

## CASE REPORT

# Possible exercised-induced rhabdomyolysis associated with terbinafine

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## Abstract

**Introduction.** Terbinafine is reported to be associated with rhabdomyolysis. We present a patient taking terbinafine who may have developed exercise-induced rhabdomyolysis. **Case Report.** A healthy 40-year-old female developed onychomycosis of the right first toe for which she was taking terbinafine. After an increase in her exercise regimen, she began experiencing notable myalgias of the triceps. During outpatient evaluation, the patient was found to have elevated and worsening creatine kinase (CK) and aspartate transaminase. At evaluation in the emergency department, CK was <5000 IU/L and had decreased. She did not have electrolyte abnormalities, kidney injury or kidney failure. **Discussion.** Patients may be at risk for exercise-induced rhabdomyolysis while on terbinafine and may need to be cautioned regarding the intensity of exercise.

## INTRODUCTION

Terbinafine is a medication used for the treatment of onychomycosis [1]. Postmarketing surveillance of terbinafine found uncommon nonspecific musculoskeletal complaints [2, 3]. Rhabdomyolysis is recognized as an adverse effect of terbinafine without a specific frequency in product documentation [4]. In our review of the English language medical literature, there were no reported cases of rhabdomyolysis associated with terbinafine, so the frequency of rhabdomyolysis associated with terbinafine is unknown. Another known cause of rhabdomyolysis is exercise [5]. We present a case of a patient who may have experienced exercise-induced rhabdomyolysis while using terbinafine to treat onychomycosis. Exercise-induced rhabdomyolysis has also been previously reported for other medications, such as quetiapine and mirtazapine, dextroamphetamine and phentermine [6–8].

## CASE REPORT

A 40-year-old Caucasian female with no active medical conditions began taking terbinafine 250 mg orally daily for onychomycosis of the right first toe 3 weeks prior to presentation to the emergency department. Baseline liver function tests obtained prior to initiation of terbinafine were normal. While using terbinafine, she continued to exercise three to four times per week. Except for regular use of whey protein, she did not take any other medications or supplements. She did not use any recreational or illicit substances. Five days prior to presentation, she increased the number of repetitions for a weight training exercise program involving her triceps. The next day, she began having myalgias involving the bilateral triceps. Because of concerns for terbinafine being the cause of the myalgias, she discontinued the terbinafine ~3 days ago.

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**Table 1:** Values of AST, CK, creatinine and WBCs. 'Day 0, Time 0' is the day and time of presentation to the emergency department. Reference ranges are 25–155 IU/L for CK, 15–41 IU/L for AST, 0.44–1.03 mg/dL for creatinine and 4000–10 000 cells/L for WBC

Time	Aspartate transaminase (IU/L)	Creatine kinase (IU/L)	Creatinine (mg/dL)	White blood cells (cells/L)
35 days prior	14			
1 day prior	66	3503	0.70	
Approximately 8 h prior	92	4774	0.62	5700
Day 0, Time 0	107	514	0.86	13 700
Day 6	21	171	0.70	

Outpatient clinicians performed the initial evaluation. Laboratory studies were obtained the day prior to presentation and were notable for elevations in aspartate transaminase (AST) and creatine kinase (CK), also known as creatine phosphokinase (Table 1). Basic metabolic panel was normal. She reported unchanged urine color. She attempted to return to exercise the day prior to presentation but was unable to tolerate her usual exercise regimen because of the continued myalgias. She took naproxen 1000 mg orally once for attempted pain relief. On the day of presentation, additional laboratory studies were collected (Table 1), including urine myoglobin of <8 ng/mL (reference range 0–45 ng/mL) and uric acid of 4.1 mg/dL (reference range 2.6–8.0 mg/dL). Basic metabolic panel was normal. She took prednisone 40 mg orally once for the myalgias. Upon finding her CK to be increasing, she increased her oral water intake.

