Nontraumatic Rhabdomyolysis with Long-Term Alcohol Intoxication

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Rhabdomyolysis, the disintegration of skeletal muscle, is a common cause of acute renal failure.[1,2] This clinical entity occurs mainly from 2 sources: traumatic and nontraumatic. Traumatic rhabdomyolysis has been described as crush syndrome during war and natural disasters.[3] In modern or peace time, the majority of cases of rhabdomyolysis are nontraumatic, and alcohol abuse is one of the most common causes.[4,5] In many cases of alcohol-related nontraumatic rhabdomyolysis reported in the literature, patients have a typical history of short-term alcohol intoxication and alcohol-induced coma or immobilization.[6] These patients are commonly diagnosed and treated in emergency settings because of a rapid onset of severe muscle pain and deceased urine output.[7,8] In contrast, nontraumatic rhabdomyolysis with long-term alcohol abuse is rarely reported in the literature and is often overlooked because of insidious and indolent onset; the lack of coma, convulsion, and immobilization in the history; and the lack of severe muscle pain in the clinical presentation.[9] It is especially important for family physicians to diagnose nontraumatic rhabdomyolysis appropriately, because it may be encountered in an outpatient setting with chief complaints of generalized malaise and weakness. The objectives of this case report are: (1) to clearly describe the clinical features, available diagnostic tools, and optimal treatment for nontraumatic rhabdomyolysis with long-term alcohol intoxication; (2) to increase the awareness among physicians, especially family physicians, of nontraumatic rhabdomyolysis with chronic alcoholism; and (3) eventually, to promote early recognition and treatment of this syndrome to prevent renal failure.

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Case Reports

A 48-year-old African American man presented to our office 1 day after a witnessed syncopal episode at work, with complaint of generalized malaise, weakness, and decreased appetite. The patient, a long-term alcohol consumer, reported that he had not eaten anything in the morning and felt dizzy around noontime before passing out. There was no seizure activity or trauma reported and no history of any alteration of sensorium, no fever, no intake of acetaminophen or anti-inflammatory drugs, and no use of illicit drugs or herbal medications. Physical examination revealed a cachectic male with jaundice, tachycardic with heart rate of 120 beats/min, and hepatomegaly to 3 cm below the right costal margin. Urinalysis at admission showed positive dipstick for blood with negative microscopic examination for red blood cells (RBCs). Serum total creatine kinase (CK) was significantly elevated with normal level of CK in cardiac muscle (CKMB) and troponin I. Other laboratory results are shown in Table 1. Once the diagnosis of rhabdomyolysis was confirmed, the patient was immediately treated with aggressive intravenous infusion of normal saline and monitored for urine output and serum total CK. The patient recovered uneventfully and was discharged with descending CK level and normal creatinine clearance.

Discussion

Rhabdomyolysis, which results in the release of large amounts of muscle cell contents into circulation, is a potentially life-threatening syndrome. Myoglobin, the 18.8-kd hemoglobin-like protein, is freely filtered by the glomeruli and reaches the tubules, where it may cause obstruction, renal tubular necrosis, and most seriously acute renal failure.[5] Approximately 38,000 cases of rhabdomyolysis were reported in the year 2000 in the United States,[10] and renal dysfunction can complicate approximately 30% of all cases.[11,12] Therefore, early diagnosis is critical for treating this serious and

Table 1. Investigations Performed

Item (Reference Range)	Day 1	Day 2	Day 3	Day 4
Hemoglobin (13.7–17.3 g/dL)	14.6	11.6	10.5	
Hematocrit (0.39–0.49)	42.2	34.2	31.4	
White blood cells (3.2–9.8 k/mm^3)	6.4	7.8	6.6	
Platelet (150–450 k/mm^3)	47	59	67	
Na^+ (135–145 mmol/L)	129	135	135	
K^+ (3.5–5.1 mmol/L)	3.6	3.9	4.5	
Cl^- (95–110 mmol/L)	90	100	102	
HCO_3^- (21–29 mmol/L)	24	26	25	
Serum urea nitrogen (7–18 mg/dL)	4	7	6	
Creatinine (0.5–1.3 mg/dL)	1.5	0.9	0.9	
Glucose (70–105 mg/dL)	105	100	97	
Calcium (8.5–10.1 mg/dL)	8.9	8.6	8.8	
Phosphorus (2.5–4.9 mg/dL)		2.4	2.8	
Magnesium (1.5–2.4 mg/dL)	1.8			
Total CK (0–232 Units/L)	13,742	11,295	9,498	6,190
CK MB (<6 ng/mL)	1.9	1.4		
Albumin (3.4–5 g/dL)	3.6			2.9
Total protein (6.2–8 g/dL)	7.6			6.3
Bilirubin (0–1 mg/dL)	3.7			1.5
Direct bilirubin (0–0.3 mg/dL)	3.0			1.3
Alkaline phosphatase (50–136 units/L)	504			353
Aspartate aminotransferase (4–37 units/L)	318			285
Alanine aminotransferase (30–65 units/L)	161			185
γ-Glutamyltransferase (0–65 IU/L)				1820
Lactate dehydrogenase (100–242 units/L)		589		
Prothrombin time (11.3–13.2 seconds)	11.2			
Activated partial thromboplastin time (24.7–33.4 seconds)	24.6			
Urine myoglobin		(−)		

