A Case of Progressive Cholestatic Drug-Induced Liver Injury Due to Terbinafine

Dana Ley, MD; Jessica Musto, MD; Adnan Said, MD, MS

ABSTRACT

Introduction: Terbinafine is commonly prescribed for onychomycosis. It rarely leads to severe, prolonged cholestatic drug-induced liver injury. Clinicians should remain vigilant for this complication.

Case Presentation: A 62-year-old woman was started on terbinafine and developed mixed hepatocellular and cholestatic drug-induced liver injury, confirmed on liver biopsy. The injury became predominantly cholestatic. Unfortunately, she developed coagulopathy with elevated international normalized ratio and progressive drug-induced liver injury with severely elevated alkaline phosphatase and total bilirubin, requiring repeat liver biopsy. Fortunately, she did not develop acute liver failure.

Discussion: Prior case reports and series have documented severe cholestatic drug-induced liver injury (although with lesser degree of bilirubin elevation) due to terbinafine, which has very rarely been associated with acute liver failure, need for liver transplantation, and/or death.

Conclusions: Non-acetaminophen drug-induced liver injury is idiosyncratic. Complications including acute liver failure and vanishing bile duct syndrome can be slow to develop, so monitoring for them is important over longitudinal follow-up.

INTRODUCTION

Terbinafine is an allylamine antifungal medication administered both topically and orally. It is active against dermatophytes affecting the skin and nails and is thought to be effective due to selective inhibition of the fungal squalene epoxidase, which kills fungal cells. Oral terbinafine is used to treat onychomycosis, typically at a dose of 250 milligrams daily for 6 to 12 weeks.[1-2] Its most common side effects include headaches, change in taste, rash, and gastrointestinal disturbances.[3]

Terbinafine also has been associated with drug-induced liver injury (DILI). Oral terbinafine may lead to any degree of elevated serum aminotransferases in less than 1% of patients. These elevations are typically asymptomatic and resolve with discontinuation of the medication.[4] Clinically apparent liver injury is rare, usually arising within the first 6 weeks of therapy when it occurs.[5] Initially, the injury pattern may be hepatocellular or cholestatic, but it typically progresses into a cholestatic pattern, which may become prolonged.[6] The exact mechanism of liver injury is unknown but may be due to a hypersensitivity reaction.[7]

Most cases of DILI secondary to terbinafine resolve within 3 to 6 months of medication discontinuation. Rarely, the liver injury is severe and progressive, potentially leading to vanishing bile duct syndrome or acute liver failure, which may require liver transplantation or prove fatal.[8] This case highlights the importance of remaining attentive to development of these complications.

CASE REPORT

A 62-year-old woman with a history of thyroid cancer (status post-thyroidectomy and parathyroidectomy 40 years prior), hypothyroidism, type 2 diabetes mellitus, hypertension, depression, posttraumatic stress disorder, and pancytopenia of unknown etiology presented initially to an outside hospital with 1 week of weakness, a 20-pound weight loss, and 3 days of jaundice, dark urine, and pale stools. About 6 weeks prior, she started a 12-week

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Author Affiliations: University of Wisconsin Hospitals and Clinics, Department of Medicine, Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin (Ley, Musto, Said); William S. Middleton Memorial Veterans Hospital, Madison, Wis (Said).

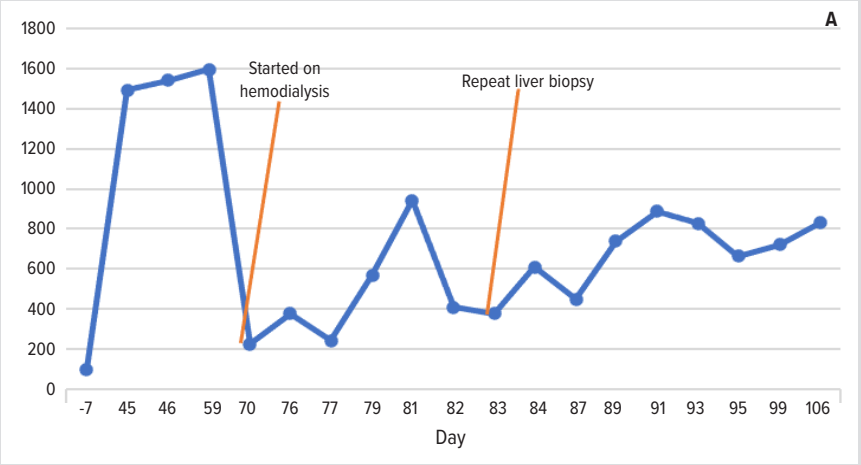
Corresponding Author: Dana Ley, MD, 1685 Highland Ave, Ste 4000, Madison, WI 53705, phone 608.263.1995; email DLey@uwhealth.org.

