Rhabdomyolysis

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Saraswathi Gopal, Amir Kazory, and Azra Bihorac

Case Presentation

A 24-yo Hispanic female (gravida 3, para 2) was admitted to a community hospital in the 24th week of pregnancy with complaints of shortness of breath and hemoptysis for 3 days. Her past medical history was significant for hypertension, systemic lupus erythematosus (SLE), and lupus nephritis (WHO type 2). SLE was diagnosed 2 years prior to this admission and she was treated with a short course of oral prednisone and azathioprine which lead to complete remission. She did not have any history of nicotine, alcohol or illicit drug abuse. On physical exam she was found to have bilateral pleural effusions and distant heart sounds. Laboratory data were significant for hemolytic anemia with a hematocrit of 19%, increased lactate dehydrogenase (LDH) levels, leukopenia, and mild acute kidney injury with a serum creatinine of 1.3 mg/dL. Echocardiogram revealed presence of pericardial effusion without any evidence of tamponade. SLE flare was suspected and she received intravenous methylprednisolone 250 mg/day. On the third day of admission, patient presented with respiratory failure and was intubated. Sedation was maintained by propofol infusion (ranging from 5.5 to 7.1 mg/kg/h) while patient was on mechanical ventilation. The following day she was transferred to a tertiary care hospital for further evaluation and management.

At the time of transfer, the temperature was 37.0 °C, the pulse was 98, and the blood pressure was 111/49 mmHg. The patient was receiving ventilatory assistance. Urinalysis revealed turbid and amber urine, with a specific gravity of 1.014, and 3+ for protein; the sediment contained greater than 100 RBCs and 30 WBCs, with numerous granular casts per low-power field. Laboratory tests are summarized in Tables 44.1 and 44.2. An electrocardiogram showed a normal sinus rhythm at a rate of 89, with non-specific T wave alterations in the precordial leads. Arterial blood gas while the patient was receiving 70% oxygen revealed a pH of 7.41, a partial pressure of oxygen of 70 mmHg, and a partial pressure of carbon dioxide of 25 mmHg. Abdominal ultrasound was normal with an intrauterine pregnancy. Echocardiogram demonstrated moderate pericardial effusion (18 mm posterior) with no evidence of hemodynamic compromise. Left and right ventricular size and systolic function were normal. Serologic testing was positive for antinuclear antibodies, anti-native DNA antibodies, anti-ribonuclear protein

S. Gopal
Division of Nephrology Hypertension and Renal Transplantation, Department of Medicine, University of Florida, Gainesville, FL, USA

A. Kazory
Medicine/Nephrology, University of Florida, Gainesville, FL, USA

A. Bihorac (✉)
Department of Anesthesiology/Division of Critical Care Medicine, University of Florida College of Medicine, Gainesville, FL, USA
e-mail: azra.bihorac@medicine.ufl.edu; ABihorac@anest.ufl.edu

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Table 44.1 Blood chemical values

	Day 1 3:30	Day 1 18:30	Day 2 3:30	Day 2 16:15	Day 2 23:30	Day 3 1:00	Day 3 2:38
Blood Urea nitrogen (mg/dl)	49	53	55	61	65		68
Creatinine (mg/dl)	1.6	1.4	1.5	2.7	3.1		3.4
Albumin (g/dl)	1.6						
Glucose	189	193	153	151	152		192
Sodium (mmol/l)	134	135	135	134	134	140	134
Potassium (mmol/l)	4.3	3.5	3.4	5.3	7.1	5.5	7
Chloride (mmol/l)	109	100	100	100	104		100
Carbon dioxide (mmol/l)	19	26	25	19	13		19
Calcium (mg/dl)	6.1	5.7	6.6	5.8	10.3		6.2
Phosphorus (mg/dl)	7.2	5.2	5.8	9.8			14.4
Aspartate aminotransferase (U/l)	14						
Alanine aminotransferase (U/l)	19						
Lactate dehydrogenase (U/l)	732		1682				
Alkaline phosphatase (U/l)	73						
Creatinine kinase (U/l)	<25					134756	
Creatine kinase-MB (ng/mL)	1.5					545	
Troponin T (U/l)	<0.01						
PH			7.41		7.27	7.48	7.42
pCO2			36		27.8	27.9	26.4

