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Case Report

## Drug-Induced Liver Injury from Anti-Tuberculosis Treatment in a Case of TB Meningitis

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### Abstract

This case study revolves around a 38-year-old male patient who arrived at the Emergency department complaining of decreased levels of consciousness, agitation, and disorientation. The case follows his admittance to the ICU, while a team of doctors worked on finding a possible diagnosis for his condition.

It was later in the course of his disease that it was found from his CSF (Cerebrospinal fluid) sample that he was suffering from tuberculous meningitis. The culture result revealed a strain of Mycobacterium Tuberculosis that was sensitive to all the major anti-tuberculous drugs. This was a favorable point for the prognosis of this patient. Once he was started on a regimen of selected anti-TB drugs, his symptoms improved to the point of successful discharge from the hospital.

However, a few days later, the patient again started experiencing symptoms that were serious enough to justify hospital admission. It was found that it was not any primary issue causing the symptoms this time, but rather the toxicity of the anti-tuberculous drugs. However, due to timely diagnosis, intervention, and management, his condition was managed effectively and he was discharged once again.

This case study aims to measure the importance of prescribing the most effective yet adequate treatment regimen for all patients, keeping in mind several overlooked yet highly important health-related factors that could either exacerbate or deteriorate pre-existing health concerns in a given patient. If the patient had been evaluated carefully for any underlying liver diseases or been given a short trial to see if he could withstand the high dose of anti-tuberculous drugs, he would not have faced such dreadful consequences, though they were managed quickly.

**Keywords:** Cerebrospinal fluid, Mycobacterium Tuberculosis, liver diseases, anti-tuberculous drugs.

## INTRODUCTION

Tuberculosis (TB) is a very ancient human disease caused by Mycobacterium Tuberculosis. This disease is seen to mainly affect the lungs, making pulmonary disease the most common presentation<sup>1</sup>. (Adigun & Singh, 2022) However, that is not all. Tuberculosis is widely accepted and recognized as a disease that affects multiple systems, and not all of them simultaneously. The organ systems that are most commonly affected include the respiratory, the gastrointestinal (GI), the lymphoreticular, the central nervous, the musculoskeletal, and the reproductive systems, and the skin and liver<sup>2</sup>. (Alzayer & Al Nasser, 2022a) Even in a growing and developed world like ours, tuberculosis remains a significant cause of both illness and death in the underdeveloped and developed countries.

As a matter of fact, tuberculosis is seen to be prevalent among individuals with a suppressed immune system. This includes people with HIV infections, who have been seen to be particularly vulnerable to death due to tuberculosis, when it becomes a superimposed infection. Children were also affected by the disease<sup>3</sup>. (Active Tuberculosis - StatPearls - NCBI Bookshelf, n.d.)

Tuberculosis is a widespread disease, present in almost all the regions of the world with different distributive patterns. Recent statistics estimate that around two billion people are infected with the M. Tuberculosis infection.

The incidence of tuberculosis surged in the earlier 21st century, but thanks to the advancements in the treatments available for the disease, rates have been seen to be declining. Asia and Africa are said to be the two continents with the most cases of tuberculosis<sup>4</sup>. (Tuberculosis in Asia and the Pacific: The Role of Socioeconomic Status and Health System Development - PMC, n.d.)

## CASE STUDY

This case study revolves around a 39-year-old male who initially had no complaints suggesting such a full-blown diagnosis. He presented to the Emergency Department with complaints of agitation, irritability, and mental status changes. The complaints only increased in intensity, indicating a worse prognosis for the patient, so it was decided that the patient should be admitted to the ICU and workup would be carried out from there towards a possible diagnosis.

Among other investigations and examinations, the patient's CSF was sent for analysis and it came back positive for Tuberculosis Meningitis. This was now understandable and the patient's condition could be easily dealt with. But before starting any form of anti-tuberculosis treatment, it was also necessary to determine if the strain of Mycobacterium that he was affected with was sensitive to the anti-tuberculosis drugs.

The CSF cultures revealed that the strain of Mycobacterium tuberculosis that he was suffering from was indeed sensitive to all four first-line medicines indicated for tuberculosis. Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, and Dexamethasone were started on the 25th of January 2022. The patient's condition started improving, and it was planned to continue the anti-TB treatment until the 25th of January 2023. The patient was discharged from the hospital on the 22nd of February 2022.