The patient presented to the emergency department for further evaluation because of the upward trend in AST and CK. Initial vital signs were oral temperature of 36.9°C, heart rate of 119 beats per minute, respiratory rate of 16 breaths per minute, oxygen saturation of 96% on room air and blood pressure of 140/92 mmHg. Physical examination of the triceps did not identify pain, swelling, redness or motor weakness, but the patient continued to have myalgias. While awaiting the results of laboratory studies, the patient received saline 0.9% intravenously for fluid resuscitation and volume repletion. Laboratory studies were notable for an improved CK, continued elevation of AST and leukocytosis (Table 1). Basic metabolic panel was sodium of 137 mEq/L, potassium of 3.8 mEq/L, chloride of 100 mEq/L, carbon dioxide of 24 mEq/L, glucose level of 124 mg/dL, blood urea nitrogen of 12 mg/dL, creatinine of 0.86 mg/dL and calcium of 9.5 mg/dL. Urinalysis found no blood, zero white blood cells per high power field (HPF), and one red blood cell per HPF. Because of the improvement in CK, no electrolyte derangements, the low risk of kidney injury and resolved tachycardia, the patient was discharged from the emergency department. The patient was advised to cease terbinafine use, which she had already done. CK and AST improved in the outpatient setting.

## DISCUSSION

Based on consensus among clinicians, the diagnostic criteria of rhabdomyolysis include a CK of at least five times the upper limit of normal. A CK of 5000 IU/L has a clinically relevant risk of renal failure and is commonly used as the threshold for active management of rhabdomyolysis [14]. While on terbinafine, the patient was asymptomatic when exercising until she increased her exercise intensity. She experienced CK values consistent with the diagnosis of rhabdomyolysis but below the threshold concerning for renal failure. CK for the initial insult (intensified exercise) at 5 days prior to presentation was not available but

was available before and after the second insult (reduced exercise). CK peaks at around 24 h [16] but is difficult to interpret in the case of this patient because of the limited measurements, multiple episodes of exercise, cessation of terbinafine and use of naproxen and prednisone. The patient took naproxen once prior to the collection of the second CK measurement, but naproxen has not been found to increase CK [9, 10]. The patient also took prednisone once prior to the collection of the third CK measurement, which was on the downtrend. Steroid-induced myopathy after one or two doses of corticosteroids has been described in case reports [11–13]. However, given the timing and dosing of naproxen and prednisone, these medications were unlikely to have precipitated the rhabdomyolysis that we reported.

Complications of rhabdomyolysis include myoglobin-induced acute kidney injury and electrolyte abnormalities such as hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, metabolic acidosis or hypermagnesemia. Our patient did not have kidney injury or electrolyte abnormalities. In addition to discontinuing terbinafine, our patient received intravenous fluids, the mainstay of treatment for rhabdomyolysis, in order to prevent these complications [14]. Oral hydration prior to presentation appeared to have had a positive effect on the measured CK in the emergency department.

Other studies besides CK, creatinine and electrolytes are relevant to the diagnostic evaluation of rhabdomyolysis. The patient did not have myoglobinuria, suggesting that her presumed myoglobinemia from damaged myocytes was below the 0.5–1.5 mg/dL necessary for renal excretion [15]. The AST elevation was likely from a skeletal muscle source [16]. The elevated white blood cells (WBCs) count may have been related to prednisone use [17].

Patients on terbinafine may not have as much tolerance for increases in muscle exertion. Causality cannot be demonstrated in this single case, but greater caution regarding exercise while using terbinafine may be necessary. Clinicians should consider advising patients to avoid intensifying exercise while using terbinafine. This effect may persist for weeks because of the terminal half-life of terbinafine being 2–4 weeks [18].

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## CONFLICT OF INTEREST

The authors do not have any financial or personal conflicts of interest to report. The views expressed in this manuscript do not communicate an official position of the University of Michigan (Ann Arbor, MI, USA) or Saint Joseph Mercy (Ypsilanti, MI, USA).

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## ETHICAL APPROVAL

Case reports do not require the review and approval of the Institutional Review Board of the University of Michigan or the Institutional Review Board of Saint Joseph Mercy.

## CONSENT

The patient provided written consent for the publication of this case. The University of Michigan and Saint Joseph Mercy do not require consent for case reports. The clinical data presented in this manuscript do not disclose the identity of the patient.

## GUARANTOR

The guarantor of the manuscript is Peter V. Bui, M.D.

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