course of terbinafine 250 milligrams daily for onychomycosis of the toenails, which is the recommended length of treatment. Four days before presentation and 41 days after starting terbinafine, she discontinued its use due to malaise. She denied herbal, alcohol, or illicit drug use. Additional medications included bupropion, cromolyn nasal spray, diclofenac gel, levothyroxine, loratadine, metformin, risperidone, and sertraline. There were no other medication changes at the same time or after starting the terbinafine. She had no recent antibiotic use. She had no history of travel outside of her home state and no recent sexual activity. She had no prodromal viral symptoms.

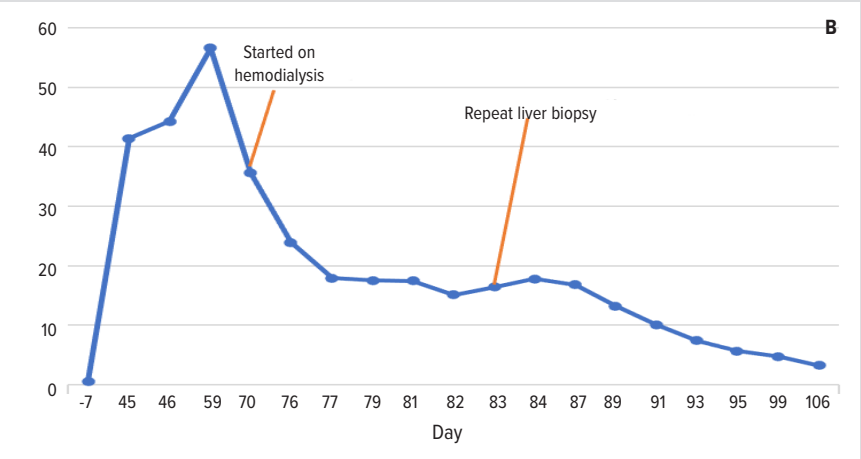
Initial labs were notable for persistent pancytopenia, characterized by a white blood cell count of 2.7, hemoglobin of 8.5, platelet count of 114, low absolute neutrophil count of 1.9, absolute lymphocyte count of 0.4, normal absolute eosinophil count of 0.1, and absolute monocyte count of 0.3. She also had an acute kidney injury with creatinine of 1.6 and liver injury with aspartate aminotransferase (AST) of 163, alanine aminotransferase (ALT) of 245, alkaline phosphatase of 1494, and total bilirubin of 41.4. The R factor—used to determine whether a liver injury is hepatocellular or cholestatic—was 0.59, suggestive of cholestatic injury. Albumin was 2.8, and international normalized ratio (INR) was 1.72. Baseline liver enzymes and creatinine were obtained 7 days prior to starting terbinafine and were normal. INR had not been obtained. Computed tomography of the abdomen and pelvis without contrast at presentation showed worsening splenomegaly and stable hepatomegaly (both present previously), nonspecific pericholecystic fluid, and a mild volume of perihepatic ascites. There was no evidence of skin rashes or fevers.

One day later, the patient was transferred to another hospital. Liver biopsy showed moderate to extensive hepatocanalicular cholestasis with mild lobular inflammation, which may consist of Kupffer cell aggregates (phagocytic cells