However, just six days later, he was admitted to the hospital again, but this time for a different set of complaints. This time, the patient was experiencing dizziness, nausea, blurred vision, and a diffuse rash all over his body. There was no abdominal pain, only intermittent nausea which rarely progressed to vomiting. His LFTs were found to be highly elevated in his initial bloodwork.

This was likely a consequence of starting anti-tuberculosis treatment less than a week ago, and therefore, the first line of management was to discontinue all anti-TB drugs that were known to cause liver toxicity. In his case, these drugs were Isoniazid, Rifampicin, and Pyrazinamide.

### Investigations:

For reference, here is an overview of the patient's LFTs:

<b>AST</b>	<b>985</b>
<b>ALT</b>	<b>900</b>

To replace the three anti-tuberculosis drugs, Linezolid (600 mg OD) and Levofloxacin (750 mg OD) were added. However, from this point forth, the patient had become a candidate for multiple screenings and investigations to see if any of the other ongoing drugs would inflict side effect on his health or affect any underlying conditions.

A brief summary of all the relevant investigations and examinations has been summarized below as follows:

Investigation Performed	Results
<b>AFB Smear</b>	Negative
<b>EBV Serology</b>	<b>IgG - Positive</b> <b>IgM - Negative</b>
<b>HIV AV/AB Screening</b>	Negative
<b>Hepatitis B &amp; C Screening</b>	Negative
<b>Sepsis Workup</b>	Negative

It was obvious that the patient had developed a form of full-blown liver toxicity due to the anti-TB medications. Stopping the medicines responsible at the right time helped contain the toxicity of the drug, and thus, the patient's condition was controlled and monitored accordingly.

As time passed, a new series of investigations were ordered to see if there were any hidden or obvious signs of pathology in any of his systems. The results of those investigations can be summarized as follows:

<b>HRCT</b>	Right side mild to moderate pleural effusion. Mild effusion on the left side associated with underlying sub-segmental passive atelectasis. Limited reticulation and some ground glass opacities.
<b>US Abdomen</b>	Enlarged liver with increased echogenicity. Remonstration of GB wall edema. No gallstones. Mild ascites. Bilateral pleural effusion. No fluid collection.
<b>Chest X-ray</b>	Minimal right basal pleural effusion. There is no consolidation, pneumothorax.

The patient's liver enzymes were also tightly controlled. They were less than 200 in later reports, which was a sign that the liver was no longer suffering from the toxic side effects of any anti-TB medications and was working as expected.

The patient's current anti-TB regimen comprises the following drugs:

- Linezolid 600 mg OD
- Levofloxacin 750 mg OD
- Ethambutol 1200 mg OD

It was decided that Rifampicin could be re-added to this regimen after controlling the liver's condition. If, after introducing Rifampicin, his LFTs remained normal after 48 hours, Isoniazid could also be added as the normal first-line drug for tuberculosis. If not, neither would be added again.

However, such trials would not work in favor of Pyrazinamide, as it is the drug which most commonly causes liver toxicity.

### Current Condition:

Presently, the patient is stable. His LFTs are controlled with an ALT level of 25 and an AST of 20. He no longer has any ongoing or increased intensity symptoms such as nausea, headache, fever, diarrhea, or coughing. There is also no sign of neck stiffness, photophobia, focal deficit, visual defects, or seizures. This indicates that he is doing well and that his condition is slowly getting better with the passage of time.

However, he will remain on the course of anti-TB medications (Isoniazid, Rifampicin, and Ethambutol) for a year. This will ensure that the infection has gone from his body.

