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Case Report

CASE REPORT ON ANTI-TUBERCULOSIS INDUCED CIRRHOSIS

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Abstract
Tuberculosis is well known disease for centuries and is the major problem widely seen all over the world. It is the significant cause for morbidity and mortality. The standard treatment for tuberculosis is isoniazid, rifampicin, pyranzinamide, ethambutol, streptomycin. Regarding the standard treatment there is one of the most common cause is liver failure, which is drug induced. Among the anti-tuberculosis drug isoniazid , rifampicin and pyrazinamide cause hepatotoxicity is the leading cause in India. Most of the patient have to be counseled regarding the treatment adherence and its adverse effect of the drug.

Keywords: Tuberculosis, isoniazid, hepatotoxicity.

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INTRODUCTION

Tuberculosis is caused by the bacteria called mycobacterium tuberculosis. It is the contagious infection and mainly attacks the lungs and it also spreads to the other parts of the body such as brain and spine. It is cured by the antibiotics. Patient must be medication adherent for a time period of 6-9 months. TB and HIV are the most common burden in India .By the 6-50 folds ,TB is been increased by the risk factor of the HIV[1]. The first line TB drugs are isoniazid, rifampicin, ethambutol ,pyrazinamide which would cause most common adverse effect of the hepatotoxicity is the significant one and sometimes patient may develop elevation of SGPT and SGOT levels (transaminase levels)also may also cause jaundice, ascities, hepatic encephalopathy, acute liver failure ,cirrohsis[2,3,4,5,6.7]

MECHANISM:

1. IDIOSYNCRATIC DAMAGE:
    - Most types of drug induced liver injury.
    - It includes metabolic or hypersensitivity reactions.
    - Largely independent dose.
    - It may occur anytime of post exposure.
    - Result from genetic or acquired variations in drug biotransformation pathway.
2. DOSE-DEPENDENT TOXICITY:
    - Acute /subacute
    - Dose related: increases with escalation of dosages.
    - Free radical mediated necrosis.
    - Usually no extra-hepatic manifestation.
3. INDUCTION OF HEPATIC ENZYMES:
    - Alter plasma drug levels
    - Enhance hepatotoxicity of other drugs
    - Associated with extra hepatic adverse drug reactions.
4. ALLERGIC REACTIONS:
    - Reactive metabolite mediated.
    - Manifests with fever, lymphednopathy, rash and severe hepatocyte injury.
5. DRUG INDUCED AUTOIMMUNE LIKE HEPATITIS:
    - Clinical, biochemical and histological signs similar to autoimmune like hepatitis; good response to steroids but expect long term remission after withdrawal of steroids.

SPECIFIC PATTERNS OF HEPATIC DAMAGE:

- DISRUPTION OF INTRACELLULAR CALICUM HOMEOSTATSIS.
- CHOLESTATIC DAMAGE.
- INTERRUPTION OF TRANSPORT PUMPS AND LOSS OF VILLOUS PROCESSES.
- REACTION INVOLVING CYTOCHROME-P450 SYSTEM.
- ACTIVATION OF APOPTOTIC PATHWAYS AND PROGRAMMED CELLDEATH.
- INHIBITION OF MITOCHONDRIAL FUNCTION.

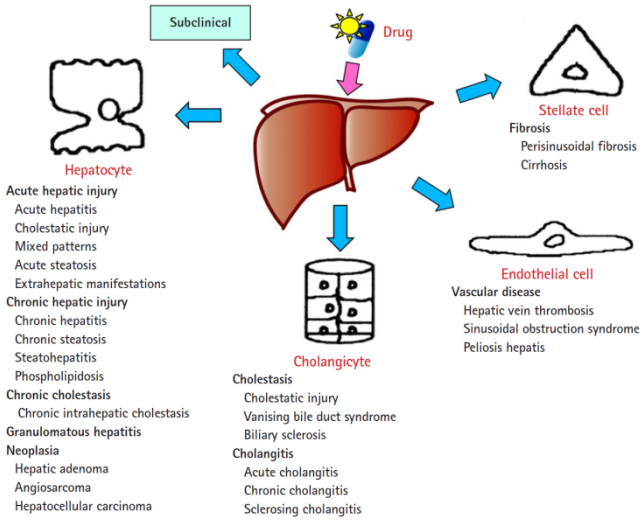

Fig: 01 Spectrum of drug-induced liver injury.Drugs can damage not only hepatocytes but also cholangiocytes, stellate cells, sinusoidal endothelial cells, and they can cause acute hepatitis, chronic hepatitis, granulomatous hepatitis, neoplasia, cholestasis, cholangitis, vascular disease, and fibrosis.

