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A 31-Year-Old Woman With Liver Cirrhosis Due to Wilson Disease and the Double Impact of Active Tuberculosis and Anti-Tuberculosis Therapy Resulting in Acute Liver Injury

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 31-year-old
Final Diagnosis: Tuberculosis and DILI
Symptoms: Abdominal pain • ascites • fever • vomitting
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Rare disease

Background: In some patients with Wilson disease, there can be a combined impact of active tuberculosis (TB) and anti-tuberculosis therapy (ATT), a "double hit", due to drug-induced liver injury that can accelerate Wilson cirrhosis and result in acute liver failure. This report presents the case of a 31-year-old woman with liver cirrhosis due to Wilson disease and the combined impact of active TB and ATT resulting in acute liver injury.

Case Report: A 31-year-old woman with genetically confirmed Wilson disease and Child-Pugh B liver cirrhosis presented in July 2025 with acute hepatic decompensation. Investigation revealed a positive QuantiFERON-TB Gold test result, lymphocytic exudative ascites, and a clinical picture consistent with extrapulmonary TB. Empiric ATT was initiated with rifampicin and isoniazid. Within 2 months, she re-presented with severe anti-TB drug-induced liver injury, which manifested as acute-on-chronic liver failure. The hepatotoxic regimen was immediately discontinued, and intensive supportive care was administered, resulting in gradual stabilization of liver function and clinical improvement.

Conclusions: This case demonstrates the critical "double-hit" vulnerability in Wilson disease, in which copper-mediated glutathione depletion leaves the liver unable to detoxify standard anti-TB drugs. Clinicians managing TB in patients with decompensated Wilson cirrhosis should avoid standard rifampicin-isoniazid regimens and use hepatosafe alternatives instead. A high index of suspicion for TB is warranted in all cirrhotic patients with fever, lymphocytic exudative ascites, and unexplained decompensation.

Keywords: Case Reports • Drug-Induced Liver Injury • Hepatology • Liver Cirrhosis • Tuberculosis • Wilson Disease

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Introduction

Wilson disease is a rare autosomal recessive disorder of copper metabolism. It is caused by mutations in the *ATP7B* gene on chromosome 13, which encodes a copper-transporting P-type ATPase [1,2]. Loss of this transporter impairs biliary copper excretion, resulting in progressive copper accumulation in the liver, brain, and cornea [1]. The global prevalence is approximately 1 in 30 000. Gene mutation carrier frequency is roughly 1 in 90 [2]. Hepatic manifestations span a broad spectrum, from asymptomatic elevation of transaminases and chronic hepatitis to established cirrhosis and acute liver failure [1]. Neuropsychiatric involvement, including dysarthria, dystonia, tremors, and psychiatric disturbance, is more common in adolescents and adults [1]. Diagnosis consists of a combination of serum ceruloplasmin, 24-hour urinary copper excretion, slit-lamp examination for Kayser-Fleischer rings, and *ATP7B* gene sequencing [1,2]. Treatment with copper chelators (D-penicillamine, trientine) or zinc salts is the long-term management [1].

Wilson cirrhosis represents end-stage hepatic copper toxicosis. Once cirrhosis is established, hepatic decompensation may be precipitated by intercurrent insults, including infection, surgery, or hepatotoxic drugs [1,2]. Decompensated cirrhosis in Wilson disease is associated with the syndrome of cirrhosis-associated immune dysfunction, which impairs both innate and adaptive immunity and predisposes patients to opportunistic infections [3].

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains one of the foremost infectious causes of death worldwide. The World Health Organization (WHO) estimated 1.25 million TB-related deaths in 2023 [4]. Patients with liver cirrhosis carry a substantially elevated risk of active TB compared with the general population. This risk increases with the degree of hepatic decompensation [5]. Extrapulmonary TB, including peritoneal TB, accounts for a disproportionate share of cases in immunocompromised patients and frequently presents without classic respiratory features [6].

