Unusual Complications of Exertional Rhabdomyolysis in a Patient with Sickle-cell Trait

Jie Ouyang, MD, PhD, Sharvari Dalal, MD, David Blumenthal, MD, Rosemary L. Wieczorek, MD, Martin Salwen, MD, and Matthew R. Pincus, MD, PhD

In addition to the more commonly reported complications of renal failure, liver failure, and disseminated intravascular coagulopathy, this young, previously healthy military service member with sickle-cell trait developed cardiac disease and septic shock that contributed to his death.

About two million Americans, and one in 12 African Americans, carry the sickle-cell trait.[1] Most of these individuals are asymptomatic unless they are exposed to a condition of low oxygen pressure, such as exists at high altitudes. On the other hand, in a small but significant number of patients with sickle-cell trait, vigorous exercise—often together with hyperthermia—has been found to induce rhabdomyolysis.[1] This condition results in elevated myoglobin levels from damaged or necrotic muscle tissue that can induce renal failure.[2] Treatment with vigorous hydration and maneuvers to decrease hyperkalemia from muscle tissue breakdown generally are employed—but are not always successful, especially when disseminated intravascular coagulopathy (DIC) develops.

Here, we report an unusual case of a young, previously healthy naval service member with sickle-cell trait who experienced sudden, acute, exertional rhabdomyolysis, compartment syndrome, and renal failure that were complicated by myocardial infarction (MI), congestive heart failure (CHF), septic shock, and acute multiple organ system failure, resulting in the patient's death. Notably, the development of severe cardiac complications and sepsis have not been documented previously as complications of exertional rhabdomyolysis in a young patient with sickle-cell trait who is otherwise healthy.

INITIAL EXAM

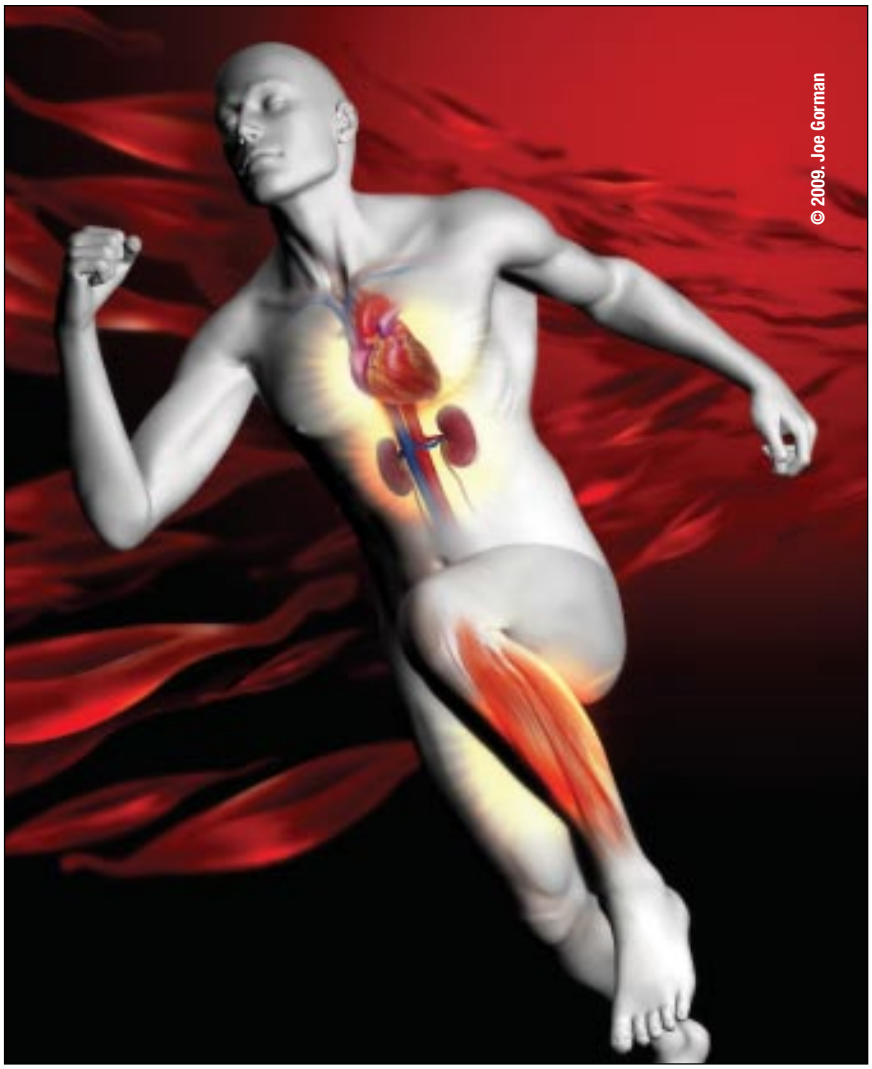
A 25-year-old, male, African American, active duty member of the U.S. Navy with sickle-cell trait (documented as hemoglobin A/S) presented to the emergency department (ED) of the Brooklyn Campus of the VA New York Harbor Healthcare System with acute bilateral thigh and calf pain (Figure). He had collapsed while performing running exercises as part of his military training. The patient reported extreme tenderness of both lower extremities, but there was no evidence of trauma to or edema of either extremity. He denied any significant medical history other than sickle-cell trait, and his only medication was an over-the-counter dietary supplement containing ephedra.

