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ANTI-KOCH'S TREATMENT INDUCED HEPATITIS WITH COAGULOPATHY: A CASE REPORT

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ABSTRACT
Hepatitis induced by anti-Koch's treatment, also known as an anti-tubercular treatment, is a rare but potentially severe complication. We present a case report of a patient who developed hepatitis and coagulopathy following the initiation of anti-Koch's treatment. A 31-year-old male with active pulmonary tuberculosis was started on a drug regimen comprising Levofloxacin, and Ethambutol. After one and half months of treatment, the patient developed symptoms of hepatitis, including jaundice, abdominal pain, and elevated liver enzymes with increased LDH. Coagulopathy was also observed, characterized by prolonged prothrombin time. The patient's clinical condition deteriorated rapidly. Proper management and supportive care are necessary for patients. This case highlights the importance of early recognition and management of hepatitis induced by anti-Koch's treatment to prevent further complications. It also shows the importance of proper follow-up of patients who initiated an anti-Koch treatment. Healthcare professionals need to be aware of this potential adverse reaction and closely monitor patients undergoing anti-Koch treatment.

Keywords: *Hepatitis, coagulopathy, anti-Koch's treatment, drug-induced liver injury, tuberculosis, liver function test*

INTRODUCTION
Tuberculosis, commonly known as TB, is a highly contagious infection that primarily affects the lungs. It is caused by a type of bacteria called Mycobacterium tuberculosis (Shaban *et al.,* 2023). Symptoms of TB include a persistent cough, chest pain, and difficulty breathing (McIntosh *et al.,* 2020). Factors such as diabetes, alcohol use, malnutrition, tobacco smoke, and indoor air pollution can increase the risk of developing TB and worsen the progression of the disease (Narasimhan *et al.,* 2013).

In the treatment of tuberculosis, a commonly used approach involves the administration of a combination of isoniazid (INH), rifampicin, pyrazinamide, and ethambutol. However, this therapy has a significant drawback in the form of drug-induced liver injury (DILI). This adverse effect can result in noncompliance, treatment failure, or the emergence of drug resistance (Zhao *et al.,* 2020). During antituberculosis chemotherapy, isoniazid, pyrazinamide, and rifampicin have the potential to cause hepatotoxic effects. While medication hypersensitivity can cause some hepatotoxic reactions, the majority of these reactions are related to the dosage of the medication (Yew *et al.,* 2006).

CASE
A 31-year-old male patient presented with the chief complaints of yellowish discoloration of the eyes and urine for 3 days, breathlessness, nausea, vomiting (for 1 week), abdominal pain, hematochezia, and lesions on both sides of the body lasting for 1 week. The patient also reported a persistent cough. He was diagnosed with active pulmonary tuberculosis and had been on anti-tuberculosis (anti-TB) drug treatment for two and a half months. HRCT thorax (plain + contrast) revealed gross left pleural effusion with fissural extension and atelectasis of the underlying lung segment. The parietal and visceral pleura appeared thickened and showed post-contrast enhancement, likely suggestive of an infective etiology.

The patient had a 3-year history of hypertension and was on regular medication. He had previously been admitted to the ICU for accelerated hypertension for 2 days. In May 2021, he complained of breathlessness and visited a nearby hospital, where he was diagnosed with chronic kidney disease (CKD) with blood pressure over 180/110 mmHg. Since then, he has been undergoing hemodialysis three times a week. In July 2021, a renal biopsy confirmed chronic glomerulonephritis. Currently, the patient is experiencing coagulopathy and Grade II and III hepatic encephalopathy. Physical examination revealed positive pallor, icterus, and cough, with decreased bilateral air entry. The detailed laboratory test results are presented in Table 1.

The patient also has swelling in both limbs with painful lesions over both feet. A dermatology consultation indicated vasculitis with erythema multiforme, possibly secondary to drugs or the underlying disease. The patient's social history revealed a five-year history of severe smoking, though he quit three years ago. Considering the patient's complex medical history and significant risk factors, including alcoholism, smoking, CKD, and lung parenchymal damage, alongside a recent tuberculosis (TB) diagnosis requiring treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol for the past two and a half months, the attending physician carefully evaluated the presenting symptoms. The symptoms, indicative of hepatitis and coagulopathy, prompted an investigation into potential causes, particularly the hepatotoxicity associated with certain anti-TB drugs.

