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A case report on therapeutic role of n-acetylcysteine in attenuating anti-tubercular therapy-induced hepatotoxicity

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Abstract
Background: Anti-tubercular therapy (ATT)-induced hepatotoxicity is one of the most clinically significant adverse effects of tuberculosis treatment, particularly associated with isoniazid, rifampicin, and pyrazinamide. N-acetylcysteine (NAC), a thiol-containing antioxidant and glutathione precursor, has demonstrated hepatoprotective potential beyond its established use in acetaminophen toxicity.
Case Presentation: We report the case of a 29-year-old female who developed hepatotoxicity secondary to ATT and showed marked biochemical improvement following intravenous NAC using a three-bag regimen, followed by oral maintenance therapy. Liver function tests normalized, allowing for safe reintroduction of ATT without recurrence of hepatotoxicity.
Conclusion: NAC may serve as an effective adjunct in the management of ATT-induced hepatotoxicity due to its antioxidant and mitochondrial-stabilizing effects. Further controlled trials are warranted to validate its role in drug-induced liver injury.

Keywords: Tuberculosis, hepatotoxicity, n-acetylcysteine, anti-tubercular therapy, drug-induced liver injury

Introduction
The mainstay of treatment for tuberculosis (TB), first-line anti-tubercular medications such isoniazid, rifampicin, pyrazinamide, and ethambutol, is often worsened by hepatotoxicity. Between 2 and 28% of people worldwide suffer from anti-tuberculosis drug-induced liver injury (AT-DILI), which might cause therapy to be stopped and raise the risk of resistance or recurrence (2). The pathophysiology includes immune-mediated liver damage, oxidative stress, mitochondrial dysfunction, and the production of reactive metabolites from isoniazid, including hydrazine and isonicotinic acid [3, 4].
N-acetylcysteine (NAC), originally developed for acetaminophen overdose, replenishes intracellular glutathione and mitigates oxidative stress. Recent studies, including randomized controlled trials and meta-analyses, support its benefit in non-acetaminophen drug-induced liver injury and ATT-related hepatotoxicity [5-7]. NAC's hepatoprotective action is attributed to improvement in hepatic microcirculation, anti-inflammatory effects, and mitochondrial stabilization [8, 9]. This case report describes successful management of severe ATT-induced hepatotoxicity with NAC in a young woman, highlighting its therapeutic potential.

Case Presentation
A 29-year-old female, weighing 40 kg and diagnosed with disseminated tuberculosis, presented to the Medicine OPD with complaints of intermittent fever, anorexia, pruritus for the past 10 days, and 4 episodes of vomiting in the last 24 hours. She had been on first-line ATT for the past 15 days. The patient belonged to a lower-middle-class rural background and was brought in by her husband. On examination, her vitals were: BP = 110/60 mmHg, PR = 120 bpm, SpO2 = 88% on room air, and RBS = 122 mg/dL. CECT chest revealed miliary nodules, and ultrasonography on both upper arms were noted. Based on clinical presentation and exclusion of viral hepatitis and other causes (negative HBsAg, Anti-HCV, Leptospira

antigen; normal HAE; non-reactive HIV), a diagnosis of ATT-induced liver injury (DILI) was made.
Laboratory evaluation revealed:

- TLC = 21,000 cells/µL (leukocytosis)
- AST = 589 U/L
- ALT = 569 U/L
- ALP = 411 U/L
- CRP = 7.02 g/dL
- Total Bilirubin = 1.38 mg/dL
- Direct Bilirubin = 1.07 mg/dL
- Total Protein = 4.70 g/dL
- Serum Albumin = 2.01 g/Dl

Initial management involved discontinuation of ATT and administration of supportive treatments (eg, intravenous fluid) and hepatoprotective agents:

- Ursodeoxycholic acid (UDCA) 300 mg BD
- Silymarin 150 mg TDS

During the first four days of supportive care, liver enzyme levels first decreased, but then they rose over the next four days, suggesting that hepatic damage was still occurring. Due to persistently increased transaminases and new evidence that N-acetylcysteine (NAC) plays a role in drug-induced liver impairment [1, 5, 6], intravenous NAC therapy was started on Day 8 using the conventional three-bag protocol. As suggested by recent clinical trials, the dosage approach included a loading dose spread out over one hour, followed by consecutive infusions at four and sixteen hours [1, 6] (Table1).
This was followed by a marked decrease in AST and ALT over the next 5 days (Figure 1). NAC was continued orally at 600 mg BD post-meals. On Day 7 post-NAC, a modified ATT regimen (isoniazid, rifampicin, and ethambutol 2 tabs/day) was cautiously reintroduced. With stable liver function tests and no clinical deterioration, full-dose HR was started after 3 days. Pyrazinamide was added 4 days later. Liver enzyme levels remained within normal limits after reintroduction, and the patient tolerated full-dose HRZE. She was discharged a week later with a 4-week follow-up plan.
Gradual improvement was observed both biochemically and clinically. ATT was reintroduced in a staggered manner, beginning with non-hepatotoxic agents. The patient was monitored closely and completed ATT without recurrence of hepatotoxicity.