In the ED, the patient became hypotensive and showed signs of respiratory distress. He reported increasingly severe pain in his lower extremities, for which he was given pain medication. An electrocardiogram (ECG) was performed and showed sinus tachycardia, evidence of inferolateral ischemia, and left ventricular hypertrophy. As a result, a blood troponin I (cardiac isoform) level was obtained (using the Biosite assay, Biosite Diagnostics, San Diego,

Dr. Ouyang and **Dr. Dalal** are both resident physicians in the department of pathology at State University of New York (SUNY) Downstate Medical Center and in the pathology and laboratory medicine service at the Brooklyn Campus of the VA New York Harbor Healthcare System (VA NYHHS), both in Brooklyn, NY. **Dr. Blumenthal** is the chief of the medical service at the Brooklyn Campus of the VA NYHHS. **Dr. Wieczorek** is a clinical associate professor of pathology at SUNY Downstate Medical Center and the chief of anatomic pathology in the pathology and laboratory medicine service at the Brooklyn Campus of the VA NYHHS. **Dr. Salwen** is a distinguished service professor of pathology at SUNY Downstate Medical Center. **Dr. Pincus** is a professor of pathology at SUNY Downstate Medical Center and the chief of the pathology and laboratory medicine service for the VA NYHHS.

CA) and was found to be 4.72 ng/mL, a level consistent with a diagnosis of MI (Table).

Arterial blood gas analysis, performed in the ED, revealed a pH of 7.16, a P_{CO_2} of 33.5 mm Hg, and a P_{O_2} of 245 mm Hg while the patient was receiving 40% O_2. Other significant results of initial laboratory testing in the ED included: a mildly elevated serum potassium level (which increased further in a second ED serum sample taken four hours later), a low serum bicarbonate level, elevated serum creatinine (SCr) and creatine kinase (CK) levels, elevated aspartate transaminase (AST) and alanine aminotransferase (ALT) levels, and an elevated anion gap. Urinalysis revealed marked myoglobinuria. A complete blood cell count (CBC) revealed elevated white blood cells (WBCs), along with a red blood cell (RBC) count, hemoglobin level, and hematocrit value that were all slightly below the reference range.



HOSPITAL COURSE

The patient was admitted to the medical intensive care unit (MICU), at which time his prothrombin time (PT) was 21.3 seconds, partial thromboplastin time (PTT) was 59.1 seconds, and D-dimer level was greater than 5,000 ng/mL. Within 48 hours of admission, the PT increased to 71.6 seconds and the PTT increased to 128 seconds.

