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Asymptomatic hepatotoxicity following exposure to oral terbinafine for onychomycosis treatment

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Abstract

Hepatotoxicity is a known but very rare side effect of oral terbinafine therapy. To our knowledge, there are no reported cases of patients with cleared hepatitis B infection prescribed oral terbinafine. We report an 82-year-old woman with previous hepatitis B exposure who experienced asymptomatic elevation of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels following 28 days of therapy with 250mg of oral terbinafine daily for onychomycosis treatment. After drug discontinuation, her liver function tests returned to baseline about three months later, without permanent liver damage. Oral terbinafine therapy, although typically efficacious and well-tolerated for onychomycosis treatment, rarely causes hepatoxicity. Physician knowledge of this rare but important side effect is necessary to prevent morbidity and mortality resulting from continued therapy. Oral terbinafine therapy might not reactivate hepatitis B in patients with past infection.

Keywords: liver function, onychomycosis, terbinafine

Introduction

Onychomycosis is a nail infection caused by dermatophytes, nondermatophytes, and yeasts [1]. Terbinafine is one of two oral drugs approved by the United States Food and Drug Administration for the treatment of onychomycosis, with efficacy against *Trichophyton rubrum* and *mentagrophyte* [2,3]. Adult dosing is 250mg daily for 6 weeks for fingernails and 12 weeks for toenails [2,3]. Terbinafine is typically preferred over itraconazole owing to its lower rate of drug interactions and higher cure rates [2,3]. General indications for oral therapy for the treatment of onychomycosis include >3 nails affected, proximal subungual onychomycosis, and distal lateral subungual onychomycosis affecting >50% of the nail plate with matrix involvement and thickness >2mm) [2]. Terbinafine is associated with gastrointestinal issues, including nausea and diarrhea. Rarer side effects include smell and taste disturbances and hepatoxicity [4,5,6]. Chronic or active liver disease are drug contraindications [7,8].

Case Synopsis

An 82-year-old woman presented to our nail specialty clinic with thickening of the left great toenail following a pedicure two years prior. She had a remote history of hepatitis B that spontaneously cleared and multiple sclerosis treated with interferon beta until 2021. Physical examination was significant for onycholysis and subungual debris of the left great toenail and left foot plantar scale. Histopathology with periodic acid-Schiff staining, polymerase chain reaction, and culture were performed, showing presence of hyphae and *Trichophyton mentagrophytes*, respectively, confirming the diagnosis of onychomycosis. She was prescribed efinaconazole topical solution 10% for her onychomycosis and econazole cream for her

tinea pedis. She presented with persistent onychodystrophy despite using efinaconazole daily and consistently for 14-months (**Figure 1**). A repeat toenail clipping was performed, which showed hyphae. Since she failed treatment with efinaconazole, therapy with oral terbinafine was discussed, including risks of nausea, diarrhea, headache, taste disturbance, rare liver failure, and neutropenia, and she decided to pursue treatment. Her baseline complete blood count and complete metabolic panel were within normal limits and she was prescribed oral terbinafine, 250mg daily, for three months.

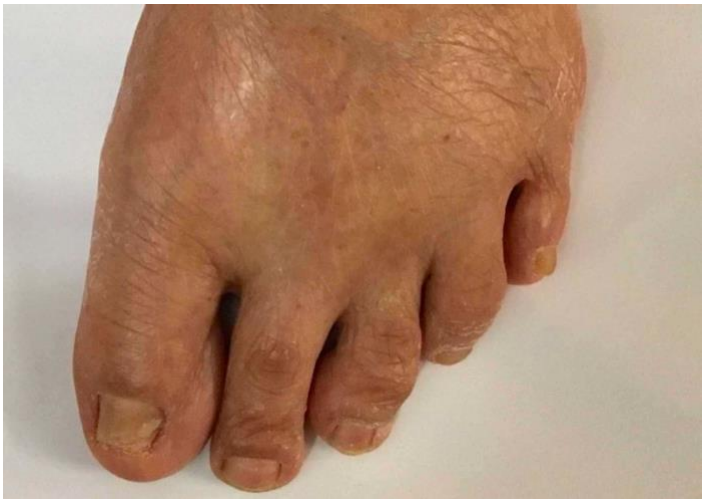

Figure 1. *Clinical image of left great toenail with onycholysis and subungual debris, immediately prior to initiation of terbinafine therapy*