Figure 1. Patient's Alkaline Phosphatase Levels and Total Bilirubin

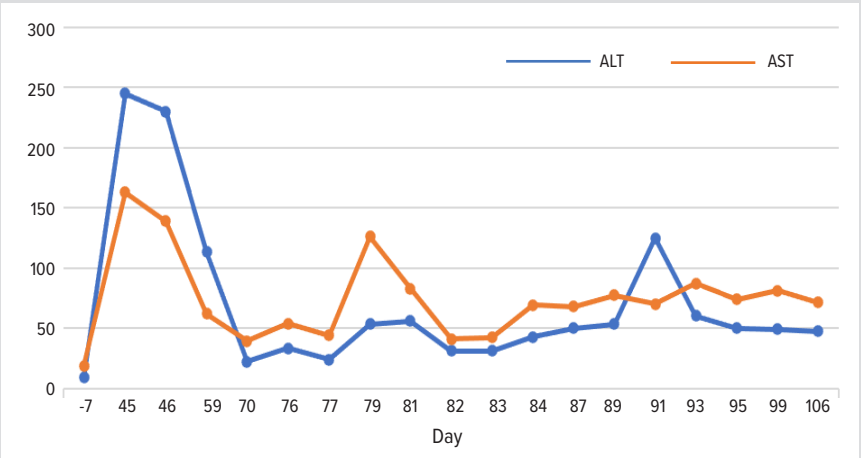


A. Trend in patient's alkaline phosphatase level over the course of her illness. X-axis shows day in relation to beginning terbinafine. Day -7 is the day where baseline labs were collected. Y-axis shows alkaline phosphatase levels measured in IU/mL.



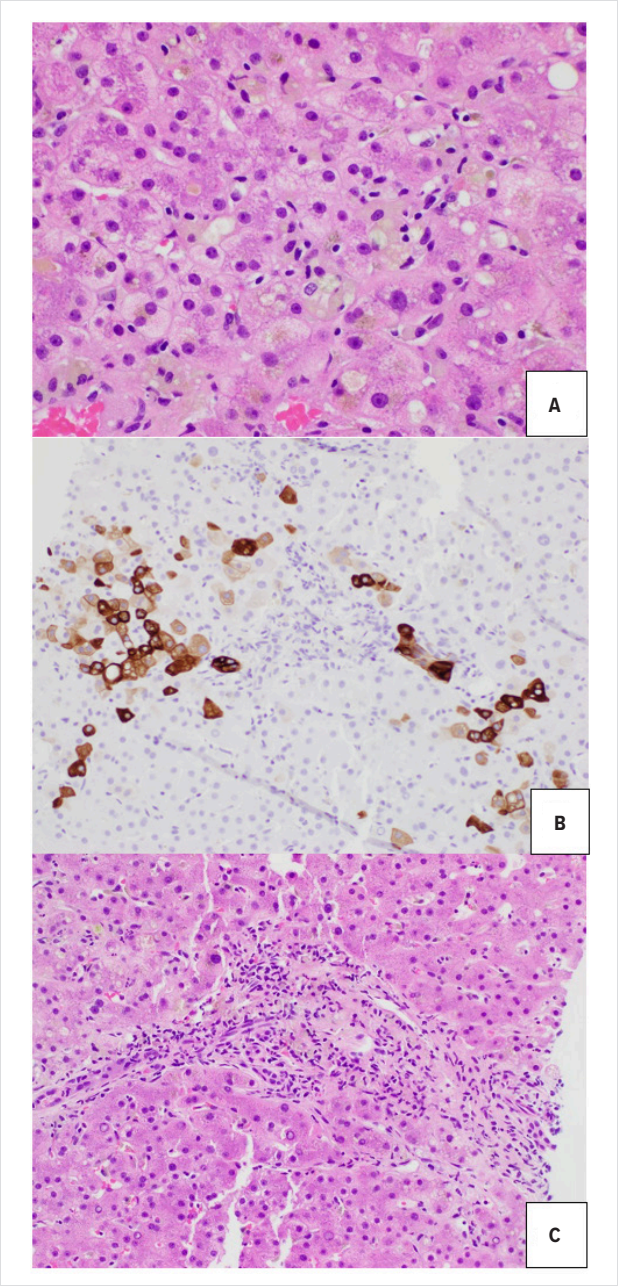
B. Trend in patient's total bilirubin level over the course of her illness. X-axis shows day in relation to beginning terbinafine. Y-axis shows total bilirubin levels measured in mg/dL.

Figure 2. Trend in Patient's Transaminases Over the Course of Her Illness



X-axis shows day in relation to beginning terbinafine. Day -7 is the day where baseline labs were collected. Y-axis shows patient's ALT and AST levels measured in IU/L.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Figure 3. Liver Biopsy Histologic Images



A. Image taken from liver biopsy done at our institution, demonstrating marked canalicular and hepatocytic cholestasis, accentuated near the efferent vein.
B. Liver biopsy image utilizing cytokeratin 7 (CK7) stain – indicating a bile ductular reaction.
C. Liver biopsy imaging demonstrating portal inflammation.

