Case Report: Treating pulmonary tuberculosis with transaminitis with standard antitubercular four drugs therapy [version 1; peer review: 1 not approved]

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Abstract
We report a case of pulmonary tuberculosis with transaminitis during the presentation but without any pre-existing liver disease or hepatotoxic drug use. This is a fairly common scenario seen in tuberculosis endemic areas; however, this is an under reported condition in the literature and guidelines for its management has not been established. Many clinicians including the authors have treated such cases with modified liver friendly regimens in fear of increasing the hepatotoxicity with standard drugs. However, the modified regimens may not be optimal in treating the underlying tuberculosis. In this report, we gave full dose standard antitubercular drugs, and the liver injury resolved evidenced by normalization of transaminases.

Keywords
tuberculosis, transaminitis, standard ATT, liver friendly regimen

This article is included in the Oxford University Clinical Research Unit (OUCRU) gateway.
Background
Tuberculosis is the biggest infectious disease killer in the world, and is endemic in Nepal with the national prevalence standing at 416 cases per 100000 population. Pulmonary tuberculosis is the most common form. It is not uncommon to find liver function test abnormalities in patients with tuberculosis at presentation to hospital. While encountering such patients, it is important to differentiate if the patient had pre-existing liver disease or if the present infection with tuberculosis has impacted on the liver, as the approach to management differs given the hepatotoxicity associated with first line drugs.

Here we present a case of pulmonary tuberculosis with predominant transaminitis, treated with standard first line antitubercular therapy (ATT) which led to resolution of liver function abnormalities. We then discuss the different forms of liver involvement associated with tuberculosis.

Case presentation
A 33 year old Newar housewife from Kathmandu, Nepal, with no known comorbidity, presented to Patan Hospital Emergency Department in November, 2019 with a history of cough with occasional sputum production over the previous 20 days and low grade fever for 10 days. There was no history of chest pain, difficulty breathing, headache, vomiting, altered mentation, abdominal pain, yellowish discoloration of eyes, burning urine, or rash but she had decreased appetite and weight loss. There was no past history of tuberculosis or jaundice. She did not consume alcohol, any drug or herbal products. Her father-in-law had been diagnosed with pulmonary tuberculosis five years earlier.

Initial examination showed temperature of 101°F with pulse of 110 beats/minute and respiratory rate of 26 breaths/minute. There was diffuse fine crepitation on the right side on auscultation of the chest. There was no lymphadenopathy or icterus. Liver and spleen were not palpable, and abdomen examination was normal.

Laboratory parameters with normal ranges in parenthesis are as follow:

Complete blood count before transfusion: white cell count 7.8 (4–10) × 10^9/L; neutrophils 80%; lymphocytes 16%; monocytes 4%; red blood cells 3.6 (4.2–5.4) × 10^12/L; haemoglobin 10.6 (12–15) g/dL; platelets 410 (150–400) × 10^9/L.

Biochemistry: random blood sugar 126 (65–110) mg/dL; urea 39 (17–45) mg/dL; creatinine 1.1 (0.8–1.3) mg/dL; sodium 138 (135–145) mmol/L and potassium 4 (3.5–5) mmol/L.

Hepatic panel: bilirubin total 1.1 (0.1–1.2) mg/dL and direct 0.5 (0–0.4) mg/dL; alanine transaminase 308 (5–30) units/L; aspartate transaminase 605 (5–30) units/L; alkaline phosphatase 149 (50–100) IU/L; albumin 3.5 (3.5–5) g/dL.

Chest X-ray (Figure 1) showed thick walled cavitating lesions in the left upper lobe and patchy infiltrates in left middle and lower zones. Sputum smear examination showed 3+ acid fast bacilli. Sputum Gene Xpert was positive for Rifampicin sensitive tubercle bacilli. Serologies for HIV, HBsAg, Hepatitis C virus (HCV), Hepatitis A virus (HAV) and Hepatitis E virus (HEV) were nonreactive. Ultrasound of the abdomen showed a normal sized liver with smooth outline and echotexture.

