

Rhabdomyolysis-Associated Acute Kidney Injury

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Clinical Presentation

A 66-year-old man presented to the emergency department with tremors, dyspnea, nausea, polyarthralgia, and dysuria. He had a history of hypertension and ischemic heart disease. His medications included amlodipine, ramipril, and low-dose aspirin.

At admission, the patient was sweaty and showed generalized tremors. Blood pressure was 210/110 mm Hg, heart rate was 80 beats/min, and axillary temperature was 36.5 C. Physical examination showed diffuse muscle tenderness, mild peripheral edema, and basal pulmonary rales, with normal heart sounds. Laboratory studies showed elevated serum creatinine (201.5 $\mu\text{mol/L}$), urea nitrogen (10.3 mmol/L), transaminase (aspartate aminotransferase, 3,488 U/L; and alanine aminotransferase, 746 U/L), and lactate dehydrogenase levels (3,416 U/L), along with marked elevation of serum creatinine kinase (CK) level (167,000 U/L). Serum potassium level was 3.6 mmol/L; calcium, 2 mmol/L; and phosphate, 1.6 mmol/L. Urine dipstick was positive for blood and leukocyte esterase; microscopic examination of urine showed only about 2 red blood cells per high-power field.

A diagnosis of severe rhabdomyolysis was made. Shortly after admission, the patient's condition worsened and he was transferred to the intensive care unit. An echocardiogram documented severely depressed right and left ventricular function (ejection fraction, 20%) with generalized hypokinesis. Electromyography showed the presence of severe muscular injury without evidence of acute denervation. The patient developed oliguric acute kidney injury (AKI), and continuous renal replacement therapy (CRRT) was initiated.

Further history revealed that the patient had recently been engaged in what was for him unusually intense physical activity. It was also learned that he had presented with a similar episode of muscle damage 6 years before, when after coronary artery bypass surgery, he developed a marked increase in CK levels (27,000 U/L) that was not associated with AKI.

In the following days, respiratory and cardiac conditions improved, while kidney injury persisted and the patient was switched from CRRT to hemodialysis therapy. Two weeks after admission, kidney function

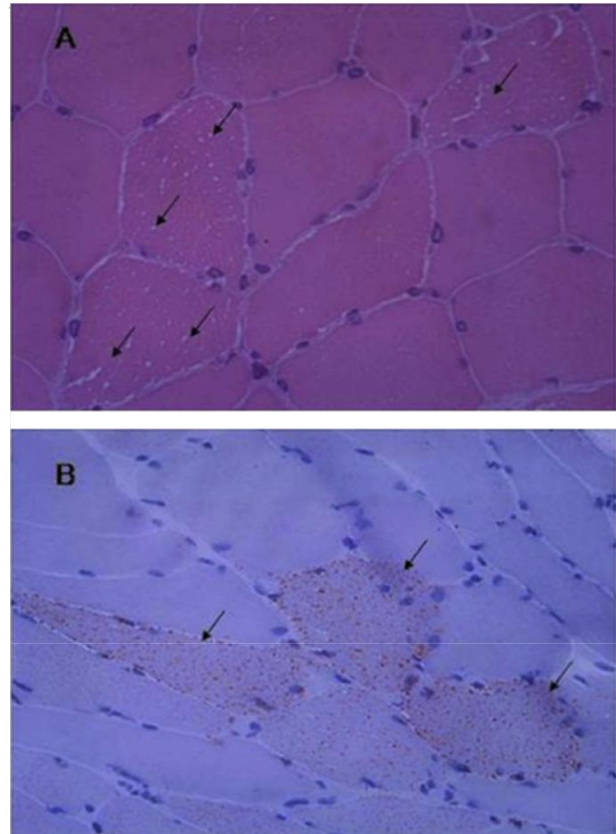


Figure 1. Skeletal muscle biopsy specimen shows small intracytoplasmic vacuoles (arrows) with (A) hematoxylin and eosin stain and (B) confirming the presence of lipid droplets (arrows) with Oil Red O stain (original magnification, $\times 400$).

improved and hemodialysis treatments were discontinued. Extensive testing was performed to elucidate the cause of the muscle injury, including a muscle biopsy (Fig 1).