Table 44.2 Hematologic values

	Day 1 3:30	Day 1 18:30	Day 2 3:30	Day 2 16:15	Day 2 23:30	Day 3 1:00	Day 3 2:38
Hematocrit (%)	19	23	24	40	43		43
Mean corpuscular volume (μm^3)	93	90	84	84	83		81
Haptoglobin		Normal					
White-cell count (per mm^3)	19,600	16,000	11,000	23,000	21,000		22,000
Differential count (%)							
Neutrophils Band forms Lymphocytes Monocytes Eosinophils Basophils	89 1 6 4 0 0	84 14 2 0 0 0	95 0 4 1 0 0				91 0 5 4 0 0
Platelet count (per mm^3)	175,000	134,000	119,000	250,000	227,000		251,000
Prothrombin time (s)	11.8						
Partial-thromboplastin time (s)	29						

antibodies and anti-smith antibodies. Complement CH50 was <10 U/ml and antineutrophil cytoplasmic antibodies were absent.

Based on the patient's clinical presentation, coupled with her past medical history and serological data, the diagnosis of lupus flare was made. Treatment with intravenous methylprednisolone at the dose of 1000 mg/day was then initiated. Supportive therapy included blood transfusions, empirical antibiotics (ampicillin and sulbactam), and mechanical ventilation with sedation by propofol drip at a mean rate of 6 mg/kg/h. She was

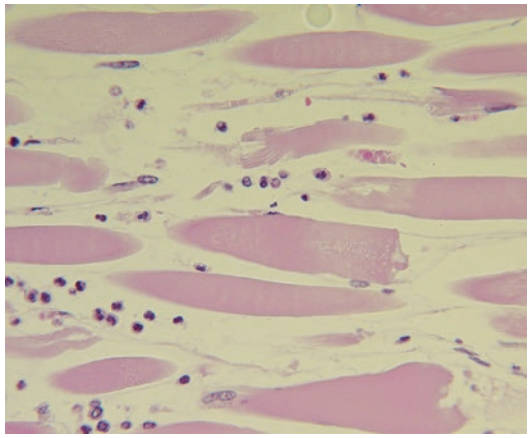

Fig. 44.1 Skeletal muscle biopsy revealed acute diffuse rhabdomyolysis with nuclear drop-out, hyaline-like myocytes with loss of striations, acute inflammation and edema

also receiving dopamine, aspirin, erythropoietin, and pantoprazole. On the third hospital day, she presented with sudden onset of hypotension and tachyarrhythmia necessitating initiation of vasopressors for hemodynamic support. Laboratory work-up revealed serum creatine kinase (CK) level rising to 134,756 U/L, severe hyperkalemia, new-onset high anion-gap metabolic acidosis, and worsening acute kidney injury (AKI) (Table 44.1).

Question What is the evidence based approach to manage this patient's acute kidney injury?

Answer In the absence of any other etiology for rhabdomyolysis, the diagnosis rhabdomyolysis due to propofol was made and propofol drip was immediately discontinued.

Due to her metabolic abnormalities (hyperkalemia, metabolic acidosis) and worsening renal failure a decision was made to initiate renal replacement therapy. However, while preparing patient for renal replacement therapy, her hyperkalemia worsened in spite of medical treatment and within 2 hours (h) she developed ventricular tachycardia rapidly followed by cardiac arrest and death. Autopsy was performed and confirmed histologic evidence of rhabdomyolysis in skeletal muscles (Fig. 44.1).

Principles of Management

There is a lack of level I evidence from which the best management plans for rhabdomyolysis may be derived. In fact, no randomized controlled trials studying treatment of rhabdomyolysis have been conducted, and most evidence is based on retrospective clinical studies, case reports and animal models.

Diagnosis

Rhabdomyolysis involves damage to the skeletal muscle fibers and the release of toxic intracellular contents into the circulation. The causes of rhabdomyolysis are summarized in Table 44.3. The clinical spectrum of Rhabdomyolysis is rather wide and variable. The classic triad of symptoms including muscle weakness, pain and reddish brown urine are present in less than 50 % of the patients [1, 2]. Most frequently, the involved muscle groups are the postural muscles of the thighs, calves and lower back [3]. Nonspecific systemic symptoms, such as malaise, fever, abdominal pain, nausea and vomiting may also be seen. Apart from history and physical examination a definitive diagnosis can be made by laboratory studies including serum creatine kinase (CK) and urine myoglobin levels. In some cases a skeletal muscle biopsy can also be used to confirm the diagnosis [4].