In the MICU, he was intubated and placed on mechanical ventilation. He was treated with aggressive hydration beginning the first hospital day and continuing over the next several days.

On the second hospital day, his RBC count decreased to 2.1 x 10^6/µL, his hematocrit dropped to 17.3%, and his hemoglobin level fell to 6 g/dL. Initially within the reference range, his platelet count decreased on the second hospital day to 70 x 10^3/µL and within one week to as low as 30 x 10^3/µL. As a result, starting on the second hospital day and continuing over the next week, he was given several transfusions of packed RBCs and fresh, frozen plasma. Also on the second day, the patient began anticoagulation therapy, which was continued over the next two weeks, and hemodialysis, which was administered over the course of hospitalization. To reduce his serum potassium levels, the patient was treated with insulin and dextrose 50% in water over the two days following admission.

During his first two days in the MICU, the patient developed a fever of 101°F. In light of this, as well as his persistent hypotension and elevated WBC count, an empiric course of antibiotics (vancomycin and piperacillin/tazobactam) was administered beginning on the second hospital day, and pan-cultures were performed over a five-day period. Serial blood cultures on the second hospital day were negative. On the 12th hospital day, however, cultures of the patient's femoral catheter tip and a urethral swab were found to be positive for *Pseudomonas aeruginosa* and *Enterococcus faecium*,

