# Rhabdomyolysis attributed to terbinafine: A rare occurrence that can be mistaken for terbinafine-induced hepatotoxicity

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## INTRODUCTION

Terbinafine is a common antifungal medication taken orally to treat onychomycosis. This drug is considered a first-line agent for this disease and has a better cure rate than other antifungal drugs.[1] Terbinafine functions as an allylamine agent, which inhibits squalene epoxidase, a key enzyme of ergosterol biosynthesis. The increase in concentration of extracellular squalene is thought to result in toxic levels that kill fungal cells.[2] Side effects of terbinafine include gastrointestinal disturbances, dysgeusia, headache, and rash.[1] Hepatotoxicity is a less frequent adverse effect of terbinafine that has an incidence of 2.5 cases/100,000.[3] Because of the potential for this feared adverse event, some physicians have chosen to monitor liver enzymes during the course of terbinafine treatment.

Rhabdomyolysis is another rare side effect that has been associated with terbinafine use. Many occurrences have been reported by physicians in adverse drug reaction reporting databases; however, there have been few published cases of this association.[4,5] Because rhabdomyolysis is not a well-known side effect of terbinafine, patients might not readily discuss symptoms of weakness, myalgia, or darkened urine. Elevated liver enzymes found on routine monitoring might also mistakenly be attributed to terbinafine-induced hepatotoxicity. As a result, it is important to have rhabdomyolysis as a differential diagnosis when monitoring patients on terbinafine.

*Abbreviations used:*

ALT: alanine transaminase
AST: aspartate aminotransferase
CK: creatine kinase

## CASE REPORT

A 40-year-old man came to the clinic for a laboratory monitoring visit 6 weeks after starting terbinafine 250 mg daily for treatment of onychomycosis. Routine laboratory test results showed an elevated aspartate aminotransferase (AST) of 417 U/L and alanine transaminase (ALT) of 145 U/L, concerning for terbinafine-induced hepatotoxicity. His alkaline phosphatase, bilirubin, and gamma-glutamyl transferase levels were within the standard ranges. Further studies revealed a significantly elevated creatine kinase (CK) at 14,400 U/L. The patient was not taking any other medications, vitamins, or supplements. Upon further questioning, he indicated he had symptoms of generalized muscle pain and weakness for the past 1-2 weeks that he attributed to starting a new exercise routine. He visited the gym about 4 times a week, spending up to 2 hours lifting weights and running. He did not report any incidence of trauma, and he did not notice any changes in the color of his urine. The patient was instructed to immediately stop taking terbinafine and remain hydrated. At the 2-week follow-up, his symptoms had resolved, and his ALT (52 U/L), AST (37 U/L), and CK (225 U/L) were improved. Kidney

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**Table I.** Case reports of rhabdomyolysis associated with terbinafine use

| Source | Age, y | Sex | Terbinafine dose | Indication | Symptoms | Laboratory values, U/L |
|---|---|---|---|---|---|---|
| Current case | 40 | Male | 250 mg QD for 6 wk | Onychomycosis | Generalized muscle pain and weakness | AST 417, ALT 145, CK 14,400 |
| Gallego Peris et al[4] | 24 | Male | 250 mg QD for 15 d | Tinea capitis | Generalized muscle pain, weakness, darkened urine | CK 1120 |
| Kwon et al[5] | 7 | Male | 125 mg QD | Tinea capitis | Leg cramps | AST 76, CK 1420 |

*ALT*, Alanine transaminase; *AST*, aspartate aminotransferase; *CK*, creatine kinase; *QD*, daily.

function was evaluated at follow-up, and the patient's creatinine (1.05 mg/dL) was within the reference range.

## DISCUSSION

Terbinafine is an oral antifungal agent that can cause hepatotoxicity. Early detection of hepatic dysfunction should prompt immediate discontinuation of this medication. Drug-induced liver injury can result in acute hepatitis, cholestasis, or a mixed picture.[6] Although abnormal liver function test results might vary depending on the type of injury, most cases of terbinafine-induced hepatotoxicity present with elevations in AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, and bilirubin.[7] Trivial elevations of <1.2 times the upper limit of normal for ALT, AST, and bilirubin have occurred in <10% of cases.[7] Common symptoms of liver injury include jaundice, icterus, flu-like symptoms, dark urine, or pruritus.[3] Our patient presented with an isolated elevation in transaminases with only symptoms of muscle pain and weakness. His clinical picture was not consistent with terbinafine-induced hepatotoxicity; therefore, further investigation was pursued.

Rhabdomyolysis associated with terbinafine use is a rare occurrence. When evaluating a patient on terbinafine with an isolated elevation in aminotransferases, rhabdomyolysis should be considered. In a retrospective study of 215 cases of rhabdomyolysis with a CK ≥ 1000 U/L, the AST was elevated in 93% cases and ALT in 75% of cases.[8] An elevated AST:ALT ratio might also support rhabdomyolysis, as the leakage of intracellular contents from skeletal muscles precipitates a favorable elevation of AST.[9] Patients should be evaluated clinically for symptoms of rhabdomyolysis, including weakness, myalgia, and darkened urine. Additional laboratory testing should be performed to distinguish rhabdomyolysis from drug-induced liver injury. This additional testing should include CK level, urine myoglobin, creatinine, and electrolytes including potassium. Diagnosis of rhabdomyolysis can be made in the presence of an acute neuromuscular illness or dark urine, plus a marked elevation in serum CK. Treatment is largely supportive with correction of electrolyte abnormalities and proper hydration to prevent kidney injury.

Rhabdomyolysis associated with terbinafine use has been reported in only a few other cases in the literature, with 1 report coming from a postmarketing surveillance study (Table I).[4,5] Due to its rarity, patients might not associate symptoms of rhabdomyolysis with terbinafine use unless prompted by their dermatologist. As a result, this adverse effect might be underreported. Routine monitoring of liver enzymes in patients taking terbinafine is still a debated topic. Some studies argue that hepatic monitoring of patients on terbinafine does not provide benefit unless the patient is clinically symptomatic with signs of drug-induced liver injury.[3] Our patient was found to have rhabdomyolysis after receiving routine liver enzyme monitoring. Only after further questioning upon receiving abnormal laboratory results did the patient mention having symptoms of muscle weakness and pain. Our case emphasizes the importance of educating patients about the potential adverse effects of terbinafine and the need to discontinue the medication and seek treatment if concerning symptoms arise.

In conclusion, rhabdomyolysis associated with terbinafine is rare. The mechanism of action is unknown, but the association with exercise in our patient suggests a drug-facilitated reaction. Similar cases of drug-facilitated rhabdomyolysis and strenuous exercise have been reported with isotretinoin.[10] Patients need to know the common symptoms of rhabdomyolysis (ie, myalgia, darkened urine, muscle weakness) and to discontinue the medication immediately if symptoms appear and seek medical attention. Our review supports monitoring patients for symptoms of myalgia or darkened urine clinically and ordering additional laboratory testing if needed. Rhabdomyolysis can cause elevated liver enzymes and should be ruled out when considering terbinafine-induced hepatotoxicity. More research is needed on this topic to further understand the pathophysiology of disease.

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