Twenty-seven days after beginning terbinafine therapy, she saw her endocrinologist for an unrelated complaint and reported tea-colored urine. Complete metabolic panel was repeated and aspartate aminotransferase (AST) and alanine transaminase (ALT) were elevated at 157U/L (normal ≤34U/L) and 225U/L (normal 10-49U/L), respectively **(Table 1)**. We instructed her to hold the medication immediately. A liver ultrasound showed a mildly heterogenous liver (**Figure 2**). About one week later, her AST and ALT remained elevated (163U/L and 266U/L, respectively), and alkaline phosphatase and total bilirubin increased to 357U/L and 0.7mg/dl, respectively **(Table 1).**

Another week later, serologic evaluation was notable for positive hepatitis B surface antibody and hepatitis B core antibody, negative hepatitis B surface antigen, and negative hepatitis C virus antibody, indicating previous exposure to, and clearance of, hepatitis B with no hepatitis C exposure. She reported that the tea-colored urine was becoming lighter. Her mixed hepatocellular-cholestatic presentation was classic for drug-induced liver injury related to terbinafine use. Laboratory tests were repeated at this visit, marking 6 weeks since the start of terbinafine therapy, with AST 160U/L, ALT 304U/L, alkaline phosphatase 350U/L, and total bilirubin 1.1mg/dl. She repeated laboratory tests and they returned to near baseline four months after starting terbinafine **(Table 1).**

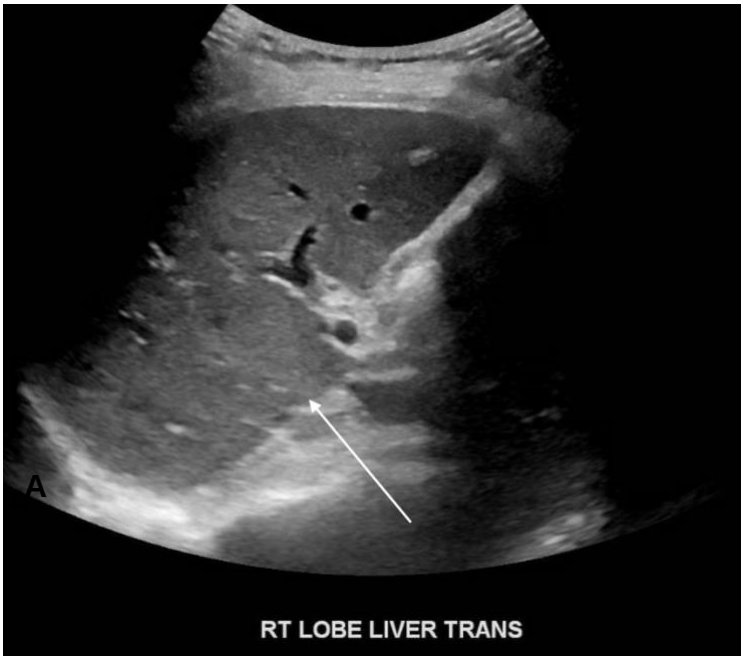

Figure 2. *The abdominal ultrasound demonstrates a smooth contoured, mildly heterogenous liver, possibly related to parenchymal disease, that measures 11.1cm in the longitudinal dimension. The white arrow points to the liver.*

