Don't you forget about me

Considering acute rhabdomyolysis in ED patients with cocaine ingestion

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Earl is a 32-year-old man who has been brought to the emergency department (ED) by his friends. They had been "partying" the previous evening. He slept on the floor at his friend's apartment for 12 hours after consuming 12 beers and using cocaine. This morning, his friends have brought him to the ED because he "isn't himself." He has a decreased level of consciousness (Glasgow Coma Scale score of 13), but responds to verbal commands. He is tachycardic at 176 beats per minute and has a blood pressure of 180/90 mm Hg. He had chest pain last night but has none now. On examination there are no obvious signs of physical trauma. The nurse asks what tests you would like to run on this patient.

The term *rhabdomyolysis* refers to the rapid breakdown of skeletal muscle and is characterized by the release of intracellular muscle cell components into circulation and extracellular fluid.[1-4] The muscle cell components include serum muscle enzymes like creatine kinase (CK), as well as electrolytes and myoglobin.[1-4] Common clinical manifestations are muscle weakness and pain, and the production of dark, tea-coloured urine that tests positive for blood on a urine dip but negative for red blood cells on microscopic examination.[1-4] Rhabdomyolysis can range from a mild, asymptomatic elevation in CK levels to a severe and even life-threatening condition with extremely high CK levels, substantial electrolyte level disturbances, acute renal failure (ARF), disseminated intravascular coagulation, and multiorgan failure.[1-3] It is reported that 13% to 50% of patients with rhabdomyolysis develop ARF, which is associated with a poor expected survival.[1] Early diagnosis and prompt and aggressive management are essential in the reduction of morbidity and mortality from this condition.

Common causes and pathophysiology

There are 2 general causes of rhabdomyolysis: 1) direct trauma to myocytes, and 2) metabolic insults, including toxin-mediated injuries (**Box 1**). The most easily recognized cause of rhabdomyolysis is muscle trauma secondary to crush injury. This direct injury to the plasma membrane of myocytes causes intracellular constituents to be expelled into circulation. This triggers postischemic reperfusion and inflammation of the involved muscles.[1] Severe physical exertion can also result in rhabdomyolysis, likely through a combination of tissue injury and adenosine triphosphate (ATP) depletion.[2] This has been seen most recently as a result of some popular muscle enhancement programs. Physiologic causes include anaphylaxis, hyperthermia, and electrocution.

Direct muscle trauma. Physical muscle damage due to prolonged immobility or pressure can cause muscle cell hypoxia, leading to ischemia and depletion of ATP from within the myocyte, inducing an unregulated increase in intracellular calcium. This causes persistent contraction of the muscle, further energy depletion, and activation of calcium-dependent enzymes. Eventually, this process leads to destruction of the myofibrils, cytoskeleton, and membrane proteins, followed by lysosomal elimination of cellular components and disintegration of the myocyte.[1] Common causes include shock states, compression secondary to loss of consciousness, stroke, falls, or immobility secondary to intoxication.[1-4]

Metabolic pathogenesis. Causes such as toxin ingestion, substance abuse, sepsis, diabetic ketoacidosis, and electrolyte imbalances are commonly overlooked. Electrolyte imbalances might also lead to rhabdomyolysis from a disruption of the sodium-potassium pumps in myocytes.[1,2] This can be secondary to extensive diuresis, or severe vomiting or diarrhea. Drugs and toxins play

Box 1. Rhabdomyolysis assessment

History
- Trauma, crush injuries
- Extreme exertion, some workout plans
- Prolonged immobility, compression (cerebrovascular accident, fall, coma, etc)
- Drug use or toxin ingestion (cocaine, heroin, etc)
- Medications (statins)

Symptoms
- Muscle pain, swelling, cramping, weakness
- Nonspecific signs: malaise, fever

Signs
- Dark, tea-coloured urine
- Decreased level of consciousness or coma—examine carefully for signs of injury

Workup
- Routine: complete blood count, blood urea nitrogen levels, creatinine levels, creatine kinase levels, electrolyte levels, glucose levels
- Urinalysis
- Creatinine levels, extended electrolyte levels (calcium, magnesium, phosphate), acetaminophen levels, acetylsalicylic acid levels, ethanol levels, serum osmolality, liver function tests, international normalized ratio
- Electrocardiography
- Follow-up: muscle biopsy after resolution if no pathogenesis

a role in almost 80% of adult cases of rhabdomyolysis.[4] Several widely prescribed medications and recreational substances are important nontraumatic causes of rhabdomyolysis. Although less relevant to ED care, there are also hereditary causes of rhabdomyolysis, the most common being McArdle disease, a glycogen storage disorder.[5] Hereditary causes are related mainly to deficiencies of enzymes needed for catabolism of energy macromolecules.[6] These include lipid-lowering agents (eg, statins), illicit drugs (eg, heroin, cocaine), and alcohol, all of which can affect use and production of ATP within the cell and disrupt the integrity of the plasma membrane, allowing leakage of intracellular components into circulation.[1,2]

