



28-Year-Old Woman With Malaise, Cough, Myalgia, and Dark Urine

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A 28-year-old woman was admitted to the general internal medicine service with a 3-day history of malaise and cough that progressed to include myalgia, generalized weakness, and dark-colored urine. Three days before admission, she had abrupt onset of a dry nonproductive cough, malaise, and anorexia that resulted in a prolonged period of fasting. On the second day of the illness, she awoke with diffuse muscle pain and progressive weakness, culminating in an inability to walk. She subsequently noted dark urine and presented to the emergency department, leading to this admission. She had no recent trauma, exercise, rash, joint pain, or foreign travel. She was taking a multi-vitamin supplement but no prescription medication.

The patient had experienced 3 similar episodes in the past that were self-limited. She had only sought medical attention for 1 of these episodes, and rhabdomyolysis was diagnosed on the basis of urinalysis and no additional testing. Each of these episodes occurred after prolonged physical exertion. She had one uncomplicated pregnancy. She lived with her husband and 10-month-old daughter, whom she was breastfeeding. She was a nonsmoker, did not consume alcohol routinely, and had never used illicit drugs. She reported no family history of disease and had 3 healthy siblings.

At presentation, she was mildly distressed but oriented. Her vital signs were within normal limits, apart from mild tachycardia (heart rate, 104 beats/min). Physical examination revealed grade 3/5 limb muscle strength, although testing was associated with obvious discomfort. Muscle bulk and tone, tendon reflexes, and sensation were normal. Notably, there was no rash, and cardiorespiratory examination yielded unremarkable findings. Initial chest radiography revealed a left lower

lobe infiltrate most consistent with pneumonia. Urinalysis was strongly positive for hemoglobin. Initial laboratory analysis (reference ranges provided parenthetically) revealed that her creatine kinase (CK) level was markedly elevated at 118,342 U/L (38-176 U/L).

1. Which **one** of the following is the **most appropriate** next step to confirm the diagnosis of rhabdomyolysis in this patient?

- Serum myoglobin measurement
- Urine microscopy
- Muscle biopsy
- CK isoform analysis
- No further testing is required

Myoglobin detected in blood or urine is pathognomonic of rhabdomyolysis; however, its rapid renal clearance underlies an inferior sensitivity as a diagnostic marker when compared to CK.¹ Furthermore, myoglobin levels have no established prognostic role and would not change this patient's management.² It is well recognized that the presence of myoglobinuria will result in a urinalysis positive for hemoglobin because of its reaction with the orthotolidine reagent used in standard urinalysis kits. Performing urine microscopy to confirm the absence of red blood cells is prudent in ruling out concomitant hematuria but is not sufficient for the diagnosis of rhabdomyolysis.² Muscle biopsy has no role in confirming rhabdomyolysis; however, it may have a role in revealing the underlying etiology in certain patients. If indicated, a deferred biopsy is preferable because early biopsy often reveals nonspecific necrotic changes.³ Although it is possible to confirm that the isoform of CK is MM, as would be expected with muscle origin, this is not necessary because our patient's clinical presentation is consistent with rhabdomyolysis. It is generally accepted that a CK level greater

See end of article
for correct answers
to questions.

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than 5 to 10 times the upper limit of normal, as in our patient's case, is sufficient to confirm the presence of rhabdomyolysis in this setting; therefore, no further testing is required.^{1,4}

Additional laboratory testing revealed the following notable findings: hemoglobin, 13 g/dL (12.0-15.5 g/dL); white blood cell count, $6.4 \times 10^9/L$ ($3.5-10.5 \times 10^9/L$); platelet count, $200 \times 10^9/L$ ($150-450 \times 10^9/L$); sodium, 137 mmol/L (135-145 mmol/L); potassium, 4.2 mmol/L (3.6-5.2 mmol/L); calcium, 8.7 mg/dL (8.9-10.1 mg/dL); phosphorus, 2.1 mg/dL (2.5-4.5 mg/dL); serum urea nitrogen, 7 mg/dL (6-21 mg/dL); creatinine, 0.5 mg/dL (0.6-1.1 mg/dL); bicarbonate, 27 mmol/L (22-29 mmol/L); lactate, 0.7 mmol/L (0.6-2.3 mmol/L); glucose, 105 mg/dL (70-140 mg/dL); lactate dehydrogenase, 4290 U/L (122-222 U/L); aspartate aminotransferase (AST), 3059 U/L (8-43 U/L); alanine aminotransferase (ALT), 1370 U/L (7-45 U/L); alkaline phosphatase, 66 U/L (37-98 U/L); total bilirubin, ≤ 1.2 mg/dL (0.2-1.2 mg/dL); direct bilirubin, 0.2 mg/dL (0.0-0.3 mg/dL); albumin, 3.7 g/dL (3.5-5.0 g/dL); C-reactive protein, 48.5 mg/L (≤ 8.0 mg/L); thyrotropin, 2 mIU/L (0.3-4.2 mIU/L); and prothrombin time, 11.7 seconds (9.5-13.8 seconds).