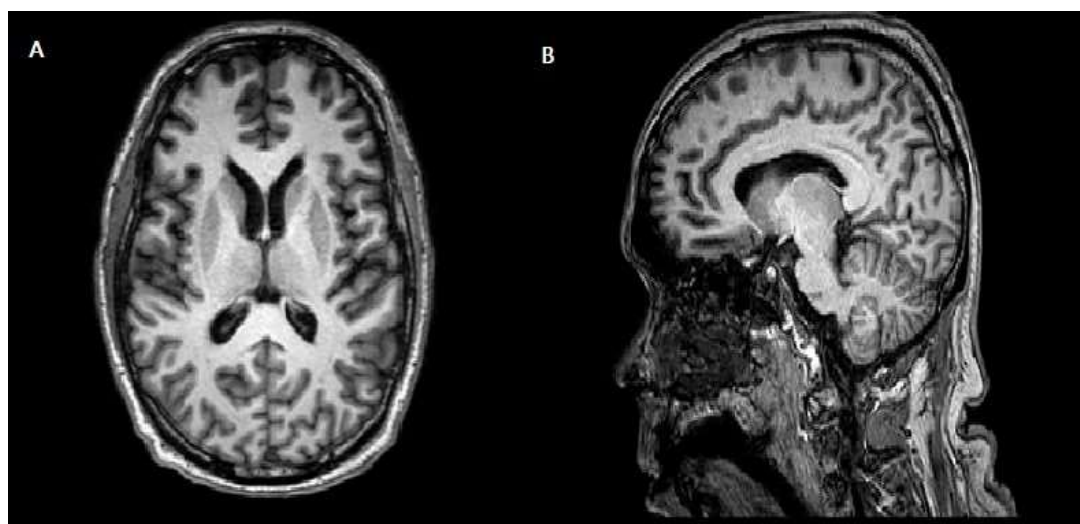


Figure 1 (A – B): Brain MRI showing evidence of multiple small focal areas of restricted diffusion, seen at the deep sub cortical area bilaterally, associated with faint leptomeningeal cortical hyperintensity.

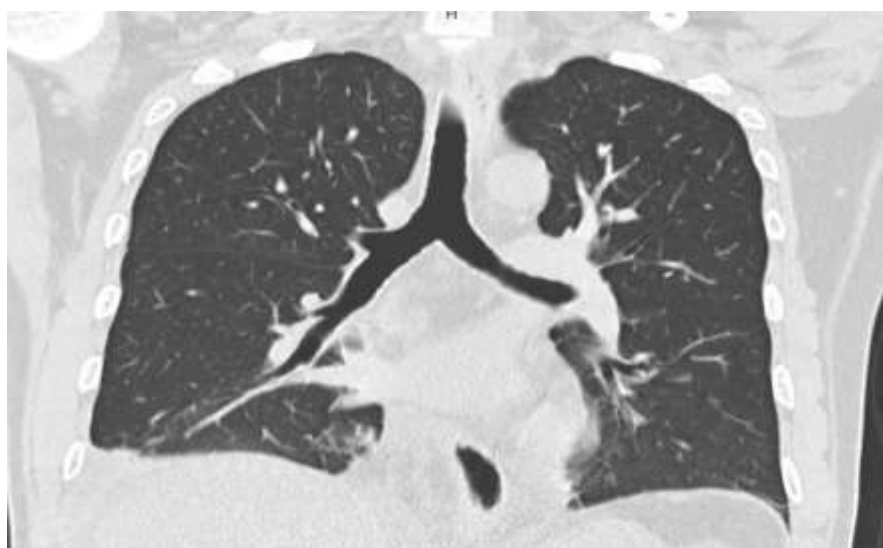


Figure 2: CT HR chest showing Right side mild to moderate pleural effusion.

## DISCUSSION

Active tuberculosis is a multi-organ disease. It can be caused either by a primary infection or as a reactivation of a latent tuberculosis infection. Whatever the etiology is, it is called primary tuberculosis or reactivation tuberculosis, accordingly<sup>1</sup>. (Adigun & Singh, 2022)

Primary tuberculosis occurs when the immune system is unable to defend itself against the Mycobacterium Tuberculosis Bacterium (MTB) infection. However, reactivation tuberculosis, as the name suggests, is the reactivation of a previously-controlled or treated mycobacterial infection. Reactivation TB is the most common form of active tuberculosis globally, accounting for up to 90% of cases<sup>5</sup>. (*The Pathogenesis of Tuberculosis: The Early Infiltrate of Post-Primary (Adult Pulmonary) Tuberculosis: A Distinct Disease Entity - PMC*, n.d.)

The lungs are the most commonly involved organ. The other organ groups commonly affected include the gastrointestinal, musculoskeletal, lymphoreticular, and reproductive systems, and the liver and skin.