Recreational drugs are a common cause of both traumatic and nontraumatic rhabdomyolysis. Cocaine, for instance, results in acute rhabdomyolysis directly through its toxic effect on muscle fibres and prolonged vasoconstriction resulting in intramuscular artery compression with associated muscular ischemia. Indirectly, it can also cause rhabdomyolysis through immobilization and compression or muscular hyperactivity, resulting in secondary muscle injury.[2,3,7] Not surprisingly, as many as 24% of patients presenting to the ED with cocaine-related disorders have acute rhabdomyolysis.[7]

Complications

Myoglobin, a dark-red, heme-containing protein released by damaged myocytes, is normally freely filtered by the glomerulus, endocytosed into tubule epithelial cells, and metabolized.[1] In rhabdomyolysis, serum concentrations of myoglobin rise considerably and can lead to life-threatening complications, such as ARF.[1-4,6] Although the exact mechanism of rhabdomyolysis-induced renal dysfunction is unclear, it appears that intrarenal vasoconstriction, direct and ischemic tubule injury, and obstruction in the distal tubules from concentrated myoglobin are all important contributing factors. Renal constriction occurs owing to intravascular volume depletion (hypovolemia) secondary to fluid retention in the damaged muscles, inducing activation of the renin-angiotensin system, vasopressin, and the sympathetic nervous system. Cytotoxicity might be due to uncontrolled leakage of reactive oxygen species after cellular release of myoglobin and free radicals that cause tissue injury.[1] In acidic environments, myoglobin can precipitate in the glomerular filtrate and occlude the distal tubules, causing further kidney injury. Myoglobin casts in the urine result from the interaction between myoglobin and Tamm-Horsfall protein in low-pH urine and are indicative of rhabdomyolysis-associated ARF.[1-3]

Other complications of rhabdomyolysis include electrolyte abnormalities resulting from release of cellular components into circulation. Hyperkalemia is an early and fast-rising manifestation of rhabdomyolysis, regardless of the underlying cause.[1] Hyperphosphatemia, hyperuricemia, high anion gap metabolic acidosis, and hypermagnesemia (with ARF) might also occur.[1-4,6,8] Hyperuricemia is a risk factor for kidney injury, as uric acid is insoluble and can contribute to renal tubule obstruction.[1] Hypocalcemia is another early common complication of rhabdomyolysis, resulting from sequestration of calcium within the damaged muscles and calcification of necrotic muscle tissue.[1] Consequently, serial extended monitoring of electrolyte levels and renal function should begin when rhabdomyolysis is diagnosed.[3]

Assessment and diagnosis

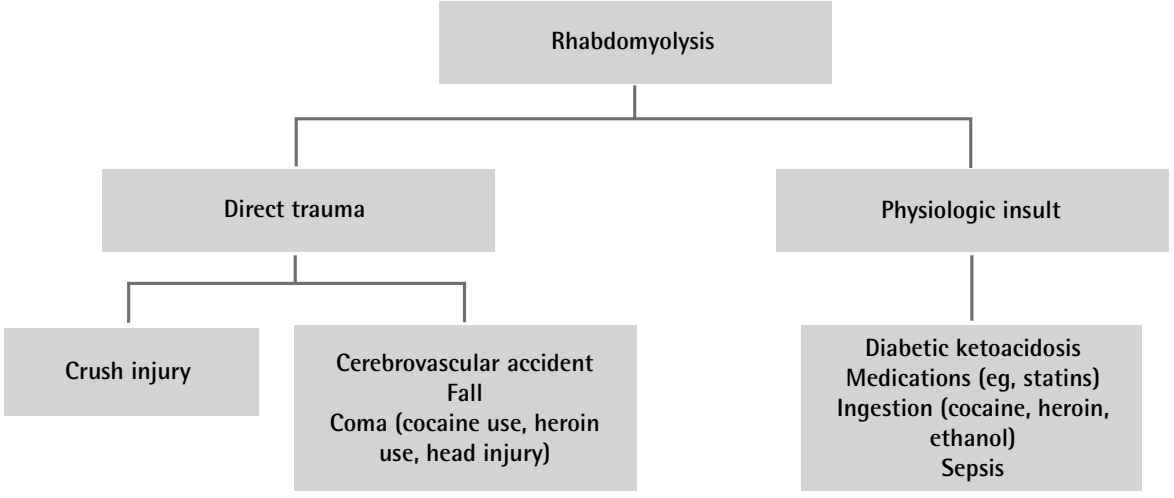
Patients with acute rhabdomyolysis classically present with the triad of muscle weakness, muscle pain, and dark urine. However, more than 50% of patients report neither muscle pain nor weakness.[3] Patients might also have fluid retention, malaise, fever, tachycardia, nausea, or vomiting.[1,2] The clinical picture, history, and physical examination might suggest rhabdomyolysis, but definitive diagnosis can only be confirmed through laboratory investigations.[1-4] Myoglobin is not measured directly in urine or plasma. Measurement of serum myoglobin actually has a low sensitivity for the diagnosis of rhabdomyolysis because serum myoglobin levels peak earlier than serum CK levels, and it has a short half-life and unpredictable metabolism.[1,2]