preventable cause of renal damage. Among the risk factors attributed to nontraumatic rhabdomyolysis, including malignant hyperpyrexia, extreme exertion, repeated seizures, bacterial and viral infections, the use of certain medications[13,14] or illicit drugs,[15] ethanol ranks highest; up to 67% cases of nontraumatic rhabdomyolysis involved alcohol.[6,16,17]

Although the cause of alcohol-related nontraumatic rhabdomyolysis is not fully understood, the pathophysiology for alcohol-related nontraumatic rhabdomyolysis can be quite different between short- and long-term alcohol abuse.[18] Under short-term alcohol intoxication, immobilization or coma induced by ethanol-related central nervous system sedation plays an important role in developing rhabdomyolysis. It causes muscle compression and muscular ischemia, which will superimpose or accelerate short-term alcohol myotoxicity,[19] resulting in a massive breakdown of skeletal muscle within a short period. Because of the rapid release of osmotically active agents into the interstitial space and rapid increase of compartmental pressure, patients with nontraumatic rhabdomyolysis with short-term alcohol intoxication are likely to present with severe muscle pain and even compartment syndromes. Because of rapid release of muscle cell contents into circulation, these patients are also likely to be complicated with hyperkalemia, metabolic acidosis, acute renal failure, multiorgan failure, or disseminated intravascular coagulation.[7,8] In contrast, the cause of muscle necrosis in long-term alcohol abuse is more complex. It has been suggested that electrolyte abnormalities (ie, hypokalemia, hypophosphatemia, or hypomagnesemia) play significant causative roles for developing rhabdomyolysis in persons with long-term alcoholism.[18,20–22] However, the causative roles of these electrolyte abnormalities are often underdetected because these abnormalities disappear after overt

muscle necrosis and renal failure have developed. In our patient, the serum potassium was 3.6 mmol/L and the phosphorus was less than 2.5 mg/dL when overt rhabdomyolysis had developed, with serum total CK over 10,000 U/L. This indicates that depletion of both potassium and phosphorus may pre-exist and may be potential causes of rhabdomyolysis. Because rhabdomyolysis with long-term alcohol abuse develops gradually and because of coexisting nutritional deprivation or peripheral neuropathy in long-term alcoholism, patients who have nontraumatic rhabdomyolysis with long-term alcohol abuse probably present with malaise and weakness instead of muscle pain among their complaints, with muscular atrophy at physical examination.[18] More importantly, as in our patient, patients who develop nontraumatic rhabdomyolysis with long-term alcohol intoxication do not necessarily have coma or immobilization in their history.[9] Because of the insidious indolent onset and nonclassical presentation, diagnosis of nontraumatic rhabdomyolysis with long-term alcohol abuse is often delayed.

The diagnosis of rhabdomyolysis in this case was first indicated by the urinalysis, which showed positive dipstick for blood and negative microscopy for RBCs, confirmed by the elevation of total serum CK with normal CKMB isoform and troponin I.[2] Similar to hemoglobin, myoglobin in the urine can also catalyze the oxidation of the chromogen in the presence of organic peroxide in the test pad, forming a green to blue color (Roche Diagnostic, Indianapolis, IN). Therefore, the distinction between myoglobinuria and hemoglobinuria must be made by other tests.[23] Most commonly, microscopic analysis of fresh sediments is used for this purpose, in which the absence of urinary RBCs after positive dipstick blood test supports the diagnosis of myoglobinuria. In addition, the color of serum specimens could be an alternative approach, in which normal serum color indicates myoglobinuria, whereas a pigmented brown or red serum indicates hemoglobinuria. However, the latter approach is not helpful when patients also have hyperbilirubinemia caused by alcoholic hepatitis, as the patient here did.