Pathology images courtesy of Yongjun Liu, MD, PhD, University of Wisconsin Department of Pathology and Laboratory Medicine.

that line the liver sinusoids) with or without fat globules, mononuclear cells, and occasional eosinophils and neutrophils, and no biliary injury or fibrosis, thought to be consistent with toxin or drug-induced liver injury. Magnetic resonance imaging showed significant gallbladder wall thickening and mural edema without gallstones, no intra- or extrahepatic biliary dilatation or choledocholithiasis, and an enlarged liver without lesions or parenchymal disease. It demonstrated features of portal hypertension, including a dilated main portal vein, marked splenomegaly, and a small volume of ascites, but the liver was not frankly cirrhotic, as there were no regenerative nodules or fibrosis. Additional laboratory evaluations included an antinuclear antibody of 1:80, normal complement levels, negative antidouble-stranded DNA, rheumatoid factor, antineutrophilic cytoplasmic antibody, antimitochondrial antibody, and antismooth muscle antibody, as well as negative serologies for viral hepatitides (Hepatitis C antibody and RNA, hepatitis B surface antigen, hepatitis A IgM, hepatitis E IgM, and cytomegalovirus and Epstein-Barr virus polymerase chain reactions). While there, she developed worsening acute kidney injury, unresponsive to crystalloid and colloid, and progressive cholestatic liver injury. She was transferred to our institution 13 days later for possible liver transplant evaluation.

At our institution, the patient developed oliguric kidney injury and rising liver enzymes (Figures 1 and 2) and was started on intermittent hemodialysis due to continued oliguria. Her acute kidney injury was thought to be secondary to acute tubular necrosis, with or without bile cast nephropathy. She never had evidence of acute liver failure, given lack of encephalopathy, but because of her rising alkaline phosphatase and relatively unchanged transaminases, total bilirubin (Figures 1 and 2), and INR—which followed a similar trend—she had a repeat liver biopsy nearly 1 month after transfer (Figure 3). At the time of her second liver biopsy, her INR was 1.2. Of note, she had received 3 days of intravenous vitamin K earlier in her admission to address the possibility that malnutrition and vitamin K malabsorption had contributed to the elevated INR.

The patient's liver biopsy demonstrated marked canalicular cholestasis, which refers to the presence of bile thrombi within the bile canaliculi, as well as hepatocytic cholestasis, which refers to the presence of bile throughout the cytoplasm of hepatocytes due to impaired secretion—especially near the efferent vein at the central zone. There was a mild inflammatory infiltrate involving most of the portal tracts and made up predominantly of lymphocytes. There was no significant steatosis, and a trichrome stain was negative for increased fibrosis. There were 10 portal tracts for evaluation, including three without native bile ducts—indicative of 30% native bile duct loss. The existing bile ducts were focally injured, characterized by unevenly distributed nuclei and nuclei irregularity without significant ductular reaction. An antihuman cytokeratin 7 (CK7) stain was used to accentuate the bile ducts and determine the degree of bile duct loss. Overall, this demonstrated a cholestatic pattern of injury, favored to be DILI. Biliary obstruction and infection were less favored. The pathology did not appear consistent with autoimmune hepatitis or chronic biliary disease.

The patient was then found to have a large pericardial effusion with early tamponade physiology, most likely secondary to uremia given her underlying renal dysfunction, for which she underwent pericardial drainage. She was also found to have *Klebsiella pneu-*

moniae bacteremia that was treated with meropenem. Her liver enzymes became stable to improved, and she was discharged to a long-term acute care hospital in her home state with recommendations for liver enzyme monitoring once to twice weekly. Nearly 6 months after discharge, her labs included an alkaline phosphatase of 480, ALT 105, AST 103, and total bilirubin 0.9. Her INR has remained normal since, and labs 16 months after discharge included a persistently elevated alkaline phosphatase of 520, ALT 30, AST 20, and total bilirubin 0.4.

Unfortunately, she was hospitalized locally 16 months after discharge for treatment of splenic marginal zone lymphoma and hemophagocytic lymphohistiocytosis, complicated by massive splenomegaly and Epstein-Barr viremia. At the time of this writing, she had received 6 cycles of rituximab, cyclophosphamide, and vincristine and continued to receive steroids and etoposide.