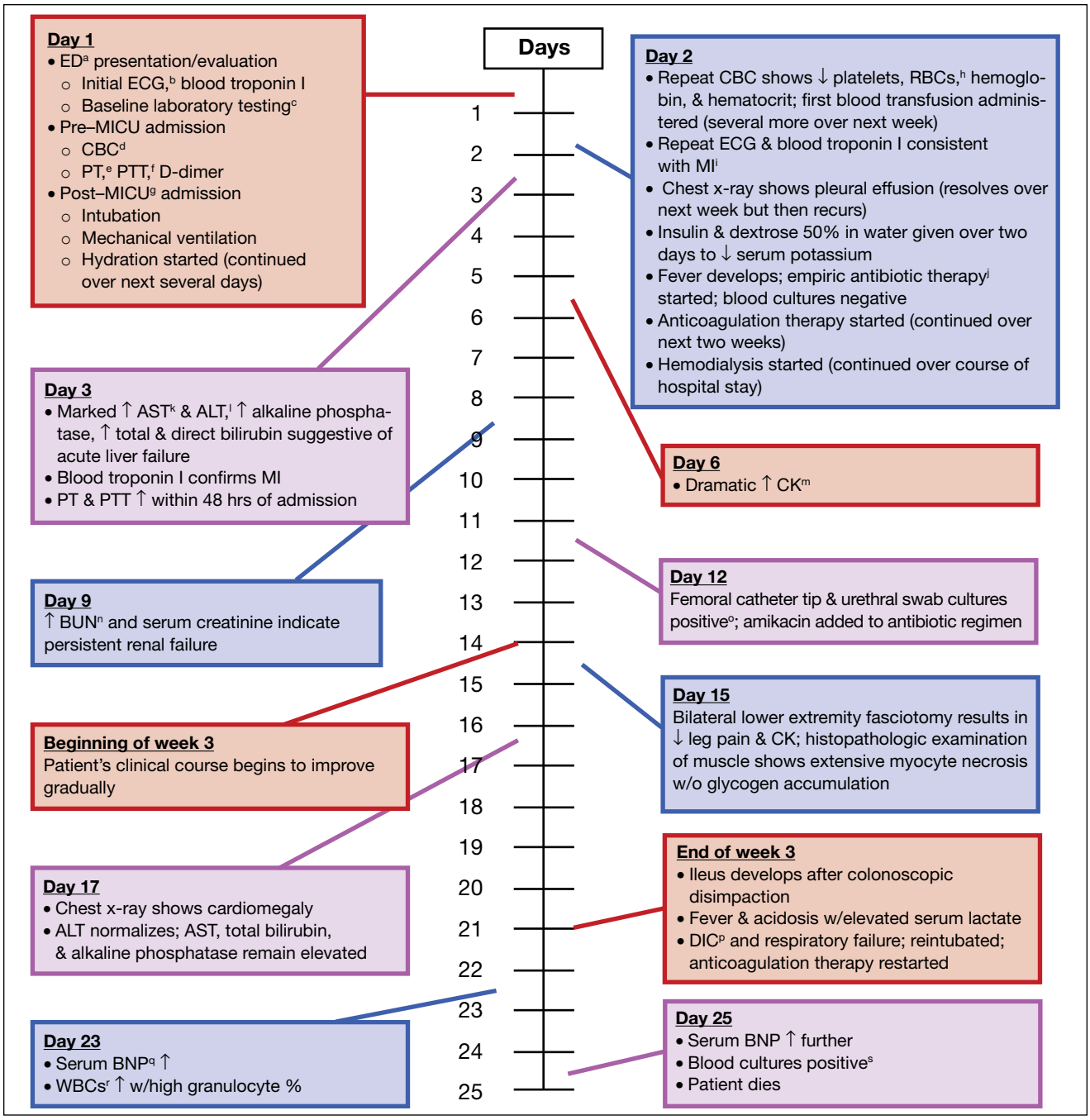


Figure. Timeline of ED evaluation and subsequent hospital course. [a]ED = emergency department. [b]ECG = electrocardiogram. [c]Initial testing included arterial blood gas analysis; serum potassium, bicarbonate, BUN, creatinine, CK, AST, ALT, alkaline phosphatase, and bilirubin levels; anion gap; a CBC; and urinalysis. [d]CBC = complete blood cell count. [e]PT = prothrombin time. [f]PTT = partial thromboplastin time. [g]MICU = medical intensive care unit. [h]RBCs = red blood cells. [i]MI = myocardial infarction. [j]With vancomycin and pipericillin/tazobactam. [k]AST = aspartate transaminase. [l]ALT = alanine aminotransferase. [m]CK = creatine kinase. [n]BUN = blood urea nitrogen. [o]For *Pseudomonas aeruginosa* and *Enterococcus faecium*, respectively. [p]DIC = disseminated intravascular coagulopathy. [q]BNP = B-type natriuretic peptide. [r]WBCs = white blood cells. [s]For multidrug-resistant *Acinetobacter baumannii* and vancomycin-resistant *E. faecium*.

Continued on page 19

Continued from page 16

Table. Significant laboratory findings for the patient initially and over the course of the hospitalization

Test	Reference range (RR)	Initial value[a]	Subsequent values
Blood troponin I, in ng/mL	< 0.09[b]	4.72	17,[c] 19[d]
Arterial blood gas			
pH	7.35–7.45	7.16	–
P_{CO_2}, in mm Hg	35–45	33.5	–
P_{O_2}, in mm Hg	75–100	245[e]	–
Serum potassium, in meq/L	3.5–5.0	4.5	6.8[f]
Serum bicarbonate, in meq/L	24–32	6	–
Blood urea nitrogen, in mg/dL	10–20	Within RR	108[g]
Serum creatinine, in mg/dL	0.4–1.2	2.1	5.7[g]
Creatine kinase, in IU/L	38–174	269	> 98,000[h]
Aspartate transaminase, in IU/L	10–42	73	11,443[d]
Alanine aminotransferase, in IU/L	10–40	84	5,949[d]
Serum alkaline phosphatase, in IU/L	42–121	Within RR	242[d]
Bilirubin, in mg/dL			
Total	0.1–1.2	Within RR	11.7[d]
Direct	0.0–0.2	Within RR	8.4[d]
Anion gap, in meq/L	3–11	33	–
Complete blood cell count			
White blood cells, in cells x 10^3/μL	4.5–11.0	16.6	17.3[i]
Red blood cells, in cells x 10^6/μL	4.5–6	4.4	2.1[c]
Hemoglobin, in g/dL	13–18	12.4	6[c]
Hematocrit, in %	40–52	37.3	17.3[c]
Platelet count, in cells x 10^3/μL	150–450	Within RR	70,[c] 30[j]
Prothrombin time, in seconds	10–13.8	21.3[k]	71.6[l]
Partial thromboplastin time, in seconds	24.7–38.4	59.1[k]	128[l]
D-dimer, in ng/mL	< 230	> 5,000[k]	–
Serum B-type natriuretic peptide, in ng/mL	0–100	86[m]	422,[i] 6,300[n]
Serum lactate, in mmol/L	0.5–2.2	21.7[o]	–

