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A CASE SERIES OF PATIENTS DIAGNOSED WITH PULMONARY TUBERCULOSIS HAVING COMORBIDITIES DEVELOPING ATT-INDUCED HEPATITIS

General Medicine

Dr Gurukanth Rao N — Associate Professor, Department of Medicine, ESIPGIMS&R, Bengaluru

Dr Abhishek Konnur* — Junior Resident, Department of Medicine, Srinivas Medical College*Corresponding Author

Dr Jayaprakash Belle — Professor, Department of Medicine, Srinivas Medical College

ABSTRACT

Key risk factors and comorbidities such as HIV infection, diabetes, malnutrition, COPD and substance use drive the global TB epidemic and are associated with poorer TB treatment outcomes. Comorbidities, particularly DM, with glycemic control being significantly poor is seen in PTB patients. TB and its treatment can complicate the management of some of these conditions. Patients receiving anti-tubercular drug frequently develop acute or chronic hepatitis. The time required for the metabolites to reach hepatotoxic levels is much earlier with isoniazid plus rifampicin treatment than isoniazid alone and this has been shown to be synergistic rather than additive. Here in this case series, we present patients with comorbidities diagnosed with tuberculosis developing ATT induced hepatitis.

KEYWORDS

Pulmonary TB, Extrapulmonary TB, Drug induced liver injury/hepatitis (DILI), COVID-19, Diabetes Mellitus (DM), Retroviral disease(HIV), Hyponatremia, COPD, Epilepsy, Addison's disease

INTRODUCTION

Most countries with a high TB burden face a concomitant burden of associated medical comorbidities. These include liver diseases, chronic kidney diseases (CKD), diabetes mellitus (DM), cardiovascular diseases, connective tissue disorders and chronic obstructive pulmonary disease.

Majority of the studies have used an elevated alanine (SGPT) or aspartate transaminase (SGOT) of 3 times upper limit of normal range (ULN) with symptoms (abdominal pain, nausea, vomiting, unexplained fatigue or jaundice) attributable to liver injury or 5 times ULN of SGPT or SGOT without symptoms to define hepatotoxicity.1 Manifestation of the anti-TB drug induced hepatotoxicity can vary from asymptomatic elevations in the liver enzymes to fulminant liver failure.1,2 DILI (drug induced liver injury) generally takes hepatocellular pattern.

Recent studies show that polymorphism of the N-acetyltransferase 2 (NAT2) genes and glutathione-S-transferase (GST) are the major susceptibility risk factors for ATT-induced hepatitis. Slow acetylators of NAT2 prove to develop more severe hepatotoxicity than rapid acetylators making it a significant risk factor.

Case 1:

A 78-year-old diabetic, hypertensive male patient was diagnosed with SARS 2-COVID-19. HRCT thorax was reported as moderate COVID-19 acute viral pneumonitis with CT severity index of 12/25. Patient was treated as per existing government guidelines which included LMWH (enoxaprin 0.4units/day). During the course of treatment in hospital, patient had persistent productive cough, sputum AFB done was reported as positive 3+. Baseline liver function(LFT), renal parameters(RFT), serum electrolytes were normal. Patient was started on ATT as per NTEP FDC weight based HRZE regimen (isoniazid(H), rifampicin(R), ethambutol(E), pyrazinamide(Z)). After 2 days of starting ATT, patient complained of nausea, vomiting and fatigue. LFT showed SGOT-542U/L, SGPT-231U/L, total bilirubin-4.8mg/dl and direct bilirubin-2.5mg/dl suggestive of drug induced hepatitis. Isoniazid, rifampicin, pyrazinamide was stopped.

He was started on ethambutol, levofloxacin and streptomycin. Patient's LFT was monitored regularly which returned to normal over a period of 2 weeks, after which individual ATT drugs were reintroduced gradually. Patient tolerated rifampicin, isoniazid and ethambutol and was continued with this regimen.