- What is the differential diagnosis of the underlying cause of rhabdomyolysis in patients such as this?
- What are the effects of rhabdomyolysis on kidney function?
- What is the optimal management of patients with AKI secondary to rhabdomyolysis?

Discussion

What is the differential diagnosis of the underlying cause of rhabdomyolysis in patients such as this?

Rhabdomyolysis may result from trauma, extreme physical exercise, prolonged immobilization associated with compression and ischemic injury, hypophosphatemia, drugs (mainly alcohol, opioids, and statins), infections, hypokalemia, certain autoimmune diseases, endocrine abnormalities such as hypo- or hyperthyroidism, hypothermia, and hyperthermia. Massive muscle damage can also occur in some genetic disorders affecting muscle structure and energy metabolism, such as glycogen storage diseases, muscular dystrophies, disorders of fatty acid metabolism, and mitochondrial diseases. Clinically, muscle injury may be asymptomatic or present as local or diffuse pain, tenderness, or weakness and may be associated with nonspecific symptoms, including fatigue, nausea, vomiting, and fever. Patients may report red or brown urine. The most specific laboratory marker of rhabdomyolysis is elevated plasma CK level, with values from 5 to 10 times the upper limit of normal frequently used to define rhabdomyolysis. Other markers of rhabdomyolysis include elevated lactate dehydrogenase and serum transaminase levels and the presence of myoglobinuria. Myoglobinuria is typically diagnosed by the presence of a very positive urine dipstick test for blood, with disproportionately few red blood cells in urine. Urine myoglobin can also be directly measured.

When a diagnosis of rhabdomyolysis has been established, patients should be queried regarding any history of unusual recent physical activity, trauma, prolonged immobilization, infections, use of illicit drugs or those associated with rhabdomyolysis, and any pertinent personal prior or family history of muscle injury. A family history of rhabdomyolysis or history of recurrent episodes consistent with rhabdomyolysis is suggestive of genetic myopathies.¹ Laboratory studies should include assessment of mineral metabolism, glucose metabolism, and autoimmunity markers such as myositis-specific autoantibodies and myositis-associated autoantibodies, including anti-Jo-1, anti-signal recognition particle, anti-Mi-2, anti-PM-Scl, and anti-SS-A/Ro antibodies. Finally, muscle biopsy may be diagnostically helpful in select cases of unexplained or recurrent rhabdomyolysis.

In this patient, a muscle biopsy performed 22 days after the acute muscle injury did not show evidence of inflammation or acute muscle damage, such as fiber necrosis or ghost fibers, but revealed mild fiber size variability and multiple small vacuoles in numerous muscle fibers. The vacuoles were filled with lipid droplets as shown by Oil Red O stain (Fig 1). The presence of lipid-rich vacuoles along with mild fiber

size variability was thought to be indicative of a metabolic myopathy. In particular, such lesions have been described in cases of carnitine palmitoyltransferase II (CPT II) deficiency, sometimes as the only abnormal finding, because muscle histology in CPT II deficiency is usually normal. Biochemical analysis of muscle CPT II showed decreased enzyme activity, and subsequent genetic analysis showed a homoplasmic mutation in the CPT II gene (a substitution of cytosine by thymine at nucleotide 338 of the coding sequence, corresponding to a serine to leucine change at amino acid 113 [c.338C>T, p.Ser113Leu]), definitively confirming the diagnosis of CPT II deficiency.²

What are the effects of rhabdomyolysis on kidney function?

AKI develops in 10% to 40% of patients with severe rhabdomyolysis. No single factor, including levels of serum CK, creatinine, potassium, calcium, or myoglobinuria, accurately predicts AKI in patients with rhabdomyolysis. However, patients with muscle injury secondary to trauma, especially in the presence of comorbid conditions, are at major risk for AKI compared with patients with elevated CK levels secondary to intensive exercise, use of statins, infections, or inflammatory myopathies.