She was admitted to the respiratory isolation unit. At first there was some hesitation in starting the full treatment for her pulmonary tuberculosis because of her liver function tests. But taking into consideration her presentation and laboratory findings, we opted for the full treatment rather than a modified TB regimen. We started standard antitubercular four drugs therapy (ATT) based on her weight as per national TB guidelines which included three tablets of HRZE given once daily with each tablet containing 75 mg isoniazid (H), 150 mg rifampicin (R), 400 mg pyrazinamide (Z) and 275 mg ethambutol (E). This led to the improvement in her clinical status. She was closely observed for possible worsening of her liver disease due to the hepatotoxic antitubercular drugs. Providentially, at 1 week after starting the treatment, she was afebrile and continuing to improve and her liver function test showed a total bilirubin of 0.7 mg/dl, aspartate transaminase of 40 IU/L and alanine transaminase of 62 IU/L.

She was discharged with advice to follow up in 1 month. At follow up she had no symptoms and therefore no further tests
were done. She was advised to continue ATT and follow up with sputum smear at 2 months as per the national protocol.

Discussion
There are different forms of liver disease in patients with tuberculosis discussed in the literature; one is drug induced liver injury, in which case treatment should be stopped and the patient monitored. Second, tuberculosis in patients with pre-existing liver disease where first line ATT should only be used with caution and frequent monitoring, modification of regimen may be required based on the severity of liver disease.

In both of these conditions (drug induced liver injury and pre-existing liver disease), predominant transaminitis is usually observed. The third association is direct involvement of the liver as part of disseminated tuberculosis (miliary) or as local hepatic tuberculosis (tuberculoma), leading to significant raised alkaline phosphatase and gamma-glutamyl transferase (cholestatic pattern) with only milder elevations of transaminases. Abdominal ultrasound and computed tomography (CT) scans show abnormalities in the liver in 76% and 88% of cases respectively. In such conditions, full course first line ATT should be started, and there is no increased risk of hepatotoxicity with the first line drugs.

In our patient, we ruled out the presence of pre-existing liver disease. There were no risk factors for liver disease such as alcohol, drugs or toxins. Her viral hepatitis serology was negative. There were no clinical features of chronic liver disease or portal hypertension. Ultrasound also showed normal liver architecture and size (CT scan of the abdomen and liver biopsy were not done in our case). The liver injury in our patient with pulmonary tuberculosis was of predominantly hepatocellular pattern (transaminitis) with only modest elevation of alkaline phosphatase, unlike the cholestatic pattern commonly seen in extra-pulmonary hepatic tuberculosis.

In our anecdotal experience, we have found many patients with pulmonary tuberculosis, similarly to subject of this case report, present with predominant transaminitis and without pre-existing liver disease or drugs-use. They are often managed with modified liver-friendly antitubercular regimens for fear of increasing the hepatotoxicity and causing acute liver failure with the use of standard regimen. Few case reports are available in literature reporting the use of the modified regimens. We believe such cases are underreported, and firm guidelines have not been established to guide clinicians in these cases. Given this, many clinicians in low-middle income countries, including Nepal, who have been treating tuberculosis patients tend to be skeptical in using full doses of first line ATT in such patients and tend to use a modified regimen. However, this practice may potentially lead to under-treatment and therefore increase fatality. Though there was some hesitation at first in our case, we soon started treatment with the standard ATT in our patient with close monitoring. This we believe led to the resolution of liver injury, evidenced by the normalization of transaminases.

We concluded pulmonary tuberculosis as the cause for transaminitis in our patient, and the normalization of transaminases after starting the standard dose of ATT further supports this conclusion. We believe pulmonary TB presenting with transaminitis is a common problem and that treatment may often be compromised because of decreased dosing of ATT.