A detailed account of the treatment administered during the patient's hospitalization is outlined in Table 2. Upon discharge, the physician prescribed specific medications aimed at mitigating severity and preventing complications, as detailed in Table 3.

Laboratory Investigations

Table 1: Laboratory investigations of the patient in hospital admission

Name of test	Observed value on day 3 (22-7-22)	Observed value on day 5 (25-7-22)	Normal Value
Hb	8.709	9.80	13.3-16.6 g/dl
Platelets	262,000	300,000	150000-410000/
RBC	3.69	3.51	4.35*5.65*10^6 / UL
PCV	25.50	30.10	38.30-48.60 *10^6 /ul
MCHC	34.20	27.96	31.5*34.58 g/dl
Absolute Neutrophils	-	16836	2000-7000/ul
Absolute lymphocytes	-	732	10000-3000/UL
Neutrophils	81 %	92	40-80 %
Lymphocytes	14 %	4	20-40 %
Eosinophils	0	0	1-6 %
Serum creatinine	1.36	3.14	0.74-1.35 mg/dl
Sodium serum	131	135	136-145 mmol/lt
Potassium serum	2.90	4.3	3.50- 5.10 mmol/lt
Chloride serum	93.00	92	98-107 mmol/lt
Protein (total)	-	6.10	6.4- 8.3 g/dl
Albumin	-	1.90	3.5- 5.2 g/dl
Globulin	-	4.20	2.32-3.5 g/dl
Bilirubin	13.93	14.96	0.22 -1.20 mg /dl
Direct Bilirubin	10.22	11.22	Up to 0.5 mg /dl
Indirect Bilirubin	3.71	3.74	0.1-1.0 mg /dl
Prothrombin time	17.20	19.60	8.97- 12.91 sec
INR value	1.57	1.79	0.85-1.15

DISCUSSION

The liver plays a crucial role in processing and detoxifying drugs, but it is vulnerable to damage. Various types of drugs cause injuries to the liver (DILI), such as hepatic adaptability and hepatocellular injury. "Dose makes the poison," according to Paracelsus, the founder of toxicology, is more suitable in the event of medication-initiated hepatotoxicity (Dey *et al.*, 2006). It has been found that between 2% and 28% of TB patients suffer from drug-related hepatotoxicity (DIH), a serious problem caused by anti-TB drugs. In India, 8 to 36% of cases of drug-induced hepatotoxicity occur, possibly due to ethnic predisposition, unique medication metabolism, or the prevalence of other recognized risk factors such as hepatitis B (HBV) infection, malnutrition, and alcoholism (Sakashita *et al.*, 2019).

The majority of reports define hepatotoxicity as an elevated alanine (ALT) or aspartate transaminase (AST) of 3 times the upper limit of the normal range (ULN) with symptoms such as abdominal pain, nausea, vomiting, unexplained fatigue, or jaundice attributable to liver injury, or 5 times the ULN of ALT or AST without symptoms (Ramappa *et al.*, 2013). Genetic variation is permitted by the rate of INH acetylation, with fast acetylators (30–40% of Indians) in the first hour and a half, and a t1/2 of INH 3 hr for slow acetylators (60–70% of Indians). Various regions of the world have different ratios of quick and slow acetylators. Though biweekly regimens are less successful in rapid acetylators, acetylator status is irrelevant if INH is administered daily. Isoniazid-induced peripheral neuritis seems to affect slow acetylators more frequently (Khan *et al.*, 2021).