ATT DURG AFFECTS THE LIVER:

.Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis [8].Sometimes in the absence of the symptoms elevation of transaminase up to 5 times the upper limit the of the normal (ULN) and the presence of the symptoms up to three times the ULN or twice the ULN of bilirubin is defined as hepatotoxicity. Schenker et al reported that elevations in the ALT and /or AST level to 50-100IU/L more than the

baseline levels might define toxicity[9]. In patients with HIV, the AIDS Clinical Trials Group criteria is used, which is as follows:

Grade 1: transaminases 1.25 - 2.5 × upper limit of normal (ULN);

Grade 2: 2.6 - 5 × ULN;

Grade 3: 5.1 - 10 × ULN; and

Grade 4: >10 × ULN.[10].

Saigal et al hepatotoxicity was diagnosed if ALT/AST levels increased to more than fivefold of the baseline level, or to more than 400 IU/L, or if the bilirubin increased by 2.5mg/dL after exclusion of superimposed acute hepatitis[11]. Fluctuation in the ALT and bilirubin levels is common while using ATT drugs which doesn't truly specify that the patient is having hepatotoxicity but the progressive levels of ALT and bilirubin is more dangerous.

HEPATOTOXIC DRUGS OF ATT	Isoniazid, Rifampicin, Pyranzinamide
NON-HEPATOTOXIC DRUGS OF ATT	Ethambutol, Streptomycin.

ISONIAZID:

- Isoniazid also known as isonicotinic acid hydrazide is an antibiotic used in treatment of tuberculosis (TB). It has been mainstay of TB treatment in both children and adults.
- It was first synthesized in 1952. It is included in World Health Organization's List of Essential Medicines. It is also available as generic medicine.
- It is derivative of isonicotinic acid.

Mechanism**:** It acts as a prodrug. It enters mycobacterial cell by passive diffusion where it is activated by mycobacterial catalase-peroxidase (KatG) into an active metabolite. This active metabolite targets the enzyme acyl carrier protein (ACP) reductase and β-ketoacyl-ACP synthase and inhibit the synthesis of mycolic acid.

Patient should use this drug for 4-6 months which may alter the levels of bilirubin and ALT which further leads to liver damage which progress and lead to fatal hepatitis. Liver damage is mainly caused by the metabolite of isoniazid called acetyl hydrazine. If the AST level is increased over 5 times than isoniazid should be discontinued. Anti-INH antibodies and anti-P450 autoantibodies are diagnosed in the patient with INH-induced liver failure[14].Warrington *et al.*'s data, which demonstrated a positive lymphocyte transformation test for mild cases of INH-induced DILI when patients lymphocytes were exposed to INH-modified proteins, and in the more severe cases of liver injury, this response spread to the recognition of the parent drug[12,13].

Adverse effects: hepatits, hepatitoxicity,peripheral neuropathy,allergic or hypersensitivity reactions.

RIFAMPICIN:

- Rifampicin, also known as rifampin, is semi-synthetic derivative of rifamycin-B which is obtained from Streptomyces mediteranei. It is used to treat several types of bacterial infections.
- Rifabutin and rifapentine are structurally similar to rifampicin. These group of structurally similar macrolide antibiotics are known as rifamycin.
- Rifampicin was discovered in 1965, marketed in Italy in 1968 and approved to use in USA in 1971. It is available as generic medicine. It is included in World Health Organization's List of Essential Medicines.
- Mechanism**:** It binds to β subunit of bacterial DNA- dependent RNA polymerase forming stable drug-enzyme complex which suppress initiation of chain formation in RNA synthesis. This results in inhibition of RNA synthesis. Compared to isoniazid (INH), rifampicin is less bactericidal but has potent sterilizing activity. It imparts orange- red color to urine, feces and other secretions.
    - Adverse effects**:** liver injury, renal damage, jaundice, proteinuria, leucopenia and thrombocytopenia. hepatatis may also occur.
    - RIF-induced liver injury is related to oxidative stress in mitochondria, apoptotic liver cell injury in rodents, cholestasis, and hepatic lipid accumulation [15,16].