The standard for confirming the diagnosis of rhabdomyolysis is the elevation of total CK with normal CKMB,[2] indicating that the elevated CK is from skeletal muscle. Because of the slow degradation and removal of CK in the serum, the concentration of CK remains elevated longer and in a more consistent manner with the severity of muscle necrosis. Because the serum level of myoglobin is unpredictably affected by the level of heptoglobin and the capacity of hepatic metabolism, and because of replacement of serum myoglobin measurement by measurement of troponins in many institutions, serum myoglobin is rarely used for diagnosis and monitoring of rhabdomyolysis. The presence of myoglobin in the urine is affected by the capacity for glomerular filtration. It has been reported that myoglobin was not demonstrated in the urine in about 50% rhabdomyolysis patients because of grossly reduced glomerular filtration rates.[16] It is important to remember that myoglobinuria does not occur without rhabdomyolysis, but rhabdomyolysis does not necessarily result in visible myoglobinuria. In our patient, urine myoglobin was negative even as serum total CK remained elevated at 11,295 U/L. Therefore, the test for urine myoglobin cannot be used as a diagnostic tool; likewise, the absence of myoglobinuria cannot rule out the presence of rhabdomyolysis.

Once the diagnosis of rhabdomyolysis is made, a rapid fluid transfusion should be initiated as early as possible to preserve renal function while monitoring urine output and levels of potassium and total CK. All patients diagnosed with rhabdomyolysis should be hospitalized for rapid fluid replacement, with isotonic saline as the treatment of choice even if there is no evidence of dehydration. In general, the infusion rate can be adjusted to keep urine output at 300 mL/hour.[2] Because less severe metabolic or electrolyte abnormalities (ie, metabolic acidosis and hyperkalemia) are involved in rhabdomyolysis with chronic alcohol abuse, and because of the known increased morbidity and mortality with administration of sodium bicarbonate,[24] alkalinization of urine is usually not needed. For our patient, the urine pH was 7.0 and bicarbonate was 24 mmol/L at admission without hyperkalemia or acidosis, so alkalinization of urine was not indicated. With the fluid hydration, the level of serum total CK was constantly dropping, with significant improvement of prior weakness. The serum phosphorus level responded to a single dose of oral phosphorus supplement (250 mg Neutra-phos) and increased to 2.8 mg/dL. Because nontraumatic rhabdomyolysis has been reported in long-term alcoholism with the use of nonsteroid anti-inflammatory drugs[25] or acetaminophen,[26] physicians

must exercise great caution when prescribing pain relief medications to patients with long-term alcohol abuse.

In addition to nontraumatic rhabdomyolysis with long-term alcohol abuse in this case, alcoholic liver disease was also diagnosed based on (1) the patient's social history; (2) elevation of aspartate aminotransferase, with nearly a 2:1 ratio of aspartate aminotransferase/alanine aminotransferase; (3) elevation of total bilirubin, with conjugated form dominant; (4) elevation of serum alkaline phosphatase and γ-glutamyltransferase, (5) abdominal ultrasound showing fatty liver without biliary tract obstruction; and (6) negative screening for hepatitis A, B, and C virus infections. Thrombocytopenia was also identified and probably resulted from the toxic suppression effect of alcohol on megakaryocyte production,[27] because no splenomegaly was found in this patient. Anemia was revealed after fluid rehydration, with decrease in hemoglobin and hematocrit during the hospital stay. Normal prothrombin time indicates that there is no evidence of apparent compromise of hepatic function.

Although the reason for the patient's syncopal episode remains undetermined, hypoglycemia could be a primary explanation. Because of depletion of glycogen in liver and muscle, and because of direct inhibition of gluconeogenesis enzymes by ethanol,[28] persons with long-term alcohol abuse are more susceptible to having hypoglycemic syncopes. It also has been demonstrated that short-term alcoholic myopathy can be triggered by sudden food withdrawal.[29]

In conclusion, history of prolonged ethanol-induced immobilization or coma and complaint of muscle pain are not necessary for the diagnosis of nontraumatic rhabdomyolysis in persons with long-term alcohol abuse. Urinalysis with dipstick for hemoglobin in combination with microscopy for RBCs can be used as a simple and cost-effective screening test. Elevation of serum total CK with normal CKMB is the test of choice for confirmation. Early recognition and prompt treatment with aggressive intravenous hydration are crucial to prevent renal damage. We believe that increased awareness and a high level of suspicion will assist physicians, especially family physicians, in diagnosing and treating nontraumatic rhabdomyolysis appropriately in patients who present with malaise, weakness, and a history of long-term alcohol abuse.

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