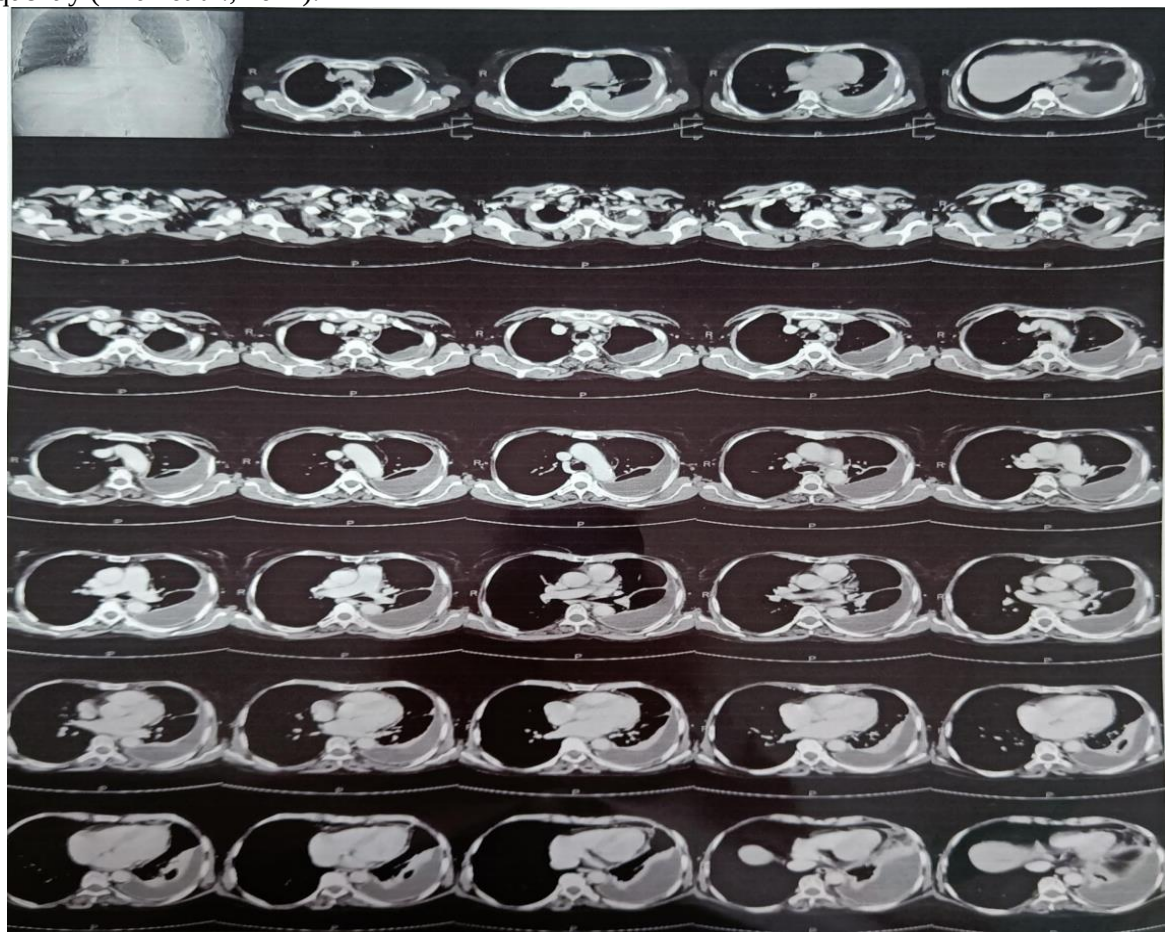

Image 1: HRCT Thorax (Plain + Contrast) Plural effusion

Hepatotoxicity caused by anti-TB drugs can range from asymptomatic increases in liver enzymes to fulminant liver failure. Discontinue antitubercular medications like INH and RIF causing hepatotoxicity,

but make the decision on a case-by-case basis, considering severity and tuberculosis treatment need. Liver function tests are used to assess liver injury, and supportive care is provided to manage symptoms. Alternative tuberculosis treatment regimens may be considered based on severity and patient's condition. Hepatoprotective agents like N-acetylcysteine can support liver function. The only FDA-approved medication for the treatment of primary biliary cholangitis as well as other cholestatic liver illnesses is ursodeoxycholic acid. Recent controlled clinical investigations show that oral administration of ursodeoxycholic acid may delay the onset of anti-tuberculosis drug-induced liver injury and hasten the healing of liver injury, although this is still experimental. During recovery, monitoring and follow-up are crucial. If underlying liver disease is present, it should be managed to prevent further damage. A multidisciplinary approach is essential for optimal management, involving infectious disease specialists, hepatologists, and other healthcare providers (Lang *et al.*, 2020).

Medications Chart

Table 2: Medications given during the period of hospitalization.