Anti-tuberculosis therapy (ATT) carries an inherent risk of drug-induced liver injury (DILI). Among first-line agents, isoniazid and pyrazinamide are the most hepatotoxic, with rifampicin contributing synergistic toxicity through potent induction of cytochrome P450 2E1 (CYP2E1) [7,8]. In patients with pre-existing liver disease, the threshold for severe DILI is substantially lower. Current guidelines from the American Thoracic Society and the European Respiratory Society recommend modified, hepatosafe ATT regimens for patients with Child-Pugh B or C cirrhosis, avoiding isoniazid and pyrazinamide and substituting fluoroquinolones and ethambutol [9].

The intersection of Wilson cirrhosis and active TB is rare. The copper-mediated depletion of hepatic glutathione (GSH) in Wilson disease renders hepatocytes uniquely vulnerable to the oxidative metabolites of isoniazid. It creates a synergistic hepatotoxicity that exceeds the additive risk seen in other cirrhotic etiologies [1,10]. Published case reports describing this combination are scarce. Stankiewicz et al described the diagnostic difficulty and the role of liver transplantation in acute liver failure due to Wilson disease, underscoring that conventional medical management is often insufficient once acute liver failure supervenes [11].

In this report, we present the case of a 31-year-old woman with liver cirrhosis due to Wilson disease and the combined impact of active TB and ATT resulting in acute liver injury.

Case Report

Initial Diagnosis and Disease Course

A 31-year-old woman was diagnosed with Wilson disease at the age of 9 years (2003), following family screening that had been prompted by the hepatic decompensation of her twin brother, who subsequently died. Her diagnosis was established by genetic confirmation of a pathogenic *ATP7B* mutation. It was also supported by a reduced serum ceruloplasmin of less than 0.10 g/L (reference range, 0.20-0.60 g/L) and markedly elevated 24-hour urinary copper excretion of 12 µmol/24 h (reference range below 0.6 µmol/24 h).

Over subsequent years, hepatic disease progressed to established cirrhosis complicated by portal hypertension and splenomegaly. Upper gastrointestinal endoscopy in 2017 demonstrated portal hypertensive gastropathy without esophageal varices. Neuropsychiatric involvement was present in the form of cognitive decline and mild intellectual disability. Kayser-Fleischer rings were absent on slit-lamp examination. Long-term management included D-penicillamine chelation therapy at 1000 mg/day, which was reduced from a higher dose due to non-nephrotic proteinuria of up to 0.61 g/24 h, together with pyridoxine (vitamin B6) supplementation.

First Hospital Admission (July 2025): Acute Decompensation and TB Diagnosis

The patient was admitted emergently in July 2025 with a 3- to 4-day history of abdominal pain, fever, vomiting, and new-onset ascites. Her Child-Pugh score was calculated as B (9 points), based on the following: moderate ascites (2 points); no hepatic encephalopathy (1 point); serum albumin, 29.1 g/L (reference range, 35-50 g/L; 3 points); serum bilirubin, 42 µmol/L (reference range, 5-17 µmol/L; 2 points); and international normalized ratio (INR) of 1.5 (reference range, 0.9-1.2; 1 point).

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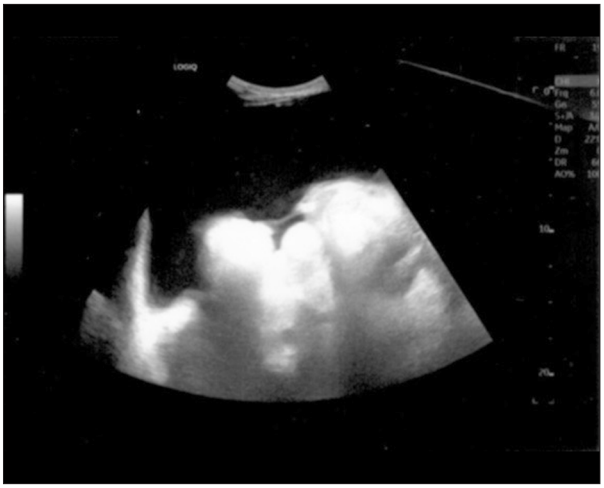

Figure 1. Abdominal ultrasound demonstrating large-volume ascites in a 31-year-old woman with Wilson disease–related cirrhosis (July 2025). The image shows free fluid accumulation in the peritoneal cavity consistent with decompensated cirrhosis. Ultrasound also confirmed a nodular cirrhotic liver morphology and splenomegaly. All images are original and were obtained from this patient during the index admission.