Case 2:

A 30 year old male patient a known case of epilepsy on oral levetiracetam and phenytoin was diagnosed to have pulmonary tuberculosis based on clinical symptoms, radiological features and sputum AFB positivity. He was started on first line ATT as per NTEP FDC weight based HRZE regimen. He was discharged after 7 days of uneventful hospital stay. Patient was lost to follow up for 2 months after which patient presented with complaints of altered sensorium and vomiting. On presentation, he had refractory hypotension. Laboratory investigations were sent and it revealed hyponatremia (serum sodium-126 meq/dl), hyperkalemia (serum potassium -6 meq/dl) and deranged liver function parameters (SGOT-224U/L, SGPT-160U/L, total bilirubin-2.2). He was diagnosed to have Addison's disease, his serum cortisol levels was found to be below reference range. He was treated with prednisolone 7.5mg/day following which his blood pressure returned to normal levels. HRZ was stopped, injectable streptomycin added and ethambutol continued. Fluroquinolones were not started as they reduce seizure threshold. After 6 days of stopping HRZ, transaminitis had resolved. INH was gradually reintroduced and 3 days later rifampicin was reintroduced. However, pyrazinamide was not restarted. Liver function tests were monitored till 2 weeks.

The patient tolerated the ATT modified regimen well with no recurrence of transaminitis. He was discharged on HRE and prednisolone 7.5mg/day. Patient was reviewed after 1 month, he had no complaints and repeat liver function test was within normal limits.

Case 3:

A 62 year old male patient known type 2 diabetes mellitus, hypertension, IHD and COPD was admitted for bilateral inguinal hernia. In view of productive cough and history of unintentional weight loss, patient was evaluated for pulmonary tuberculosis. He was found to be sputum AFB positive (2+). Laboratory investigations done showed hyponatremia (Serum Sodium- 124 meq/dl), liver function test and renal parameters were normal. He was started on ATT as per NTEP HRZE regimen. Cause for hyponatremia was evaluated and was diagnosed with SIADH (urine sodium-76 meq, plasma osmolality-255 mOsm/kg) and treated with oral tolvaptan 15mg/day. After 12 days of initiation of ATT, his liver function parameters were found to be deranged (SGOT-220U/L, SGPT-184U/L, total bilirubin-1.9mg/dl). Tolvaptan was stopped and ATT was withheld for total period of 11 days. Individual drugs HRZ were reintroduced in a phased manner along with ethambutol, streptomycin and levofloxacin. Patient did not tolerate any of reintroduced medications. Patient developed severe gastritis with rifampicin even though his LFT was within normal limit. INH and pyrazinamide induced significant liver enzymes derangement, and hence were discontinued. Patient was discharged on ethambutol, streptomycin and levofloxacin. Patient's renal and audiometry results were normal prior to starting streptomycin.

After 4 weeks, patient returned with complaints of hearing loss, dizziness. He was diagnosed with ATT induced vestibulitis. Audiometry reported moderate hearing loss at high frequency and severe hearing loss at low frequency. Ototoxicity due to streptomycin was suspected and consequently the drug was stopped. Patient was started on modified ATT regimen ethambutol 750mg, levofloxacin 750mg and rifampicin 450mg for longer duration with no further consequences.

Case 4

A 42 year old male patient known case of type 2 diabetes mellitus, hypertension, right hemiparesis due to old hemorrhagic stroke presented with swelling over chest since 3 months, abdominal distension since 2 months and productive cough since 1 month. Patient was clinically stable, with physical examination revealing a cold abscess over chest, fluid aspirate was positive for AFB. Abdominal examination showed ascites, no organomegaly. The CT chest revealed heterogeneous enhancing loculated lesion with thoracic cage involvement suggestive of chest wall tuberculosis and atelectatic fibrotic changes in the anterior segment of right upper lobe. CT abdomen revealed diffuse oedematous wall thickening of small bowels with peritonitis suggestive of abdominal tuberculosis. Hence patient was started on ATT 4 drug regimen HRZE.

Two weeks later, patient had multiple episodes of vomiting, generalised pruritus. Liver function tests revealed SGOT-220U/L, SGPT-120U/L, total bilirubin-1.4mg/dl, ALP-334U/L. Suspecting ATT induced hepatitis, HRZ was stopped and ethambutol, injectable streptomycin was added. 4 days later, patient was gradually reintroduced with rifampicin and isoniazid in a graded manner. Patient was discharged with isoniazid, rifampicin and ethambutol and patient tolerated this regimen. Injectable streptomycin was stopped at discharge.