The main mechanism of kidney damage in patients with rhabdomyolysis is the massive release of myoglobin into the circulation, with myoglobinuria.³ Myoglobinuria, which becomes visible when urine myoglobin excretion exceeds 100 to 300 mg/dL, causes cast formation and accumulation of iron in proximal tubules, with intratubular obstruction and proximal tubular cell injury. Another factor involved in the pathogenesis of acute tubular injury and AKI includes volume depletion due to sequestration (“third spacing”) of fluids into injured muscles. Release of cellular constituents from damaged muscles can lead to high anion gap metabolic acidosis, hyperkalemia, hyperphosphatemia, and hyperuricemia. Hypocalcemia is commonly seen as the result of calcium deposition in damaged muscles. Metabolic acidosis and the resulting aciduria might further exacerbate tubular damage because at low urinary pH, myoglobin dissociates into globin and ferrihemate, which has a direct nephrotoxic effect.

What is the optimal management of patients with AKI secondary to rhabdomyolysis?

The mainstays of efforts to prevent AKI in patients with rhabdomyolysis are saline solutions to expand/restore intravascular volume and treatment of the underlying cause of rhabdomyolysis. Although there is general agreement on early and aggressive volume resuscitation aimed at increasing urine flow (about 200-300 mL/h), there is no strong evidence about the best types of fluids

to administer. The rationale for using sodium bicarbonate infusions rather than isotonic saline solutions is that urinary alkalization could avoid myoglobin precipitation and inhibit reduction–oxidation cycling of myoglobin and lipid peroxidation. However, although widely used, this approach is not evidence based and may increase the risk for metastatic tissue calcification and ionized hypocalcemia. The use of diuretics (ie, mannitol or furosemide) to increase diuresis has not been tested in clinical studies and is not generally recommended.

Various forms of dialytic therapy have been used if AKI develops, but there is no evidence supporting the use of a specific dialysis modality. Dialysis has also been hypothesized to enhance recovery through removal of myoglobin released into the circulation from injured muscles. Although some hemodialysis and CRRT filter membranes can remove myoglobin, there is little evidence that this is beneficial after AKI has been established. Intermittent hemodialysis is generally ineffective in sustaining a reduction in plasma myoglobin levels because of rapid rebound in levels following a single hemodialysis treatment. CRRT or hemofiltration is more effective, with much greater clearance of myoglobin than conventional filters,^{1,3} but again, without evidence that this prevents AKI or improves its subsequent course once developed. In the current case, because of oliguria and severe AKI, continuous venovenous hemodiafiltration therapy with a high-flux membrane (AN69; Hospal Medical) was initiated. After 5 days, CK levels decreased to 22,000 U/L. Two weeks after admission, the patient was switched from CRRT to intermittent hemodialysis therapy. In the following days, diuresis ensued and kidney function progressively improved, so that it was possible to withdraw hemodialysis therapy.

CPT II deficiency is a rare disorder of the fatty acid beta-oxidation cycle, caused by homozygous or compound heterozygous mutations in the *CPT2* gene.⁴ CPT II works as a shuttle for long-chain fatty acids to enter mitochondria, where they are used as the main energy source of muscles during prolonged exercise. CPT II deficiency leads to ATP depletion and dysfunction of the adenosine triphosphatase sodium/potassium pump (Na^+/K^+ -ATPase) and the calcium-transporting adenosine triphosphatase (Ca^{2+} -ATPase) and activates phospholipases and proteases, which lyse cellular membranes and disrupt mitochondrial function. Diagnosis of CPT II deficiency, when clinically suspected, is confirmed by a combination of enzyme assay and molecular genetic testing for pathogenic mutations in the *CPT2* gene.

This patient represents a typical case of CPT II deficiency, with a history of recurrent rhabdomyolysis exacerbated by physical activity and postsurgery stress. After resolution of the AKI, prophylactic

measures consist of preventing muscle energy depletion by avoiding intense physical activities. Following this recommendation, the patient did not develop other rhabdomyolysis episodes during 2 years of follow-up, at which time serum creatinine level was 111.8 $\mu\text{mol/L}$ and CK (51 U/L) and myoglobin (65 ng/mL) levels were within the reference ranges.

Final Diagnosis

Acute kidney injury caused by rhabdomyolysis due to a mutation in the gene for the carnitine palmitoyltransferase II enzyme.

Article Information

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