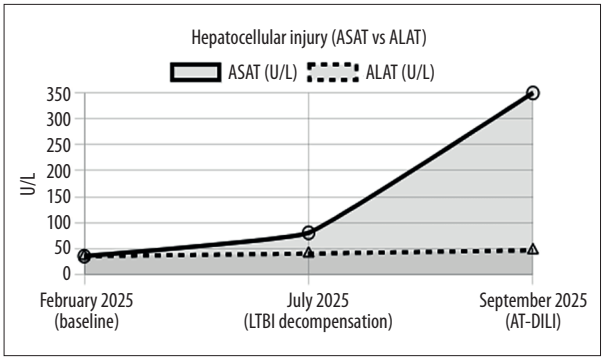

Figure 2. Trend of serum aminotransferases aspartate aminotransferase (AST; reference range 10-40 U/L) and alanine aminotransferase (ALT; reference range 7-40 U/L) across 3 hospital admissions. Values from February 2025 (stable baseline), July 2025 (first acute decompensation with extrapulmonary tuberculosis), and September 2025 (second admission with severe antituberculosis drug-induced liver injury, AT-DILI) are shown. The steep rise in both aminotransferases in September 2025 coincides temporally with the initiation of first-line anti-tuberculosis therapy (rifampicin and isoniazid).

Table 1. Sequential liver biochemistry across 3 hospital admissions. Aaspartate aminotransferase (AST; reference range 10-40 U/L); alanine aminotransferase (ALT; reference range 7-40 U/L); total bilirubin (reference range 5-17 µmol/L); albumin (reference range 35-50 g/L); international normalized ratio (INR; reference range 0.9-1.2). The steep rise in AST and ALT in September 2025 coincides with the initiation of rifampicin and isoniazid. Antituberculosis drug-induced liver injury, AT-DILI.

	Total bilirubin [µmol/L]	AST [U/L]	ALT [U/L]	INR
February 2025 (baseline)	22.1	45	27	1.25
July 2025 (LTBI decompensation)	42	60	15	1.51
September 2025 (AT-DILI)	84	349	46	1.61

Abdominal ultrasound confirmed a cirrhotic liver morphology, splenomegaly, and large-volume ascites (**Figure 1**). Full blood count demonstrated leukopenia. Biochemical results showed an elevated erythrocyte sedimentation rate and C-reactive protein level, direct hyperbilirubinemia, significant hypoalbuminemia, and a prolonged INR. Aspartate aminotransferase (AST) was elevated to approximately twice the upper limit of normal (ULN), with alanine aminotransferase (ALT) comparably raised (**Table 1, Figure 2**).

Diagnostic paracentesis showed an exudative ascitic fluid with a serum-ascites albumin gradient below 11 g/L and a pronounced lymphocytic predominance, making spontaneous bacterial peritonitis unlikely. An immunological panel showed markedly elevated immunoglobulins (IgA, IgG, and IgM), a positive antinuclear antibody titre of 1: 1280, and a beta-gamma bridge on serum protein electrophoresis, all consistent with advanced cirrhosis rather than a primary autoimmune hepatitis flare. Computed tomography of the abdomen confirmed progressive hepatic atrophy, mild splenomegaly, and new-onset ascites, with no significant lymphadenopathy to suggest lymphoma.

Given the persistent fever, elevated inflammatory markers, lymphocytic exudative ascites, and the absence of an alternative diagnosis, a QuantiFERON-TB Gold In-Tube (QFT-G) test was performed and returned positive. Sputum cultures for *M. tuberculosis* were negative. Ascitic fluid culture for mycobacteria was requested but returned no growth. Owing to the high clinical probability of peritoneal TB and the patient's deteriorating condition, empiric ATT was initiated after infectious disease consultation.

It should be noted that histopathological confirmation of Wilson disease and cirrhosis by liver biopsy was not performed in this patient. Liver biopsy was considered prohibitively high-risk given coagulopathy (INR, 1.5) and portal hypertension. Laparoscopic

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biopsy for TB diagnosis was similarly contraindicated. The diagnosis of Wilson disease was based on genetic, biochemical, and clinical grounds; the diagnosis of cirrhosis was based on ultrasound, endoscopic, and clinical findings; and the diagnosis of extrapulmonary TB was based on the positive QFT-G test, lymphocytic exudative ascites, and the systematic exclusion of alternative diagnoses.