[a]Obtained in the emergency department (ED) unless otherwise noted. [b]This range is indicative of a negative result. [c]On hospital day 2. [d]On hospital day 3. [e]While the patient was receiving 40% O_2. [f]Four hours after the initial ED sample. [g]By hospital day 9. [h]On hospital day 6. [i]By hospital day 23. [j]Within one week. [k]At admission to the medical intensive care unit (MICU), on hospital day 1. [l]Within 48 hours of MICU admission, on hospital day 3. [m]One week after MICU admission, on hospital day 7. [n]By hospital day 25. [o]On hospital day 17.

respectively—both of which were sensitive to amikacin, which was added to his antibiotic regimen.

An ECG performed the day after admission showed a widened QRS complex and ST elevations, compatible with an anterior wall MI, in addition to the findings of the previous day. The troponin level at this time rose to 17 ng/mL and then to 19 ng/mL on the next hospital day, confirming the diagnosis of MI. Chest x-ray showed pleural effusions that resolved over the week following admission but then recurred. By the 17th hospital day, chest x-ray showed cardiomegaly. Serum B-type natriuretic peptide (BNP) levels ranged

from 86 ng/L one week after admission to 422 and 6,300 ng/L at 23 and 25 days after admission, respectively, confirming the presence of CHF.

By the third hospital day, the liver function profile showed marked elevations of AST and ALT to 11,443 and 5,949 IU/L, respectively. These increases were accompanied by elevations of serum alkaline phosphatase to 242 IU/L, total bilirubin to 11.7 mg/dL and direct bilirubin to 8.4 mg/dL, suggesting acute liver failure.

On the sixth hospital day, the patient's serum CK level was greater than 98,000 IU/L. By the ninth hospital day, his serum blood urea nitrogen (BUN) and SCr levels had increased to 108 and 5.7 mg/dL, respectively, indicating persistent renal failure.

After the second week, the patient's condition began to improve gradually. On the 15th hospital day, after his coagulation profile had stabilized, he underwent a bilateral lower extremity fasciotomy to relieve compartment syndrome. This procedure reduced his leg pain and decreased his serum CK level. Histopathologic sections of lower extremity muscle specimens from the debriding procedure revealed extensive myocyte necrosis with no evidence of accumulation of glycogen within myocytes.

By the 17th hospital day, the patient's ALT level had normalized—although his AST, total bilirubin, and alkaline phosphatase levels remained elevated. By the end of the third hospital week, the patient developed ileus following colonoscopic disimpaction. He developed another fever and became acidotic, with an elevated serum lactate level of 21.7 mmol/L; developed DIC and respiratory failure; and was reintubated. Anticoagulation therapy was reinstituted. By the 23rd hospital day, his WBC count had increased to 17.3 x 10^3/µL, with a high granulocyte percentage (85.5%).