PYRAZINAMIDE:

Pyrazinamide is synthetic pyrazine analogue of nicotinamide. It was first synthesized in 1936 and its use as anti-tubercular drug was not known before 1952. It is included in World Health Organization's List of Essential Medicines. It is also available as generic medicine.

- Mechanism**:** It is a prodrug. It enters *M. tuberculosis* by passive diffusion and gets converted to active compound pyrazinoic acid by nicotinamidaze/ pyrazinamidase

which inhibit bacterial synthesis of mycolic acid resulting in cellular damage.

- Adverse effects**:** major side effect is hepatic injury. other side effects are nausea, vomiting, arthralgia, anorexia, malaise and mild skin rashes.
- In the Centre for Diseases Control (CDC) update, 48 cases of hepatotoxicity were reported in association with a 2-month regimen of Rifampin-pyrazinamide for the treatment of latent tuberculosis between October 2000 and June 2003[17].

ETHAMBUTOL:

Ethambutol inhibits arabinosyl transferases which is involved in cell wall biosynthesis. By inhibiting this enzyme, the bacterial cell wall complex production is inhibited. This leads to an increase in cell wall permeability.

Adverse effects**:** optic neuropathy.

STERPTOMYCIN: It irreversibly binds to the 16S rRNA and S12 protein within the bacterial 30S ribosomal subunit, thereby inhibiting the initiation of protein synthesis.

Adverse effects**:** ototoxicity.

FIRST LINE DRUGS ADVERSE EFFECTS:

DRUG	MAIN EFFECTS	RARE EFFECTS
ISONIAZID	Peripheral neuropathy Skin rash Hepatitis Sleepiness and letheragy	Convulsions Psychosis Arthralgia Anemia
RIFAMPICIN	GIT problems Hepatitis Generalized cutaneous reactions Thrombocytopenic purpura	Osteomalacia ARF Pseudoadernal crisis Haemolytic anemia Pseudomembraneous colitis
PYRAZINAMIDE	Arthralgia Hepatitis GIT problems	Cutaneous reactions Sideroblastic anemia
ETHAMBUTOL	Retrobublar neuritis	Generalized cutaneous reactions Arthralagia Peripheral neuropathy Hepatitis(rare)

SECOND LINE ATT DRUGS WITH SIDE EFFECTS

DRUGS	SIDE EFFECTS
INJECTABLES: kanamycin capremomycin	• Ototoxicity • Nephrotoxicity • Vertigo • Electrolyte imbalance
QUINOLONES: Ofloxacin Levofloxacin moxifloxacin	• Gastro intestinal problems • CNS symptoms • Phototoxicity and photosensitivity • Tendinopathy and tendinitis • Skin rash • Cardiotoxicity :QT prolongation • Arthralgia
Ethionamide	• Gastro intestinal problems • Hepatitis • Hypothyrodisim and goiter • Gynaecomastia,impotence • Pheripheral neuropathy
cyclosporine	• CNS symptoms • Psychiatric problems • Hypersensitivity reaction
PAS	• Gastro intestinal problems • Skin rash • Hepatic dysfunction • Hypokalemia • Hypothyroidism and goitre.

CASE REPORT:

A male patient of 52 years of age admitted to general medicine department with a chief complaint of abdominal distension since 1 month associated pedal edema, associated with shortness of breath grade-3. He was also suffering with constipation and decrease urine output. He has a past medical history of diabetes milletus and pulmonary tuberculosis since 3 months. His personal history of taking mixed diet, bowel and bladder disturbed, decrease sleep and appetite. He also has a past personal history of alcohol intake since 10 years and stopped 2-3 years back. He also smokes 4 chutters in a day since 5 years. On oberservation he is not pallor, cyanosis, clubbing, lymphedenopathy and has icterus and pedal edema. With a diagnosis of chronic liver disease with known case of pulmonary TB with type-

2 DM. His CT abdomen was significant ascites and subnormal size of lines with surface irregular cirrhosis. The patient has Hbs Ag not significant and Hbe Ag negative with HBV DNA of 585IU/L.