Initiation of ATT

Empiric first-line ATT was prescribed by an infectious disease specialist as rifampicin plus isoniazid, following standard infectious disease protocols. At this juncture, the specific pharmacological vulnerability of the Wilsonian liver to CYP2E1-mediated oxidative injury was not factored into the prescribing decision.

Second Hospital Admission (September 2025): Severe Anti-TB DILI

Approximately 2 months after starting ATT, the patient was readmitted with severe malaise, worsening jaundice, anorexia, marked hypokalemia, and clinical signs of advancing hepatic failure. Laboratory test results demonstrated a steep rise in AST and ALT to levels substantially above their prior values, worsening hyperbilirubinemia, a further decrease in serum albumin, and a prolonged INR (**Table 1, Figure 2**). The clinical and biochemical picture met diagnostic criteria for severe anti-TB DILI (AT-DILI) and acute-on-chronic liver failure.

Rifampicin and isoniazid were discontinued immediately. Intensive supportive care was instituted and consisted of intravenous ademetionine 800 mg/day as a glutathione precursor and methyl donor; intravenous human albumin 20%, 50 mL/day for oncotic support; lactulose for hepatic encephalopathy prophylaxis; and intravenous correction of hypokalemia. D-penicillamine was continued throughout at the established dose. Over the following days, transaminase levels began to fall and bilirubin levels stabilized (**Table 1, Figure 2**).

Discharge and Follow-Up

The patient was discharged with instructions to defer further ATT until complete hepatic recovery. At 1-month outpatient follow-up, she reported weight gain, restored appetite, and a reduction in abdominal girth and peripheral edema, consistent with stabilization of hepatic decompensation. She had not yet attended objective clinical review or laboratory monitoring at that point. Re-initiation of ATT was deferred pending return of transaminases to below 2 times the ULN and normalization of bilirubin, at which point a hepatosafe regimen, consisting of fluoroquinolone plus ethambutol, without isoniazid or pyrazinamide, was planned (**Table 1**).

Discussion

The main lesson from this case is that standard rifampicin-isoniazid ATT carries a life-threatening risk in patients with Wilson disease and decompensated cirrhosis, exceeding the elevated risk seen in other cirrhotic etiologies. The mechanism is biochemically specific: not merely an additive hepatotoxic insult, but a synergistic failure rooted in the pre-existing depletion of the liver's principal defense against reactive metabolites.

The patient's susceptibility to extrapulmonary TB is readily explained by cirrhosis-associated immune dysfunction. This syndrome involves a dual paradox of systemic immune activation and acquired immune deficiency, whereby the reticuloendothelial system is compromised, reducing bacterial clearance; T-lymphocyte activation and neutrophil phagocytosis are impaired; and portal-systemic shunting further reduces hepatic immune surveillance [3,12]. Thulstrup et al demonstrated a substantially elevated relative risk of TB in cirrhotic patients that rises with decompensation severity [5]. In the present patient, hematogenous seeding to the peritoneum is the most plausible route of infection, consistent with the lymphocytic exudative ascites and positive QFT-G test.

The diagnostic challenge is representative of peritoneal TB in the cirrhotic population. Both conditions produce ascites, fever, abdominal pain, and cachexia, making clinical differentiation unreliable [6]. Smear microscopy of ascitic fluid for acid-fast bacilli yields positive results in fewer than 5% of cases due to the dilution effect of high-volume ascites [13]. Mycobacterial culture of ascitic fluid has a turnaround of weeks. Laparoscopic biopsy with tissue culture is the gold standard but was contraindicated in the present case by coagulopathy and portal hypertension. A positive QFT-G test combined with lymphocytic exudative ascites and a serum-ascites albumin gradient below 11 g/L therefore constituted sufficient grounds for empiric therapy, a widely accepted approach in immunocompromised patients with high pre-test probability [6,14]. Adenosine deaminase measurement in the ascitic fluid, which has sensitivity and specificity above 90% for tuberculous peritonitis [14,15], was not documented in this case and would have further strengthened diagnostic confidence. This is a limitation we acknowledge for future practice.