Renal failure was persistent, and hemodialysis was continued. Despite intensive treatment with transfusion, fluid, and antibiotics, the patient died on the 25th hospital day. Cultures from blood samples taken on this day were positive for multidrug-resistant *Acinetobacter baumannii* (sensitive only to ampicillin-sulbactam and tobramycin) and vancomycin-resistant *E. faecium* (sensitive to linezolid, quinupristin-dalfopristin, and tetracycline). The family declined an autopsy.

ABOUT THE CONDITION

Sickle-cell trait is a known predisposing factor for sudden death in recruits to the U.S. armed forces.[1] In a past survey by Army Medical Corps physicians, it was found that the risk of unexplained exercise-induced sudden death was nearly 30-fold higher in African-American recruits with sickle-cell trait than in African-American recruits without this condition.[3] Most deaths occurred in the first month of training when maximal exertional efforts were required. If muscle necrosis was observed, death resulted mainly in those recruits who were found to have rhabdomyolysis. Other contributing factors were hyperthermia, dehydration, viral syndromes, and increased age.[1,3] Based on these observations, each branch of the military has formulated policies with regard to screening for sickle-cell trait. These vary from no screening at all to screening with no exercise restrictions for recruits who screen positive to screening with the option of declining service offered to recruits who screen positive.[1]

While the correlation between sickle-cell trait and exercise-induced sudden death is well established, the pathophysiology underlying the phenomenon remains largely unknown. In autopsy studies of patients who have died from this condition, sickling of RBCs has been found in the microvasculature.[1] Based on this finding, it has been hypothesized that small vessel obstruction may cause infarction of tissues (as in sickle-cell disease), thus leading to tissue necrosis, including necrosis of skeletal muscle.[1] Skeletal muscle necrosis often leads to rhabdomyolysis, which, in turn, causes the release of large amounts of myoglobin into the vasculature, which is filtered by the kidneys. Since myoglobin is toxic to the renal tubules, patients with this condition present with renal failure. Additionally, small vessel occlusion related to sickling of RBCs could cause renal infarction, leading to papillary necrosis and the inability of the kidneys to concentrate the urine.

The autopsy results, however, are ambiguous since it is not clear whether the observed sickling may have been the result of postmortem hypoxia rather than a premortem phenomenon.[1] Furthermore, it has been observed in patients with sickle-cell trait that the concentrating ability of the kidneys diminishes with increasing age, even when there is no evidence of sickling.[1] Thus, the origin of exercise-induced tissue necrosis in patients with sickle-cell trait is still in question.[1–4]

Rhabdomyolysis can induce severe systemic pathology that predisposes patients to an unfavorable clinical course. Besides triggering the release of nephrotoxic myoglobin, this condition also precipitates the release of intracellular enzymes from damaged skeletal muscle, which can cause tissue damage.[2] Moreover, massive release of intracellular potassium results in hyperkalemia that can cause life threatening cardiac arrhythmias. Particularly in cases of massive myonecrosis, release of procoagulant tissue products induces DIC that can result in multisystem failure and death.[4]

Continued on page 25

Continued from page 20

Our patient experienced severe exercise-induced rhabdomyolysis as evidenced by anterior compartment syndrome, markedly elevated serum CK levels, and muscle histology showing extensive myonecrosis. This condition may have been exacerbated by his prior use of a dietary supplement containing ephedra, which has been implicated as a cause of rhabdomyolysis.[5] His coagulation profile revealed DIC. He experienced multisystem failure, including renal failure, liver failure (as evidenced by a "shock liver" pattern of liver function analytes[6]), and respiratory failure requiring intubation. Hepatic dysfunction has been observed in 25% of patients with rhabdomyolysis and is thought to be due to release of proteases from injured muscle.[7]

Unusual features of this case

In addition to renal, liver, and respiratory failure and DIC, our patient experienced MI and subsequent CHF—both highly unusual complications of exertional rhabdomyolysis. In a survey of the literature, we found no association of exertional rhabdomyolysis, including that induced by performance enhancing dietary supplements (like ephedra), with myocardial pathology in previously healthy patients with sickle-cell trait. Only one recent case report suggested the possible presence of MI in a college athlete with sickle-cell trait who experienced severe exercise-induced anterior compartment syndrome with many of the stigmata observed in our patient. In this case, troponin levels were equivocal while CK-MB levels suggested the possibility of MI or myocardial damage.[8]