Sr. No.	Drug Name	Dose	Fre-quency	ROA	Day -1	Day-2	Day -3	Day-4	Day-5	Day-6	Day -7	Day-8	Day-9	Day -10
1	Tab. Levofloxacin	500 mg	A/D	Oral	+	+	+	+	+	+	+	+	+	+
2	Tab. Ethambutol	1.2 mg	A/D	Oral	+	+	+	+	+	+	+	+	+	+
3	Inj. Streptomycin	0.75 mg	A/D	IV	+	+	+	+	+	+	+	+	+	+
4	Tab. Dicyclomine + Mefenamic acid	50 mg	BD	Oral	+							+	+	+
5	Tab. Clonidine	100 mg	QID	Oral	+		+					+	+	+
6	T. Atorvastatin + Aspirin	75/20 mg	OD	Oral	+		+				+	+	+	+
7	Tab. Nifedipine	30 mg	TID	Oral	+		+				+	+	+	+
8	Inj. Vit K	10 mg	OD	IV			+	+	+	+	+	+	+	+
9	Nebulizer Levosalbutamol & Ipratropium		TID	Inhalation			+				+			
10	Nebulizer Budesonide		TID	Inhalation			+				+	+	+	+
11	Calamine lotion		TID	Dermal application			+				+			
12	Tab. Pregabalin	75 mg	OD	Oral				+						
13	Inj. Ondansetron	4 mg	TID	IV								+	+	+
14	Tab.Prazosin	5 mg	TID	Oral	+		+				+	+	+	+
15	Tab. Pantoprazole	40 mg	OD	Oral			+				+	+	+	+
16	Syr. Sucralfate	2 tsp	BD	Oral				+						
17	Tab. Metoprolol	50 mg	BD	Oral							+	+	+	+
18	Inj. Tramadol	1 in 100 ml NS	BD	IV								+	+	+
19	Inj. Metoclopramide	10mg/2 ml	STAT	IV								+	+	

Discharge Medications

Table 3: Discharge Medications.

Sr. no	Generic Name	Dose	Frequency	Route
1.	Inj. Streptomycin	0.75 mg	A/D	IV
2.	Tab. Levofloxacin	500mg	OD	Oral
3.	Tab. Ethambutol	1.2 mg	A/D	Oral
4.	Tab. Calcium + Vitamin D3	500 mg	BD	Oral
5.	Tab. Acetaminophen	300 mg	SOS	Oral
6.	Tab. Ursodeoxycholic acid	300 mg	BID	Oral

CONCLUSION

In conclusion, this case report highlights the potentially severe and life-threatening complication of hepatitis with coagulopathy induced by anti-Koch's treatment. Healthcare professionals must be vigilant in monitoring patients undergoing anti-tubercular therapy and promptly recognize the signs and symptoms of drug-induced liver injury. Early detection and immediate discontinuation of the offending agents are crucial to prevent further liver damage and associated complications. Moreover, this case emphasizes the need for ongoing research to identify risk factors, develop preventive strategies, and improve the management of this rare but significant adverse reaction.

SUMMARY

Anti-tuberculosis treatment carries a risk of drug-induced liver injury (DILI), especially for patients with pre-existing conditions like hypertension and chronic kidney disease. The symptoms include jaundice, abdominal pain, and elevated liver enzymes. Supportive therapy, early recognition, and close monitoring are crucial for successful management and recovery. Further research is needed to better understand risk factors and develop preventive strategies for this serious complication.

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Conflict Of Interest

No potential conflict of interest relevant to this article was reported.

Consent

Patient consent has been collected and preserved by the author(s).

Author Contribution

Conceptualization: GK, RG, PP, KP. Data curation: GK. Methodology: RG. Visualization: GK, RG, PP. Writing - original draft: PP, GK, RG, KP. Writing – review- GK, RG, KP.

Abbreviations

TB: Tuberculosis; **DILI:** Drug-induced liver injury; **CKD**: Chronic kidney disease; ATT: Antitubercular drug therapy; **DOT:** Direct observe therapy; **INH:** Isoniazid; **HB:** Haemoglobin; **RBC:** Red blood cells; **PCV:** Pack cell volume; **MCHC**: Mean corpuscular hemoglobin concentration; **HBV:** Hepatitis B virus; **ALT:** Alanine transaminase; **AST:** Aspartate transaminase; **ULN:** Upper limit normal; **UDCA**: Ursodeoxycholic acid; **FDA:** Food and drug administration.

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