Case 5

38 year old male patient known retroviral (RVD) disease defaulter with ART presented with complaints of fatigue, altered sensorium and was diagnosed with shock. He was admitted to ICU and laboratory findings showed Hb-4.1g/dl, platelet-63,000L/cu.mm, total count-7650cells/cu.mm, total bilirubin-1.2mg/dl, SGOT-44U/L, SGPT-29U/L, serum albumin-2.5mg/dl, serum sodium-128meq, serum potassium-3.8meq, ESR-155mm/hr. Peripheral smear was reported as normocytic normochromic anaemia with relative neutrophilia and thrombocytopenia. In view of hypotension and anemia, patient was transfused packed cells. USG abdomen showed moderate splenomegaly. HRCT thorax showed left lower lobe consolidation with effusion and right sided pleural effusion which was suggestive of disseminated tuberculosis. Patient was started on ATT as per NTEP guidelines. Patient developed hepatitis after 2 weeks and ATT was stopped. He was started on hepatosafe regimen with injectable streptomycin, oral levofloxacin and ethambutol with dose adjusted to body weight. During the stay in the hospital patient clinical condition gradually improved and he was discharged with streptomycin, levofloxacin and ethambutol. Since he was financially constrained, he was advised to visit nearby government antiretroviral treatment centre to restart ART.

DISCUSSION

Smoking has long been linked to tuberculosis with evidence becoming stronger from a recent population-based study from China that showed a two-fold risk of pulmonary tuberculosis with smoking.[7]

In India, an estimated 2·2 million cases of tuberculosis are recorded per year and about 60 million people have diabetes mellitus; 14.8% of the tuberculosis burden has been attributed to diabetes mellitus.[10]

A hospital-based study in northeast India by Bhattacharya et al8 stated that various medical comorbidities were present in 53.17% of the patients, of which diabetes mellitus (26.58%) and hypertension (17.34%) were the most common, with higher association with PTB than EPTB. The presence of diabetes has been shown as an independent risk factor for death in TB in a large retrospective cohort study.[9]

In our series, most of the patients developed DILI in the first 2 weeks. A retrospective study from a large TB centre in UK by Abbara et al5 stated that more than half (53%) of DILI occurred in first 2 weeks and 87% occurred within first 2 months of starting ATT.

Guidelines from professional bodies provide advice on choice of drugs, combinations and duration of therapy that are considered suitable to different clinical scenarios.3,4 The commonest symptoms in our DILI patients were nausea and vomiting.

As isoniazid and rifampicin are highly efficacious, their use in the treatment of latent or active TB infection is desirable. However, considering that combination therapy increases the risk of DILI, mono-therapy with either isoniazid or rifampicin is preferable for the treatment of latent TB when particular individual is at higher risk of hepatotoxicity. In patients with advanced liver disease, if the serum alanine aminotransferase level is more than 3 times normal at baseline, the following regimens should be considered.

Possible regimens include4
Two hepatotoxic drugs regimen

- 9 months of isoniazid and rifampicin, plus ethambutol
- 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;
- 6–9 months of rifampicin, pyrazinamide and ethambutol.

One hepatotoxic drug regimen

- 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.

No hepatotoxic drug regimen: in patients with advanced cirrhosis or portosystemic encephalopathy

- 18–24 months treatment with a combination of ethambutol, fluoroquinolone, cycloserine and capreomycin or aminoglycoside has been suggested as an option.

Regular clinical review of patients is helpful to monitor treatment. A survey conducted by Nolan et al6 stated careful clinical monitoring without routine laboratory tests, the rate of hepatotoxicity in 11,141 patients was much lower (0.1%–0.15%) than previously expected (1%) with no deaths.

CONCLUSION

In this study, we demonstrate DILI in patients having various comorbidities. This study indicates that monitoring of LFT during the first 2 months of ATT should identify the majority of DILI early, possibly shortening treatment interruption and reducing mortality.

CONFLICTS OF INTEREST

Nil

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