previous day of his admission to the hospital. This is one of the major exacerbating factors. Secondly the patient was on therapy with the ATT drugs even after certain symptoms of hepatic failure were evident. Therapy with all CAT I ATT made it difficult to predict the culprit drug. Among INH, RIF, Ethambutol. Hence discontinuation of INH and RIF was made. Streptomycin 500mg was added to the treatment regimen including T. Ursodeoxycholic acid (UDILIV) 300mg, Syp Lactulose 10g, C.Rifaximin 550mg OD, Inj H.Albumin 10g infusion, Inj Heparin 5000 units, Syp Potassium chloride 15ml TDS.

Pharmacist Role

The following strategies must be followed in order to prevent and minimize the morbidity and mortality of ADR associated with ATT;

- Liver function tests must be done, before and after the initial startup drug therapy, to analyze the enzymatic conditions of liver.
- Health education must be provided to the patients undergoing anti-tuberculosis drug therapy on the actions of the drugs and the side effects associated. This would help the patient identify the symptoms and immediately stop the therapy and take it to physicians notice.
- The patients must report if loss of appetite, nausea, vomiting and jaundice appear during the course of treatment.
- The ATT must be withdrawn if any suspicious signs and symptoms appear.
- ATT therapy is not to be continued until jaundice or hepatotoxicity is diagnosed.

- Startup ATT with Ethambutol and Streptomycin in case of toxicity and do not re-challenge with Rifampicin.

CONCLUSION

Almost all the CAT I ATT drugs are metabolized by the liver and when the therapy lasts for a long time there are increased chances of hepatotoxicity and liver injuries. The physicians and pharmacists could help the patients out by making them understand the adverse effect and side effects of each of the drugs so that immediate withdrawal of the drug could be done by the patient itself and letting it know to the physician. This would prevent the further worsening of the condition, remaining as the exacerbating condition in most of the cases.

Abbreviations:

ATT: Anti-Tuberculosis Therapy

INH: Isoniazid

RIF: Rifampicin

PYZ: Pyrazinamide

SGOT: Serum Glutamate Oxaloacetate Transaminase

SGPT: Serum Glutamate Pyruvate Transaminase

DILI: Drug Induced Liver Injury

ADR: Adverse Drug Reaction

HIV: Human Immunodeficiency Virus

TB: Tuberculosis

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Compliance with Ethical Standards

Written informed consent was obtained from the patient for publication of the case study, inclusion of the accompanying images. Copies of written consent may be requested for review from the corresponding author.

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