The World Health Organization (WHO) estimates that around eight million people develop active tuberculosis globally each year. Out of this figure, approximately two million people die from the disease<sup>2</sup>. (Alzayer & Al Nasser, 2022b)

Despite medical advancements and drastic global efforts to eradicate tuberculosis, the disease still accounts for significant morbidity and mortality worldwide. Developing countries like India, Pakistan, the Philippines, China, South Africa, and Indonesia are seen to experience the highest morbidity and mortality rates.

After the primary infection, most patients remain asymptomatic or the symptoms resolve on their own. However, a major portion of these patients are seen to enter a “latent” phase. Symptomatic individuals (around 10 percent) develop a primary lung infection, with some suffering spread to distant organs, particularly in immune-compromised patients like those suffering from HIV AIDS, Hepatitis B or C, etc. <sup>6</sup>. (Suárez et al., 2019)

Prolonged fever is the most commonly reported symptom. Only one-third of patients develop respiratory symptoms, including chest pain, cough, and shortness of breath. The cough may be productive or non-productive, while the fever

almost always follows a diurnal pattern of increasing during the day and resolving by itself at night. It can also be associated with night sweats.

The initial or the gold-standard therapy for the management of Tuberculosis is a six-month course of certain anti-TB drugs. This regime is supposed to be followed strictly to yield the best results. In the initial 'Intensive Phase' of this treatment plan, Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol are taken for two months<sup>7</sup>. (*Tuberculosis Treatment and Drug Regimens - PMC*, n.d.) This is followed by the 'Continuous Phase' which involves four months of taking Isoniazid and Rifampicin.

However, there are several downsides to this anti-TB therapy program. The main one is the compliance factor. Patients are not eager to follow this extensive treatment plan and many leave the treatment halfway or avoid completing it due to non-compliance factors. This leads to an incomplete cessation of the disease in such individuals<sup>8</sup>. (*Antituberculosis Drug-induced Hepatotoxicity: Concise Up-to-date Review - Tostmann - 2008 - Journal of Gastroenterology and Hepatology - Wiley Online Library*, n.d.)

Anti-TB medications also have several side effects. One of the major adverse effects is anti-TB drug-induced hepatotoxicity. This presents itself in the form of jaundice or the presence of high concentrations in liver function tests, namely of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (APT), or Total Bilirubin<sup>9</sup>. (*Drug-Induced Hepatotoxicity of Anti-Tuberculosis Drugs and Their Serum Levels - PMC*, n.d.)

Once a patient with tuberculosis experiences these symptoms or an abnormal blood tests, it is advised to interrupt or stop the anti-tuberculosis treatment immediately.

Once things seem to be in control, another wise approach is to employ an alternative regime for the patients. The most suitable alternative anti-TB regime is for those patients who have up to three times elevated ALT levels, in the presence of hepatitis or jaundice. Elevated AST or ALT levels could also indicate pathologies in the muscles, tissues, or kidneys, which are another alarming signal for the patient<sup>10</sup>. (Saukkonen et al., 2006)

Although all four first-line anti-TB drugs are known to cause significant hepatotoxicity in vulnerable patients, it has been noticed that Pyrazinamide contributes to a higher percentage of toxicity cases, compared to the other drugs.

Once this happens, it is better to customize and employ an anti-TB regimen based on the patient's needs, the resistance pattern (if present) of the Mycobacterium strain, and the organ affected by the disease.

An appropriate anti-TB regimen could help save the patient's lives without causing any significant problems or complications, while at the same time ensuring that the patient does not have to suffer the unlikely and unwanted effects of any drug.

## CONCLUSION

Although tuberculosis is a multisystem disease that is seen to involve the lungs in the majority of the cases, it is also a very

highly curable disease. Favorable prognosis factors include the early detection and treatment of the causative agent. Detecting which strain has caused the tuberculosis makes it much easier for doctors to approach the disease and treat it with an effective treatment regimen.

In this case, the patient's underlying health conditions did not allow him to make the most of his anti-tuberculosis treatment, and he suffered from the consequences of the drugs. The patient's liver was affected and the toxicity it bore could have had serious implications had it not been for the timely detection and treatment of the symptoms.

At the end of the day, the patient's life was saved and he was discharged from the hospital with the hope that he would suffer no further effects of his ongoing treatment.

This case study is a great lesson for all the doctors in how to prescribe the safest yet most efficient drugs. The benefits need to outweigh the risks for the patient at any given moment.

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