The patient was admitted to the inpatient medicine service, and treatment for community-acquired pneumonia and rhabdomyolysis was initiated.

2. Which one of the following is the best next step in this patient's management?

- Use a risk stratification tool to guide further therapy
- Initiate continuous renal replacement therapy
- Administer intravenous crystalloid infusion
- Hold all outpatient medications
- Administer high-dose corticosteroid

A risk prediction model for rhabdomyolysis has recently been derived that estimates the likelihood of requiring renal replacement therapy or mortality.⁵ Our patient had a substantial CK increase with an unclear etiology, mandating inpatient admission for monitoring. Although the aforementioned model has been proposed to identify low-risk patients who may be appropriate candidates for

outpatient management, it has no role in guiding inpatient management. Continuous renal replacement therapy has been investigated as a specific therapeutic intervention in rhabdomyolysis, aimed at removing myoglobin and preventing acute kidney injury (AKI), irrespective of traditional indications for dialysis. Although meaningful reductions in myoglobin levels can be achieved, no clear reduction in AKI has been reported.² Early aggressive intravenous fluid administration to support urine output and correct concomitant hypovolemia reduces AKI in patients with rhabdomyolysis,⁶ and this is the most appropriate option in our patient. Substantial debate remains regarding the fluid of choice; however, normal saline is frequently utilized. Intravenous administration of sodium bicarbonate to alkalinize urine to reduce myoglobin precipitation is also used, although no clear additional benefit has been confirmed.⁴

Eliciting a thorough medication history is important in the assessment of rhabdomyolysis. Antipsychotics were the most frequently implicated group of prescription medications in one large cohort of cases, followed, in order, by statins, zidovudine, colchicine, selective serotonin reuptake inhibitors, and lithium.⁷ Over-the-counter medications are less frequently associated with rhabdomyolysis, but case reports have implicated the antihistamines diphenhydramine and doxylamine.⁴ In addition, patients should be asked about illicit drug use because heroin, cocaine, and methamphetamine are other potential etiologic agents.⁸ This patient was taking a multivitamin preparation alone, for which there is no association with muscle toxicity. Corticosteroids are widely used in the treatment of inflammatory myopathies. However, polymyositis typically presents insidiously with primarily proximal muscle weakness, and our patient had no evidence of the rash characteristic of dermatomyositis. The previous self-limiting episodes described, with apparent normal muscle strength between episodes, is further evidence against an inflammatory myopathy.⁹ Interestingly, empirical corticosteroid use in patients with rhabdomyolysis refractory to initial treatment has been described in a small number of case reports, with apparent benefit.¹⁰ At present, there is insufficient evidence to support the use of this intervention in routine practice.

We administered normal saline intravenously at 250 mL/h. The next morning, the patient reported complete resolution of her symptoms. Physical examination findings were normal, including resolution of her limb weakness. Repeated laboratory testing revealed the following: creatinine, 0.5 mg/dL; CK, 50,400 U/L; AST, 1849 U/L; and ALT, 1044 U/L.