Conclusion
When treating a tuberculosis patient with transaminitis, it is important to look for any possibility of pre-existing liver disease. If none is found, then the use of standard ATT from the beginning may be essential for optimal management of tuberculosis, and this may help resolve any liver injury caused by the tuberculosis.

Consent
Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

References
Open Peer Review

Vivek Neelakantan
Independent Medical Historian, Mumbai, India

Title:

Drug-resistant TB is a hot topic in medicine today. Research on TB treatment-associated transaminitis would further the existing scholarly understanding on drug-resistant TB. A close keyword search on PubMed revealed only 17 hit on TB AND transaminitis. For this reason, the case report is potentially publishable but suffers from several drawbacks in its current draft that must be remedied before the contribution is re-refereed.

But the title itself is unclear. “With” is repeated twice. It is not clear to a medical historian what transaminitis is. A better framing of the title is urgently needed. A cogent argument can be organised around the title. What is four-drugs therapy? It is clear to medical practitioners but not clear to the larger scholarly community. Avoid jargons in the title.

1) What is transaminitis? Why not provide a brief explanation at the start so that the general reader can follow the rest of the article.
2) The two levels of transaminitis:
(a) pre-existing liver disease leads to transaminitis.
(b) Hepatoxicity of anti-TB drugs.

This needs to be made explicit in the very beginning. The authors have not been explicit about the two levels of transaminitis and that is where the problem begins.

“While encountering such patients, it is important to differentiate if the patient had pre-existing liver disease or if the present infection with tuberculosis has impacted on the liver, as the approach to management differs given the hepatotoxicity associated with first line drugs.”

Rewrite this sentence. Make more explicit.

Summary and Abstract:
The writers present a case of pulmonary TB with transaminitis without pre-existing liver damage. The therapeutic regimen of the authors included anti-TB drugs and liver injury resolved evidenced...
by normalization of transaminase.

The abstract merits rewriting for clarity.

**Background:**
Background: Needs to sketch out the larger socio-economic picture of TB patients in Nepal. Medicine for whom?

**Case Presentation:** How do you define compliance with TB treatment? How socio-economic factors militate against the successful completion of treatment?

Specific quote from the report: “In our anecdotal experience, we have found many patients with pulmonary tuberculosis, similarly to subject of this case report, present with predominant transaminitis and without pre-existing liver disease or drugs-use. They are often managed with modified liver-friendly antitubercular regimens for fear of increasing the hepatotoxicity and causing acute liver failure with the use of standard regimen. Few case reports are available in literature reporting the use of the modified regimens. We believe such cases are underreported, and firm guidelines have not been established to guide clinicians in these cases. Given this, many clinicians in low-middle income countries, including Nepal, who have been treating tuberculosis patients tend to be skeptical in using full doses of first line ATT in such patients and tend to use a modified regimen. However, this practice may potentially lead to under-treatment and therefore increase fatality. Though there was some hesitation at first in our case, we soon started treatment with the standard ATT in our patient with close monitoring. This we believe led to the resolution of liver injury, evidenced by the normalization of transaminases.”

What is your sample size? Unclear. What guidelines can be established with the aid of the study?” Make explicit and elaborate.

**Conclusion:**

The report lacks an inevitable conclusion. The conclusion needs to point to the “so what” question? So, what are the implications of this study? What protocols could be devised? How does this case history further medical practitioners' as well as policymakers’ understanding of drug-resistant TB?

**Other points:**

Please make sure that the manuscript is thoroughly copyedited for legibility of prose, clarity of argument, and grammar.

The social context of TB in Nepal merits attention (alcoholism is a contributing factor).

You need to compare transaminitis with case studies from other countries. Carefully refer to the PLoS

**One article below:**


How does your case differ from the 2 references mentioned above?

**References**  

**Is the background of the case's history and progression described in sufficient detail?**  
No

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**  
Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**  
Yes

**Is the case presented with sufficient detail to be useful for other practitioners?**  
No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** History of Tuberculosis, Global Health, South and Southeast Asia, Medical Humanities

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.