In our patient, MI was diagnosed based on ECG changes and on elevations in blood levels of cardiac troponin inhibitory subunit (cTnI). It is important to note that, in a number of studies, elevations of this marker for MI and myocardial damage have been found in patients with rhabdomyolysis who had no evidence of myocardial damage on ECG or echocardiography.[9,10] In one study, it was suggested that the false-positive rate for MI diagnosis in these patients was about 15%.[9] In addition, transient elevations of both cTnI and BNP have been found in athletes who have run in marathons[11]—although at much lower levels than those found in our patient. In the case of our patient, marked elevation in cTnI was accompanied by ECG abnormalities strongly suggestive of MI. The presence of BNP elevations and x-ray findings demonstrating cardiac enlargement and pulmonary effusions were strongly suggestive of CHF.

It's possible that our patient's heart involvement could have represented exacerbation of preexisting disease, although he denied any history of heart disease at admission. We considered the possibility of glycogen storage disease, such as Pompe disease, which is known to affect heart tissue.[12] This condition usually is accompanied by glycogen inclusions in myocytes, however, and we observed no such inclusions. Nonetheless, muscle biopsies of patients with this and other glycogen storage diseases do not always show glycogen inclusions and have no consistent, specific histopathologic findings.

Another unusual feature of this case was the development of recurrent infections and sepsis—specifically, a urinary tract infection with *P. aeruginosa*, which was treated successfully with amikacin, and septicemia from two drug-resistant organisms, multidrug-resistant *A. baumannii* and vancomycin-resistant *E. faecium*.

Only a few isolated cases of septicemia in patients with rhabdomyolysis have been reported in the medical literature, none of which had histories at all similar to that of our patient.[13,14] Both organisms found in our patient have been implicated in nosocomial infections, occur frequently in patients undergoing prolonged hospitalizations, and tend to exhibit multidrug resistance. Notably, though, only two other patients who were in the MICU during the month-long period when our patient was hospitalized were diagnosed with infections due to *A. baumannii*. Furthermore, of the drug-resistant enterococci, *Enterococcus faecalis* is significantly more common than *E. faecium*.[15] One of the predisposing factors for the development of drug-resistant enterococci (including vancomycin-resistant organisms) is prior treatment with antibiotics.[15] Our patient had undergone prior successful antibiotic therapy with amikacin.

While the source of infection by *A. baumannii* is unclear,[16] this organism is known to cause infections in immunocompromised patients—especially those who, like our patient, undergo prolonged stays in intensive care units.[16] Additional predisposing factors have been identified as male sex, cardiovascular disease, mechanical ventilation, and prior treatment with antimicrobial drugs (especially metronidazole)[16]—all of which applied to our patient. The findings of recurrent infections and, specifically, sepsis involving an organism (*A. baumannii*) that occurs mainly in immunocompromised hosts suggest that this patient was immunocompromised, possibly due to extensive myonecrosis and its sequelae.

IN SUMMARY

Our patient experienced all of the known sequelae of extensive myonecrosis, including compartment syndrome, DIC, renal failure, and liver failure. Any or all of these conditions

can cause death.[1–4] Superimposed on these conditions, however, were MI, CHF, and sepsis—all of which are unusual in otherwise healthy patients who develop exercise-induced rhabdomyolysis. Thus, this case suggests that rhabdomyolysis, if severe enough, may involve heart muscle or that severe exercise-induced sickling may induce coronary artery occlusion. Particularly when combined with the more traditional complications of exertional rhabdomyolysis, these conditions carry a high risk of mortality, and, in the case presented here, contributed to the patient's death. Another contributor to death in this case was the development of sepsis by two drug-resistant organisms. The likelihood of immunocompromise indicated by *A. baumannii* sepsis in this patient further suggests that severe rhabdomyolysis may induce immunologic anergy.