CK rises in rhabdomyolysis within 12 h of the onset of muscle injury, peaks in 1–3 days, and declines 3–5 days after the cessation of muscle injury. Although various values of CK have been postulated to define rhabdomyolysis, the magnitude of elevation is rather arbitrary; and there is no cut-off value that conclusively diagnoses rhabdomyolysis. Abnormal CK levels are commonly seen in injured intensive care unit patients, and a level of 5000 U/l or greater is related to renal failure [5]. Myoglobin is normally bound to plasma globulins. During muscle injury the amount of myoglobin spilled in the circulation exceeds the plasma binding capacity (>1.5 mg/dl) and is excreted in the urine [6, 7]. It is the myoglobin, which imparts the reddish brown color to the urine in rhabdomyolysis. Serum myoglobin usually increases before a rise in

CK and drops more rapidly than does the decline in CK concentration (in 1–6 h) [8]. Moreover, myoglobinuria may not be visible or may resolve early in the course of rhabdomyolysis. Due to these factors neither serum myoglobin nor urinary myoglobin levels can be used as reliable diagnostic indicators for rhabdomyolysis.

Muscle biopsy is not necessary, although it can be used to confirm the diagnosis of rhabdomyolysis. The histopathological findings usually include loss of cell nucleus and muscular stria with the absence of inflammatory cells [9].

Fluid Therapy

There is evidence to suggest early hydration is essential to prevent and limit the severity of renal failure in rhabdomyolysis [10]. There is no data to support or guide the amount of fluids that need to be administered. Most patients with rhabdomyolysis are hypovolemic, so fluid resuscitation to maintain a minimum urine output goal of 2 ml/kg/h is recommended [11]. A Foley catheter should be placed in order to monitor the urine output closely. In severe cases of crush injury,

Table 44.3 Causes of rhabdomyolysis

Trauma	Any trauma leading to muscle damage Motor vehicle accidents especially crush injuries Physical torture/abuse Prolonged immobilization Overexertion (long distance running or prolonged exercise) Delirium tremens Epilepsy
Vascular	Any vascular occlusion Thrombosis Embolism Iatrogenic-Prolonged vessel clamping during surgery
Sepsis	
Hyperthermia	Neuroleptic malignant syndrome malignant hyperthermia
Electric current	Cardioversion, high voltage electric current
Electrolyte abnormalities	Hypernatremia Hypocalcemia Hyponatremia Hypokalemia Hypophosphatemia
Metabolic diseases	Carnitine deficiency Creatinine palmitoyl transferase deficiency Myophosphorylase deficiency (McArdle disease) Mitochondrial respiratory chain enzyme deficiencies Phosphofruktokinase deficiency
Infections	Coxsackievirus Falciparum malaria Herpes viruses Human immunodeficiency virus Legionella Salmonella Streptoccocus Tularemia
Endocrine disorders	Hyperaldosteronism Hypothyroidism Ketoacidosis Hyperaldosteronism
Toxins	Heavy metals Insect venoms Snake venoms
Autoimmune diseases	Polymyositis

Table 44.3 (continued)

Drugs	Sedatives/ hypnotic drugs Benzodiazepines Diazepam Nitrazepam Flunitrazepam Lorazepam Triazolam Barbiturates Gluthetimide Drugs of addiction Heroin Cocaine Amphetamine Methadone D-lysergic acid diethylamide (LSD) Antidepressants and Antipsychotic drugs Amitriptyline Fluoxetine Fluphenazine Haloperidol Lithium Protriptyline Phenelzine Perphenazine Promethazine Chlorpromazine Loxapine Promazine Trifluoperazine Amoxapine Doxepine Antilipemic drugs Lovastatin Pravastatin Simvastatin Bezafibrate Clozafibrate Ciprofibate Clofibrate Others Alcohol Amphotericin B Azathrioprine Butyrophenones Epsilon-aminocaproic acid Halothane Moxalactam Oxprenolol Paracetamol Penicillamine Pentamidine Phencyclidine Phenylpropanolamine Propofol Quinidine Salicylates Strychnine Succinylcholine Theophyline Terbutaline Thiazides Vasopressin Diphenhydramine Doxylamine

administration of blood products and intravenous fluids simultaneously is important to correct severe hypovolemic state [12].

Treating Reversible Causes of Muscle Damage

Underlying causes of muscle damage must be identified to prevent ongoing muscle destruction. Causes such as infections, trauma, hyperthermia, electrolyte abnormalities and medication induced muscle damage should be identified and addressed appropriately. In cases of drug induced rhabdomyolysis the offending agent should be identified and stopped immediately, if necessary drugs and toxins should be eliminated (e.g., gastric lavage, antidotes and/or haemodialysis) whenever possible [4].