The hepatotoxicity observed in September 2025 reflects a precise pharmacological storm. In Wilson disease, free copper catalyzes the generation of hydroxyl radicals through the Fenton and Haber-Weiss reactions, causing sustained oxidative stress that progressively depletes hepatic GSH stores and produces chronic mitochondrial dysfunction [1,16]. When isoniazid is then introduced, it is metabolized via N-acetyltransferase 2 to acetylisoniazid, hydrolyzed to acetylhydrazine, and subsequently oxidized by CYP2E1 to highly reactive electrophilic

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metabolites [7]. Under normal conditions, these are rapidly conjugated by GSH. In the patient with Wilson disease, however, GSH reserves are already pathologically depleted, leaving hepatocytes defenseless against these intermediates and precipitating rapid hepatocellular necrosis [10]. Rifampicin compounds this by powerfully inducing CYP2E1, amplifying the generation of toxic acetylhydrazine derivatives, a mechanism of toxic synergy well documented in the anti-TB literature [7,8]. This is qualitatively distinct from AT-DILI in viral hepatitis, in which immune flares predominate, or in alcoholic cirrhosis, in which alcohol-induced CYP2E1 upregulation increases isoniazid toxicity but GSH depletion is less fixed. In Wilson disease, copper-driven GSH depletion is a near-permanent metabolic state.

A further pharmacological interaction is worth noting. Long-term D-penicillamine binds pyridoxal 5-phosphate (the active form of vitamin B6) to form an inactive thiazolidine complex that is rapidly excreted [17,18]. Isoniazid independently inactivates pyridoxal 5-phosphate by forming hydrazones. The simultaneous administration of both drugs risks compounded pyridoxine depletion, impairing GABA-mediated neurotransmission and potentially worsening neurotoxicity in a patient already carrying neuropsychiatric Wilson disease. Adequate pyridoxine supplementation is essential whenever isoniazid and D-penicillamine are co-administered.

The management response, which consisted of immediate cessation of ATT, intravenous ademetionine as a GSH precursor, albumin infusion, and lactulose, was appropriate and resulted in clinical stabilization consistent with published reports of recovery following ATT withdrawal in DILI [8]. The case of Stankiewicz et al reinforces that conventional medical management is often insufficient once acute liver failure supervenes in Wilson disease, and that early hepatology and transplant referral should be part of the contingency plan in such patients [11].

Looking forward, current American Thoracic Society and European Respiratory Society guidance for patients with Child-Pugh B or C advocates a hepatosafe ATT regimen: a fluoroquinolone (levofloxacin 750 mg/day or moxifloxacin 400 mg/day), ethambutol (15 mg/kg/day), and when needed, an injectable agent such as streptomycin (15 mg/kg/day) [9]. This eliminates isoniazid and pyrazinamide at the cost of a prolonged treatment duration of 18 to 24 months. Should partial reintroduction of first-line drugs ever be considered after full hepatic recovery, sequential cautious reintroduction of rifampicin alone—the least hepatotoxic of the first-line agents—may be attempted with weekly liver biochemistry monitoring [9]. Isoniazid should not be reintroduced in patients who have experienced severe AT-DILI in the context of Wilson disease. Throughout any future ATT course, AST, ALT, and bilirubin levels should be monitored weekly for the first month and once every 2 weeks thereafter; any AST or ALT increase above 3 times the ULN with symptoms, or above 5 times the ULN without symptoms, mandates immediate cessation [9].

Conclusions

This case demonstrates the lethal potential of standard rifampicin-isoniazid ATT in a patient with Wilson cirrhosis, in which copper-mediated GSH depletion renders the liver uniquely susceptible to CYP2E1-generated toxic metabolites. When TB is diagnosed in the setting of decompensated Wilson disease, hepatosafe ATT regimens incorporating a fluoroquinolone and ethambutol, without isoniazid or pyrazinamide, should be the default treatment strategy. A high index of suspicion for extrapulmonary tuberculosis is warranted in all cirrhotic patients presenting with fever, lymphocytic exudative ascites, and unexplained decompensation, particularly in TB-endemic regions.

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Declaration About Informed Consent

Written informed consent was obtained from the patient's guardian. Proof of consent is available from the corresponding author upon reasonable request.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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