3. Which one of the following is the most likely cause of this patient's elevated AST and ALT levels?

- a. Myoglobin-induced hepatotoxicity
- b. Release of muscle-derived AST and ALT
- c. Reduced renal clearance of AST and ALT
- d. Ischemic hepatic injury
- e. Alcoholic liver disease

Elevated AST and ALT levels are observed in 95% and 73% of rhabdomyolysis cases, respectively, and often trigger concern for concomitant hepatic disease.¹¹ When first recognized, several explanations were proposed, including the possibility that the release of muscle-derived proteolytic enzymes could be leading to hepatocellular toxicity. Myoglobin, although an important factor in the pathogenesis of AKI in rhabdomyolysis, has not been proposed to have a hepatotoxic effect to date. This patient's markers of synthetic and catabolic hepatic function were normal despite markedly deranged AST and ALT levels. The AST to ALT ratio observed in the initial phase approached 3:1, and a rapid decrease in CK was accompanied by a similar decrease in AST. These features are consistent with muscle release of AST and ALT, a well-characterized phenomenon.¹² Aspartate aminotransferase is present in abundance in muscle, and ALT to a lesser extent, and fluctuations in AST and CK levels have been found to correlate.¹¹ Preclinical studies suggest that these enzymes are cleared via hepatic metabolism, and intriguingly, a decrease in glomerular filtration rate has been associated with clinically significant reductions in AST and ALT rather than elevations.¹³

Although recognition of the association between rhabdomyolysis and transaminase abnormalities may avoid unnecessary investigation, the possibility of a hepatic cause must be considered in each case. This patient's history and clinical examination findings did not raise

further concern for liver disease. The patient had no risk factors for viral hepatitis, and she was not taking any hepatotoxic medications. She did not describe any episode concerning for hypotension sufficient to produce an ischemic liver injury nor did she have risk factors for thrombosis. An AST to ALT ratio greater than 2:1 secondary to a hepatic process is associated with alcoholic liver disease; however, less severe transaminase elevations are typical,¹⁴ and regular alcohol intake was strongly denied by this patient.

Further questioning revealed that the patient had not engaged in sustained exercise since finishing high school. Brief bouts of exertion, such as climbing stairs, did not result in symptoms; however, she was unable to tolerate attempts at exercise beyond 30 minutes. When symptoms did occur, brief rest did not restore her ability to exercise. This clinical information informed further testing, which included an acylcarnitine profile that revealed increased levels of C16 and C18 acylcarnitines.

4. Which one of the following is the most likely etiology of this patient's recurrent rhabdomyolysis?

- a. Nontraumatic exertional rhabdomyolysis
- b. McArdle disease (glycogen storage disease type V)
- c. Carnitine palmitoyltransferase II (CPT-II) deficiency
- d. Very long-chain acyl coenzyme A dehydrogenase deficiency
- e. Mitochondrial myopathy

Elevations in serum CK are well recognized to occur after exertion in normal individuals. With more prolonged or strenuous exercise, rhabdomyolysis can occasionally be observed. Common historical features in this scenario include a lack of prior training, repeated eccentric exercise such as squats, and persistence beyond the normal limit of activity, often due to supervision or group activity.¹⁵ Exertional rhabdomyolysis is associated with a more benign prognosis and fewer complications compared with other etiologies.⁵ In this case, recurrent episodes of rhabdomyolysis with an impaired ability to exercise when well strongly suggest an underlying metabolic defect.

The most prominent groups of metabolic disorders that can present as rhabdomyolysis

include disorders of glycogen metabolism, disorders of fatty acid oxidation, and mitochondrial respiratory chain defects. Triggers for rhabdomyolysis and the pattern of exercise intolerance present can be highly informative. McArdle disease is a deficiency of skeletal muscle glycogen phosphorylase and is characterized by early muscle pain and stiffness in association with intense exercise, during which muscles rely on glycogen stores for energy.⁸ This patient is asymptomatic during this type of exertion and also denies a “second-wind” phenomenon (a consistently encountered hallmark of McArdle disease), whereby mobilization of hepatic glycogen stores allows resumption of exertion after a brief rest.¹⁶

The primary source of muscle energy during prolonged exercise, fasting, and illness is fatty acid oxidation. Disorders in this pathway can lead to rhabdomyolysis after prolonged exertion but also in association with a wider range of triggers relevant to this patient, including infection, fever, and fasting.⁸ The most frequently encountered disorder presenting as recurrent rhabdomyolysis is CPT-II deficiency. Acylcarnitines are required intermediates in the transport of long-chain fatty acids from the cytosol to the mitochondria for β -oxidation, and their accumulation can be used to detect specific disorders in this metabolic pathway. The observed elevation of C16 and C18 acylcarnitines in this case strongly suggests CPT-II deficiency as the diagnosis.¹⁷ Very long-chain acyl coenzyme A dehydrogenase deficiency, which can have a similar clinical presentation, would be suggested by prominence of C14 acylcarnitine. Disorders of mitochondrial respiratory chain enzymes can present with a variety of symptoms including myopathy but tend to be multisystem disorders, and elevated lactate is frequently noted.¹⁷

Given the patient's clinical and biochemical improvement, she was discharged after 3 days as an inpatient to follow-up with the genetic service as an outpatient.