Diagnosis focuses instead on CK levels and the presence of myoglobinuria. Normal CK levels are between 45 and 260 U/L.[2] Creatine kinase levels initially rise within the first 12 hours of muscle destruction, peak after 1 to 3 days, and decline 3 to 5 days after muscle injury ends.[2,3] In the absence of cerebral or myocardial infarction, it is generally agreed that CK levels 5 times the normal concentration (approximately 1000 U/L) are highly suggestive of rhabdomyolysis.[3] Levels above 5000 U/L indicate substantial muscle injury and are closely related to the likelihood of renal involvement.[1] Myoglobinuria should be suspected when a urine dipstick test is positive for blood in the absence of red blood cells. Early in rhabdomyolysis, myoglobinuria—with its classic red-brown urine colour—might be transient or absent, making it diagnostically unreliable. It is important to note that patients with myoglobinuria might have positive test results for blood on urinary dipsticks, but no red blood cells in the urine sediment. The false-positive results occur because dipsticks cannot distinguish myoglobin from hemoglobin. This test has a sensitivity between 50% and 80% for detecting rhabdomyolysis.[1]

Aspartate aminotransferase levels might also be elevated; however, in the context of rhabdomyolysis, we are unaware of any relationship between the degree of aspartate aminotransferase level elevation and that of CK level elevation.

The cause of the rhabdomyolysis must also be identified and managed (**Figure 1**).[8] Although some causes of rhabdomyolysis, such as crush injuries or immobilization, might be evident from the patient history or physical examination, causes such as inherited metabolic myopathies, endocrinopathies, toxin ingestion, or infections might be less obvious and should be investigated further to avoid possible recurrence.[4,8] If no trigger can be identified, a muscle biopsy after resolution of the acute symptoms can yield structural information that might help identify a cause.[4]

Figure 1. Differential diagnosis for rhabdomyolysis



Management

After stabilization and resuscitation, the most important step in managing patients with rhabdomyolysis is early and aggressive repletion of fluids to maintain or improve kidney function.[1-4,7-9] Volume repletion with normal saline should be initiated promptly at a rate of 200 to 1000 mL/h, depending on the setting and severity of the condition. Urine outpu t should be monitored, with a target of 300 mL/h.[1,3,6]

If myoglobinuria is present, alkalinization of urine through intravenous sodium bicarbonate solution should be initiated, with the objective of reaching a urine pH greater than 6.50 and a serum pH between 7.40 and 7.45.[3,6] Some reports also suggest the use of osmotic diuretics, such as mannitol, to remove fluid from the damaged muscle interstitium.[9] Diuretics might only be beneficial when there is a strong suspicion of compartment syndrome and should only be used after the patient's hypovolemia has been corrected.[6] Although both alkalinization and osmotic diuresis are common practices in the treatment of rhabdomyolysis, there is no strong evidence of clear benefit.[1,2,6]

Evidence demonstrates benefit for patients who receive early and aggressive rehydration, with a reduction in their risk of developing ARF. For those who present with rhabdomyolysis complicated by acute renal injury and receive supportive rehydration, long-term survival is almost 80%, and most patients recover renal function.[1] Electrolyte disturbances need to be corrected quickly, with special attention to the hyperkalemia that often occurs early in the course of rhabdomyolysis.[1-4,6] Hypocalcemia will often self-correct with supportive management.[6] If ARF occurs, along with severe hyperkalemia and acidosis, patients require close monitoring of metabolic parameters and consideration of hemodialysis.[2]

There are 2 reasons for us to suspect rhabdomyolysis in Earl's case—previous chest pain and cocaine use. His workup should include toxicology screening for acetylsalicylic acid and acetaminophen; measurement of electrolyte, serum glucose, CK, and serum alcohol levels and renal function; and complete blood count. An electrocardiogram should also be part of Earl's initial workup even in the absence of chest pain. Prompt diagnosis will permit early, rapid rehydration, the key to preventing many complications of this condition. The most important and often missed step in caring for patients like Earl is including rhabdomyolysis in your differential diagnosis.

BOTTOM LINE

- Consider rhabdomyolysis in patients who are using cocaine.
- Measure serum creatine kinase levels for all patients at risk of rhabdomyolysis.
- Prompt, aggressive volume repletion should be done with normal saline at a rate of 200 to 1000 mL/h.
- Correct electrolyte imbalances and treat other complications such as acute renal failure and electrolyte level abnormalities.

POINTS SAILLANTS

- Envisagez une rhabdomyolyse chez les patients qui consomment de la cocaïne.
- Mesurez les niveaux de créatine kinase sérique chez tous les patients à risque d'une rhabdomyolyse.
- Une réplétion prompte et vigoureuse du volume devrait être faite avec une solution saline normale à raison de 200 à 1 000 ml/h.
- Corrigez les déséquilibres dans les électrolytes et traitez les autres complications comme l'insuffisance rénale aiguë et les anomalies des niveaux d'électrolytes.

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Competing interests
None declared

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