Case Discussion

Our case highlights that hepatotoxicity is a rare but concerning side effect of terbinafine treatment. Although the package insert for oral terbinafine advises baseline liver function tests for all patients before initiating therapy, the need for liver function testing during a course of terbinafine has been debated [7,9]. In the study by Stolmeier et al, 4985 adults and children taking terbinafine or griseofulvin

for dermatophyte infections, laboratory abnormalities were rare and were mild when they did occur. The drug was continued in the vast majority of cases without adverse effects [10]. Similarly, in Wang et al.'s retrospective study of 944 adults diagnosed with onychomycosis who were prescribed oral terbinafine for 12 weeks, laboratory test result abnormalities were uncommon and when they did occur, they were mild and more likely to occur in older adults [11]. Taken together, routine laboratory monitoring of liver function in healthy individuals taking oral terbinafine may be unnecessary [10,11].

Most reported cases of liver injury with terbinafine occur after four to six weeks of therapy [12]. However, deranged laboratory values may occur in less than two weeks. In most cases, evidence of liver injury, including elevated liver function tests and clinical symptoms, will normalize after discontinuation of terbinafine, typically within one to five months [13,14].

Rare cases of severe liver damage have been reported with terbinafine administration. In most cases, patients present with obvious symptoms of liver toxicity, including nausea, vomiting, fatigue, yellowing of the skin, anorexia, and dark urine [12,14]. Although many cases of terbinafine-induced liver injury resolved completely with drug discontinuation, some have necessitated liver transplantation or caused death [12,15].

Hepatotoxicity without severe symptoms of liver damage, such as nausea, vomiting, and skin yellowing, is a concerning phenomenon that may occur with terbinafine administration and may only be detected with routine liver function test monitoring [12,16]. Khurana et. al described the case of a 26-year-old healthy man prescribed 500mg of terbinafine daily. Despite an AST 7.5 times the upper limit of normal and ALT 3.6 times the upper limit of normal, he was completely asymptomatic [13]. We observed mostly asymptomatic hepatotoxicity even at the 250mg dose of terbinafine in our patient, with the exception of the sign of tea-colored urine.

Our case is unique in that our patient had a history of hepatitis B exposure. Shehi et al described a case of a 48-year-old man with chronic inactive hepatitis B infection who was prescribed oral terbinafine, 250mg daily, for 12 weeks. He experienced reactivation of hepatitis B with a hepatocellular pattern of liver injury [17]. In contrast, our patient did not have any evidence of hepatitis B reactivation despite serology showing prior cleared infection. To our knowledge, this is the first case of a patient with previous exposure and clearance of hepatitis B prescribed oral terbinafine without viral reactivation.

Conclusion

We present an 82-year-old woman who experienced mostly asymptomatic liver toxicity, other than dark urine, following 27 days of a 250mg daily dose of oral terbinafine for onychomycosis treatment. She had prior hepatitis B infection and terbinafine administration was not associated with viral reactivation. Therefore, physicians should be cautious in prescribing terbinafine to older adults. After a discussion of risks and benefits, a discussion on warning signs of liver toxicity in patient friendly terms is necessary. We recommend baseline liver function testing and monthly monitoring in this population.

Potential conflicts of interest

The authors declare the following potential conflicts: Dr. Lipner has served as a consultant for Moberg Pharmaceuticals and BelleTorus Corporation.

References

1. Lipner SR, Scher RK. Onychomycosis: Clinical overview and diagnosis. *J Am Acad Dermatol*. 2019;80(4):835-851. [PMID: 29959961].
2. Lipner SR, Scher RK. Onychomycosis: Treatment and prevention of recurrence. *J Am Acad Dermatol*. 2019;80(4):853-867. [PMID: 29959962].
3. Lipner SR, Joseph WS, Vlahovic TC, et al. Therapeutic Recommendations for the Treatment of Toenail Onychomycosis in the US. *J Drugs Dermatol*. 2021;20(10):1076-1084. [PMID: 34636509].
4. Yan J, Wang X, Chen S. Systematic review of severe acute liver injury caused by terbinafine. *Int J Clin Pharm*. 2014;36(4):679-683. [PMID: 24986266].