5. Which *one* of the following is the *most appropriate* recommendation for this patient at discharge?

- Bezafibrate
- L-carnitine supplementation
- Creatine supplementation

- Dietary modification
- Strict exercise avoidance

There have been no large-scale clinical trials conducted in patients with CPT-II deficiency. Bezafibrate has been investigated as a treatment with the potential to increase residual CPT-II activity, but the only randomized clinical trial performed to date did not find benefit.¹⁸ Although carnitine supplementation is the standard of care in patients with carnitine deficiency, use in CPT-II deficiency is limited to the severe childhood forms of the disease. Low-dose creatine supplementation has been investigated in McArdle disease, but it is not an established therapy in CPT-II deficiency. At present, the only evidence-based intervention for this patient is dietary modification with a regimen including a higher proportion of daily carbohydrate to achieve improved exercise tolerance.¹⁹ Anaplerotic diet therapy, in which dietary supplementation of the triglyceride triheptanoin, hypothesized to support adenosine triphosphate production in a CPT-II-independent manner, has been reported to be effective in preventing rhabdomyolysis and improving exercise tolerance in another small study.²⁰ Avoidance of factors known to precipitate rhabdomyolysis such as prolonged strenuous exercise or fasting is another important consideration for this patient. Although total avoidance of exercise is not necessary, limiting the duration of exercise to 30 minutes has been advocated.

DISCUSSION

Rhabdomyolysis is a commonly encountered medical condition with the potential for severe, life-threatening complications and for which minimal high-quality evidence exists to inform management. Arresting ongoing muscle injury, the prevention of AKI, and monitoring for metabolic complications are considered the short-term management priorities in rhabdomyolysis.⁴ If a rectifiable cause of rhabdomyolysis is identified, further muscle injury may be prevented, for example by withdrawing an offending medication or correcting hypothermia.

Early aggressive volume resuscitation, which corrects hypovolemia and increases urine production, is the intervention of choice

to reduce the incidence of AKI and is supported by a number of observational studies conducted in the trauma setting.⁶ Recommendations regarding the volume of fluid to be administered vary, but large requirements up to 10 to 12 L in 24 hours are often quoted, with ongoing monitoring of volume status and urine output.^{2,4} Sodium bicarbonate in place of 0.9% sodium chloride is utilized by some physicians. Although there is a biological rationale for urinary alkalinization to reduce myoglobin precipitation within the renal tubules, no clear additional benefit has been established in humans.²

A period of vigilant monitoring of renal function and electrolyte status is indicated until rhabdomyolysis resolves. Hyperkalemia, hyperphosphatemia, hypocalcemia, and an elevated anion gap metabolic acidosis are the anticipated derangements.¹ Declining renal function and administration of large volumes of normal saline or sodium bicarbonate can also impact electrolyte and acid base status, and this should be considered when interpreting the electrolyte panel. Hyperkalemia can emerge rapidly and must be treated aggressively when recognized.⁴

A small proportion of rhabdomyolysis cases occur secondary to an underlying metabolic defect, suggested by recurrent or unexplained episodes, exercise intolerance, or family history. Precipitating factors such as exertion or fasting are commonly identifiable, and failure to consider an underlying genetic defect predisposing the patient to muscle injury can delay diagnosis.¹⁷ Rhabdomyolysis triggers and the pattern of exercise-related symptoms guide the initial diagnostic work-up. Carnitine palmitoyltransferase II deficiency, the disorder of fatty acid oxidation underlying this case, is the most common cause of recurrent rhabdomyolysis in adults.

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CORRECT ANSWERS: 1. e. 2. c. 3. b. 4. c. 5. d