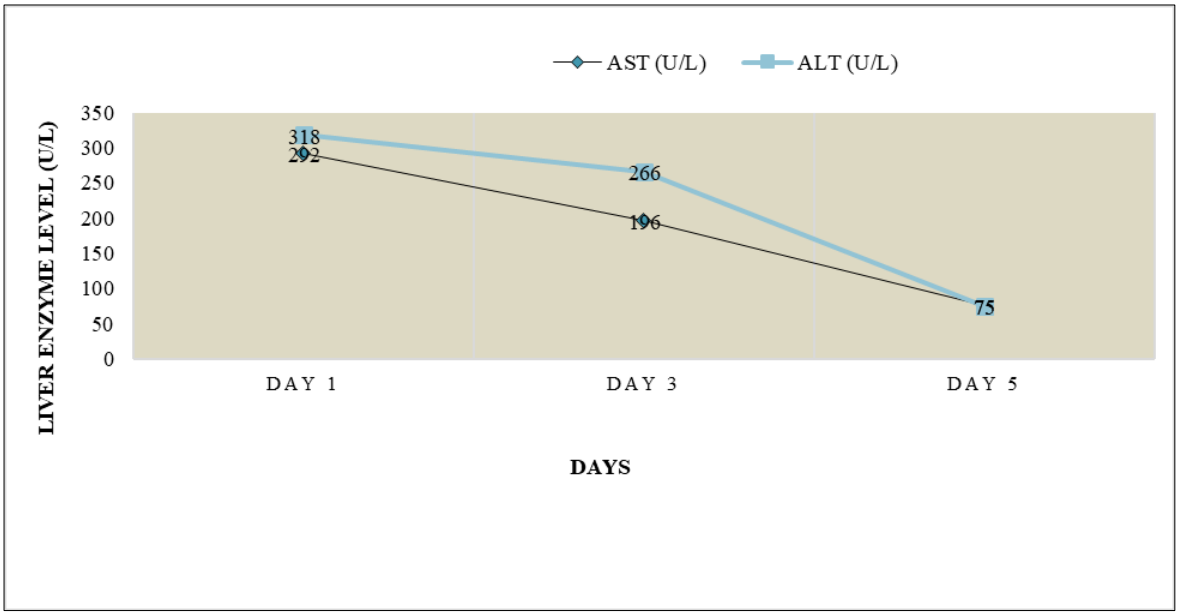

Fig 1: The fall in Aspartate Aminotransferases (AST) and Alanine Aminotransferases (ALT) levels following administration of intravenous N-Acetylcysteine (NAC) 3-bag dosing regimen

Table 1: Standard 3-bag regimen of intravenous N-acetylcysteine (NAC)

Dose	Medication & Diluent	Infusion Duration
Loading Dose	Injection NAC 6 g in 200 ml of 5% Dextrose	1 hour
Second Dose	Injection NAC 2 g in 500 ml of 5% Dextrose	4 hours
Third Dose	Injection NAC 4 g in 1000 ml of 5% Dextrose	16 hours

Discussion

ATT-induced hepatotoxicity remains a major challenge in tuberculosis management. Mechanistically, isoniazid is metabolized to hydrazine, a reactive intermediate that depletes hepatic glutathione and causes oxidative damage. Genetic factors (e.g., NAT2 slow acetylator phenotype) and concurrent rifampicin use enhance this risk (2,3). NAC counteracts these mechanisms by restoring glutathione, scavenging free radicals, and improving mitochondrial function [5, 6].
Recent studies substantiate the hepatoprotective role of NAC in ATT-DILI. Moosa *et al*. (2021) demonstrated that NAC shortened recovery time and reduced hospital stay in AT-DILI patients [1]. Baniasadi *et al*. (2022) reviewed that NAC supplementation improved liver enzyme recovery and overall tolerance to ATT. Sanabria-Cabrera *et al*. (2022) and Nikbaf-Shandiz *et al*. (2023) further confirmed NAC's benefit in non-acetaminophen DILI through improved liver function and antioxidant effects. In the present case, intravenous NAC resulted in rapid normalization of transaminases, permitting early reintroduction of ATT.
Although NAC's mortality benefit in non-acetaminophen

liver failure remains debated, its safety, low cost, and physiological rationale support its adjunctive use in ATT-induced hepatotoxicity [7, 9]. Our case aligns with recent evidence suggesting NAC as a feasible, evidence-based intervention in DILI, including ATT-related liver injury.

Conclusion

This case highlights the therapeutic potential of N-acetylcysteine in mitigating ATT-induced hepatotoxicity. By replenishing glutathione and reducing oxidative stress, NAC accelerates hepatic recovery and facilitates safe reintroduction of ATT. Controlled clinical trials are warranted to establish standardized dosing protocols and confirm efficacy in diverse patient populations.

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Conflict of Interest: None declared.

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