Overall, this case emphasizes the necessity of monitoring the exercise activities of individuals with sickle-cell trait. Especially in the military setting, it is vital to monitor such events as viral prodromes and signs of renal compromise (such as polyuria) in recruits with sickle-cell trait. It is also important to elicit information about dietary habits, such as the consumption of performance enhancing supplements (like the ephedra containing supplement taken by our patient). The presence of any of these factors may result in exercise-induced rhabdomyolysis that can lead to severe and uncorrectable sequelae.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Quadrant HealthCom Inc., the U.S. government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

REFERENCES

1. Mitchell BL. Sickle cell trait and sudden death—Bringing it home. *J Natl Med Assoc*. 2007;99(3):300–305.
2. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. *Intern Emerg Med*. 2007;2(3):210–218.
3. Kark JA, Posey DM, Schumacher HR, Ruehle CJ. Sickle-cell trait as a risk factor for sudden death in physical training. *N Engl J Med*. 1987; 317(13):781–787.
4. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine (Baltimore)*. 2005;84(6):377–385.
5. Stahl CE, Borlongan CV, Szerlip M, Szerlip H. No pain, no gain—Exercise-induced rhabdomyolysis associated with the performance enhancer herbal supplement ephedra. *Med Sci Monit*. 2006;12(9): CS81–CS84.
6. Sunheimer R, Capaldo G, Kashanian F, et al. Serum analyte pattern characteristic of fulminant hepatic failure. *Ann Clin Lab Sci*. 1994;24(2):101–109.
7. Akmal M, Massry SG. Reversible hepatic dysfunction associated with rhabdomyolysis. *Am J Nephrol*. 1990;10(1):49–52.
8. Harrykissoon RI, Patel B, Warner MT, Estrada-Y-Martin R. Fatal rhabdomyolysis in a college athlete due to sickle cell trait. *Chest*. October 2007;132(4)(suppl):673S. http://meeting.chestjournal.org/cgi/content/abstract/132/4/673. Accessed March 13, 2009.
9. Li SF, Zapata J, Tillem E. The prevalence of false-positive cardiac troponin I in ED patients with rhabdomyolysis. *Am J Emerg Med*. 2005;23(7):860–863.
10. Punukollu G, Gowda RM, Khan IA, et al. Elevated serum cardiac troponin I in rhabdomyolysis. *Int J Cardiol*. 2004;96(1):35–40.
11. Neilan TG, Januzzi JL, Lee-Lewandrowski E, et al. Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. *Circulation*. 2006; 114(22):2325–2333.
12. Lynch CM, Johnson J, Vaccaro C, Thurberg BL. High-resolution light microscopy (HRLM) and digital analysis of Pompe disease pathology. *J Histochem Cytochem*. 2005;53(1):63–73.
13. Kataoka H, Shinozaki S, Nagata S, Sato Y, Hanai H. Fatal sepsis complicating rhabdomyolysis on the extremities. *Intensive Care Med*. 2000;26(7):1007.
14. Tomiyama J, Hasegawa Y, Nagasawa T, Abe T, Horiguchi H, Ogata T. *Bacillus cereus* septicemia associated with rhabdomyolysis and myoglobinuric renal failure. *Jpn J Med*. 1989;28(2):247–250.
15. Huycke MM, Sahm DF, Gilmore MS. Multiple-drug resistant enterococci: The nature of the problem and an agenda for the future. *Emerg Infect Dis*. 1998;4(2):239–249.
16. Abbo A, Navon-Venezia S, Hammer-Muntz O, Krichali T, Siegman-Igra Y, Carmeli Y. Multidrug-resistant *Acinetobacter baumannii*. *Emerg Infect Dis*. 2005;11(1):22–29.