DISSCUSSION:

A male patient was diagnosed by TB three months back but he was not having any past history of liver disease before taking the anti-tuberculosis drug. Few months later he was admitted to hospital with chief complaint of SOB,pedal edema and abdominal distention. In USG abdomen it was impressed as inflammation of liver. Before the patient used to taking the first line TB drugs such as isoniazide ,rifampicin,pyrazinamide .Due to the combination of isoniazid and rifampicin it lead to the inflammation of liver i.e drug induced hepatitis. There was an increase in bilirubin and normal AST ,ALT levels

CONCLUSION:

According to WHO ,if the patient has abnormal bilirubin levels or abnormal AST/ALT levels. stop all the first line ATT drugs and start giving second line drugs such as ethambutol, levofloxacin and streptomycin ,but the streptomycin is given based upon the patient weight. Monitor LFT levels and start first line drugs after the levels come to normal.

REFERENCES:

1. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003;163:1009–21.
2. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf. 2006;5:231–49.
3. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008;23:192–202.
4. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935–52.
5. Senousy BE, Belal SI, Draganov PV. Hepatotoxic effects of therapies for tuberculosis. Nat Rev Gastroenterol Hepatol. 2010;7:543–56.
6. Kumar R, Shalimar, Bhatia V, Khanal S, Sreenivas V, Gupta SD, et al. Antituberculosis therapy-induced acute liver failure: magnitude, profile, prognosis, and predictors of outcome. Hepatology. 2010;51:1665–74.
7. Devarbhavi H, Dierkhising R, Kremers WK. Antituberculosis therapy drug-induced liver injury and acute liver failure. Hepatology. 2010;52:798–9.
8. . Benichou C. Criteria for drug-induced liver disorder: report of an international consensus meeting. J Hepatol 1990;11:272–276.
9. Schenker S,Martin RR,Hoyumpa AM.Antecedent liver disease and drug toxicity.J Hepatol 1999;31: 1098-1105 [PMID:10604586 DOI:10.1016/S0168-8278(99)80325-0].
10. AIDS Clinical Trials Group. Table of grading severity of adult adverse experiences. Rockville, MD: Division of AIDS, National Insttute of Allergy and Infectious Diseases; 1996.
11. Saigal S, Agarwal SR, Nandeesh HP, Sarin S. Safety of an ofloxacin-based antitubercular regimen for the treatment of the tuberculosis in patients with underlying chronic liver disease;a prelimeinary report .J Gastroenterol Hepatol 2001;16: 1028-1032 {PMID:119595068 DOI:10.1046/j.1440-1746.2001.02570.x]
12. Warrington RJ, McPhilips- Feener S, Rutherford WJ. The predictive value of the lymphocyte transformation test in isoniazid- associated hepatitis. Clin Allergy 1982; 12: 217–22.
13. Warrington RJ, Tse KS, Gorski BA, Schwenk R, Sehon AH. Evaluation of isoniazid- associated hepatitis by immunological tests. Clin Exp Immunol 1978; 32: 97–104.
14. Metushi IG, Sanders C, Acute Liver Study G, Lee WM, Uetrecht J. Detection of anti- isoniazid and anti- cytochrome P450 antibodies in patients with isoniazid- induced liver failure. Hepatology 2014; 59: 1084–93.
15. 15. Huang J.H., Zhang C., Zhang D.G., Li L., Chen X., Xu D.X. Rifampicin-induced hepatic lipid accumulation: Association with up-regulation of peroxisome proliferator-activated receptor gamma in mouse liver. PLoS ONE. 2016;11:e0165787. doi: 10.1371/journal.pone.0165787.
16. Chowdhury A., Santra A., Bhattacharjee K., Ghatak S., Saha D.R., Dhali G.K. Mitochondrial oxidative stress and permeability transition in isoniazid and rifampicin induced liver injury in mice. J. Hepatol. 2006;45:117–126. doi: 10.1016/j.jhep.2006.01.027

17. CDC: Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection-United States, 2003. MMWR 2003; 52 (31):735-9.