5. Wang Y, Lipner SR. Retrospective analysis of adverse events with systemic onychomycosis medications reported to the United States Food and Drug Administration. *J Dermatolog Treat*. 2021;32(7):783-787. [PMID: 31865826].
6. Ishack S, Miller RC, Lipner SR. Insights into the "fear factor" regarding terbinafine-associated hepatoxicity in an assessment of online information. *J Am Acad Dermatol*. 2022;86(6):e269-e271. [PMID: 35150758].
7. Wang Y, Lipner SR. Retrospective analysis of laboratory abnormalities in patients with preexisting liver and hematologic diseases prescribed terbinafine for onychomycosis. *J Am Acad Dermatol*. 2021;84(1):220-221. [PMID: 32918937].
8. Kyriakidis I, Tragiannidis A, Munchen S, Groll AH. Clinical hepatotoxicity associated with antifungal agents. *Expert Opin Drug Saf*. 2017;16(2):149-165. [PMID: 27927037].
9. Muddasani S, Housholder A, Fleischer AB Jr. The cost of liver function tests for terbinafine: an unnecessary expense. *J Dermatolog Treat*. 2022;33(3):1789. [PMID: 33103507].
10. Stolmeier DA, Stratman HB, McIntee TJ, Stratman EJ. Utility of Laboratory Test Result Monitoring in Patients Taking Oral Terbinafine or Griseofulvin for Dermatophyte Infections. *JAMA Dermatol*. 2018;154(12):1409-1416. [PMID: 30347032].
11. Wang Y, Geizhals S, Lipner SR. Retrospective analysis of laboratory abnormalities in patients prescribed terbinafine for onychomycosis. *J Am Acad Dermatol*. 2021;84(2):497-499. [PMID: 32387655].
12. Kramer ON, Albrecht J. Clinical presentation of terbinafine-induced severe liver injury and the value of laboratory monitoring: a Critically Appraised Topic. *Br J Dermatol*. 2017;177(5):1279-1284. [PMID: 28762471].
13. Khurana A, Sardana K, Bhardwaj V. Terbinafine induced liver injury may be asymptomatic: need for regular monitoring. *Br J Dermatol*. 2018;178(3):807-808. [PMID: 29150832].
14. Kaushal M, Tolani P, Kumar N, Sharma S. Terbinafine-induced liver injury. *Natl Med J India*. 2017;30(6):321-323. [PMID: 30117442].
15. Perveze Z, Johnson MW, Rubin RA, et al. Terbinafine-induced hepatic failure requiring liver transplantation. *Liver Transpl*. 2007;13(1):162-164. [PMID: 17192859].
16. Albrecht J, Kramer ON. Terbinafine-induced liver injury may be asymptomatic: need for regular monitoring: reply from the authors. Br J Dermatol. 2018;178(3):808-809. [PMID: 29370453].
17. Shehi E, Alemam A, Mantri N, Patel H. Terbinafine-Induced Hepatitis B Reactivation in a Patient With Chronic Hepatitis B. Cureus. 2020;12(12):e11958. [PMID: 33312827].

Table 1. *Liver Function Panels*

Lab Value	Baseline laboratory tests	Day 27*	Day 35	Day 37	Day 43	Day 49	Day 56	Day 63	Day 70	Day 84	Day 112	Reference Range
AST (U/L)	25	157	154	163	160	110	117	103	85	53	36	≤34 U/L
ALT (U/L)	17	225	275	266	304	222	198	151	116	57	26	10-49 U/L
ALP (U/L)	59	191	363	357	350	353	321	282	247	174	100	41-133 U/L
Total Bilirubin (mg/dL)	0.5	0.7	1.5	1.4	1.1	1.2	1.0	0.9	0.8	0.7	0.7	0.1-0.8 mg/dL

AST, aspartate aminotransferase, ALT, alanine aminotransferase, ALP, alkaline phosphatase

*Indicates date that patient was instructed to hold terbinafine.