Management of Complications

Complications of rhabdomyolysis include acute renal failure, acidosis, compartment syndrome, hepatic dysfunction, disseminated intravascular coagulation, arrhythmias and cardiac arrest.

Acute renal failure (ARF) develops in 33 % of patients [2] with rhabdomyolysis. Factors known to contribute to rhabdomyolysis-induced acute renal failure include hypovolemic, acidosis or aciduria, tubular obstruction, and the nephrotoxic effects of myoglobin. Aggressive rehydration is considered the standard of care in preventing acute renal failure in patients with rhabdomyolysis.

Hyperkalemia and hypocalcaemia occurring after muscle damage can predispose to cardiac arrhythmias. Hyperkalemia should be managed aggressively when present. Treatment can be initiated with insulin and dextrose. Intravenous calcium can be administered but becomes less effective when hyperphosphatemia is present since calcium and phosphorus can precipitate removing both of them from circulation [13]. Dialysis should be considered as a lifesaving procedure for patients with a rising or elevated potassium level, persistent acidosis, or oliguric renal failure with fluid overload.

Disseminated intravascular coagulation (DIC) results from complement activation of clotting cascade by components released after muscle injury. This usually occurs after severe rhabdomyolysis, leading to hemorrhagic complications [3]. DIC usually resolves spontaneously after several days if the underlying cause is corrected, but if hemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary.

Compartment syndrome is another complication of rhabdomyolysis. Most skeletal muscles are confined to compartments formed by fascia, bones and other structures. When muscle fibers are ischemic and edematous, it raises the intra compartment pressure potentiating a vicious cycle of more ischemia and damage [2, 6]. Compartment syndrome requires immediate orthopedic consultation for fasciotomy.

Evidence Contour

Bicarbonate Therapy

Alkalinization of the urine is also a common intervention in rhabdomyolysis, but evidence of a clinical benefit is lacking. The concept of urine alkalinization derives from the precipitation of myoglobin in an acidic environment, and therefore, urinary alkalinization (pH. 6.5) theoretically can decrease the deposition of myoglobin in renal tubules. Animal studies and small retrospective studies have shown that alkalinization is better than using intravenous fluids alone in patients with rhabdomyolysis [14, 15]. However, subsequent retrospective studies have failed to establish this benefit. Based on available evidence, it can be concurred that alkalinization with sodium bicarbonate is not necessary and is not superior to giving intravenous fluids alone [16, 17].

Diuretics and Mannitol

In some experimental studies Mannitol is suggested to have a protective effect due to the diuresis, which minimizes intratubular heme

deposition [11, 18, 19]. It has also been suggested that mannitol acts as a free-radical scavenger, thereby minimizing cell injury [20]. Loop diuretics have also been used to increase urine output in patients with acute renal failure secondary to rhabdomyolysis. While diuretics and mannitol have been used in preventing acute renal failure, there is little clinical evidence to support the use of these agents in rhabdomyolysis. While randomized controlled trials are lacking, the available evidence suggests that mannitol and diuretic therapy have no benefit over and above aggressive fluid resuscitation [16, 18, 21, 22].

Antioxidants and Free Radical Scavengers

Free radical scavengers have shown to reduce the ischemia reperfusion injury in rhabdomyolysis in experimental models [23]. Pentoxyphylline improves microvascular circulation, acts to decrease neutrophil adhesion and cytokine release [24]. Vitamin E (alfa tocopherol), vitamin C (ascorbic acid), lazaroids (21-aminosteroids) and minerals such as zinc, manganese and selenium all have antioxidant activity [25, 26]. These agents might have a role in the treatment of rhabdomyolysis, but further studies are needed to validate their use.

RRT for Prevention of Acute Kidney Injury

Attempts have been made to study myoglobin removal by renal replacement therapy. Based on the size of myoglobin protein, conventional hemodialysis is not effective in clearing myoglobin from the circulation. Evidence from isolated studies have shown that continuous venovenous hemofiltration or hemodialfiltration has some efficacy in removing myoglobin [27], but the effect of this removal on the outcome (acute kidney injury) is not known. Until further studies are done, renal replacement therapy cannot be recommended as a preventive method to avoid acute kidney injury in patients with rhabdomyolysis.

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