DISCUSSION

This patient developed severe, progressive, and prolonged cholestatic DILI secondary to terbinafine, which has been described in other case reports but not to the same degree of severity of our patient's injury.[9-11] DILI has been reported after oral but not topical terbinafine use. Our patient had evidence of portal hypertension at the time of her presentation, which may have been prehepatic due to her splenomegaly. It is possible that all along, her pancytopenia and splenomegaly could have been explained by an underlying hematologic process such as lymphoma, which may lead to splenomegaly and subsequent portal hypertension. Alternatively, an acute hepatic injury (which our patient had initially) may sometimes lead to intrahepatic portal hypertension.

Our patient would be considered to have chronic DILI, as chronic cholestasis (meaning the reduction or cessation of bile flow) typically refers to cholestatic liver injury persisting greater than 3 months.[12] In general, cholestatic DILI may occur when a drug leads to inhibition of the export of bile salts and drug metabolites from the hepatocytes into bile, leading to cholestasis in susceptible patients—especially those with mutations in genes that encode these transporters.[12] In most cases of DILI, the liver enzyme abnormalities resolve with drug cessation. However, for cholestatic DILI, including those secondary to antifungals such as terbinafine, the time course for improvement tends to be prolonged when compared to hepatocellular DILI. There is no medical therapy specifically for the treatment of cholestatic DILI. The mainstay of treatment is withdrawal of the drug, avoiding drug rechallenge, and treating the symptoms. Ursodeoxycholic acid can be used, but there are limited data to support this.[12] There is a role for management of pruritis with agents such as cholestyramine and antihistamines. That being said, in patients with non-acetaminophen–related DILI and acute liver failure, N-acetylcysteine has been found to significantly improve overall survival and transplant-free survival. In rare cases, acute liver failure due to cholestatic DILI may require liver transplantation.[12]

The development of cirrhosis and end-stage liver disease is another possible indication for liver transplantation. One of the rarest types of cholestatic DILI—vanishing bile duct syndrome, which is diagnosed when less than 50% of bile ducts are seen on liver biopsy—could potentially lead to cirrhosis by leading to prolonged, near complete absence of bile ducts. Cholestatic DILI—mostly secondary to chemotherapeutic agents—may lead to development of secondary sclerosing cholangitis and subsequent cirrhosis; and chronic cholestasis alone may lead to cirrhosis through the development of ductal sclerosis, periportal fibrosis, and bile duct loss.[12]

Our patient did not require liver transplant evaluation during her hospitalization, as she did not meet criteria for acute liver failure. Per the American Association for the Study of Liver Diseases, the criteria for acute liver failure includes evidence of coagulation abnormality (usually INR ≥1.5), any degree of encephalopathy in a patient without preexisting cirrhosis, and an illness of less than 26 weeks' duration.[13] Though our patient had an elevated INR, she did not develop encephalopathy.

Given her prolonged course and severely elevated alkaline phosphatase and total bilirubin, development of vanishing bile duct syndrome was a concern, and we obtained repeat liver biopsy. This syndrome is defined by loss of intralobular bile ducts with less than 50% of portal areas with a bile duct in a biopsy with at least 10 portal areas. Thus, our patient did not meet the criteria, although she had a lesser degree of bile duct loss, indicative of severe biliary injury or ductopenia.[14]

This case exemplifies key differences between DILI secondary to acetaminophen versus non-acetaminophen drugs, including terbinafine. DILI due to acetaminophen is dose-dependent and rarely occurs at therapeutic doses. There is a clear timeframe to development of DILI secondary to acetaminophen. At 24 to 72 hours post-ingestion, patients develop aminotransferase elevations. At 72 to 96 hours, they may develop jaundice, encephalopathy, coagulopathy, and acute liver failure. Recovery typically occurs 4 days to 2 weeks post-ingestion. Acetaminophen-induced DILI tends to have a better prognosis and more self-limited duration of injury due to faster hepatocyte regeneration. This differs from non-acetaminophen DILI, which is idiosyncratic, without a clear dose-response relationship. The timeframe for development of severe liver injury is unpredictable, often slower in onset and progression. Complications, including vanishing bile duct syndrome or liver failure, can be slow to develop, occurring as late as 6 months after initial onset of clinical liver injury. Thus, it is important to remain vigilant until complete recovery occurs.[14-15]

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