

CASE REPORT

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A case of rhabdomyolysis with rigors

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ABSTRACT

Introduction: Rhabdomyolysis is a potential life-threatening condition caused by extensive skeletal muscle breakdown with leakage of toxic muscle contents into the circulation. The most dreaded complication is acute renal failure caused by toxic effects of myoglobin in the kidneys. The causes of rhabdomyolysis are classified into traumatic, non-traumatic exertional, and non-traumatic rhabdomyolysis. The pathophysiologic hallmark of rhabdomyolysis regardless of etiology is increased free ionized calcium due to cellular energy depletion (ATP) or direct plasma membrane rupture and consequent intensified muscle contractility, mitochondrial dysfunction, and production of oxygen radicals.

Case Report: We report a case of a middle-aged black woman with rhabdomyolysis that was caused by intense shivering chills, and rigor from pneumonitis. She had no personal or family history of muscle disorder and was admitted to the hospital after a weeklong history of upper and lower respiratory symptoms that led to the worse shivering and shaking chills she ever had. She was noted to have elevated creatine phosphokinase (CPK) of 200,000 uL (26–192 uL) and creatinine level of 5.52 (0.81–1.2 mg/dL). She was started on intravenous fluid with half-isotonic saline (0.45%) or 77 mmol/L sodium, 75 mmol/L sodium bicarbonate, and hemodialysis with progressive improvement in kidney function that took up to seven weeks to full recovery.

Conclusion: Shivering and shaking chills from respiratory infection can cause rhabdomyolysis with severe muscle damage and renal failure in a patient with no known underlying muscular-skeletal disorder condition but has good recovery with fluid management and hemodialysis. Renal function has returned back to normal.

Keywords: Dialysis, Renal insufficiency, Rhabdomyolysis, Shivering

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INTRODUCTION

Rhabdomyolysis is a syndrome characterized by damage to skeletal muscle leading to the release of creatinine kinase (CK) and myoglobin into the circulation with or without consequent renal failure. It is therefore defined as an increase in CK values that is 5× upper limit of normal or absolute level of >1000 uL associated with an increase in serum and urine myoglobin [1–5]. While elevated CK is the most sensitive laboratory test for muscle damage, there does not appear to be a consistent correlation of CK levels to severity of muscle damage with renal failure [6]. The so-called classical triad of myalgia, weakness, and myoglobinuria with or without renal failure is seen in only 10% of patients and 50% of patients do not complain of muscle pain or weakness on initial presentation [7].

The three main etiological categories of rhabdomyolysis are traumatic, non-traumatic exertional, and non-traumatic non-exertional. Traumatic causes

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include crush injuries, intense struggling against restraint, prolonged immobilization, and high voltage electrical injury. When associated with surgery it is usually a result of prolonged positioning, or vascular occlusions with clamping or tourniquets. Non-traumatic exertional rhabdomyolysis can occur in the presence of normal muscle integrity in which there is less supply for the excessive demand put on the muscle function. These are seen in long-distance runners, untrained athletes, and in ethnic black men with sickle cell trait with physical activities [8] and in hyperkinetic states such as grand mal seizures, delirium tremens, thermal extremes, severe agitation, and shivering [9, 10]. When associated with inheritable muscle disorders of glycogenolysis, glycolysis, and lipid metabolism, recurrent episodes are common.

Non-exertional, non-traumatic rhabdomyolysis is seen mainly with drugs, toxins, endocrinopathies, inflammatory myopathies, drugs such as statin, and infection including pneumonia. Alcohol is the most common toxin associated with non-exertional rhabdomyolysis. Various infections have been associated with rhabdomyolysis and mechanisms include direct muscle invasion, toxic effects of metabolites from pathogens, immunotoxicity with consequent inflammatory process, and muscle damage from fever, rigors, and hypoxemia.

CASE REPORT

A 43-year-old black woman presented to the emergency department (ED) with weakness and myalgias. One week prior to admission she developed fever from upper and lower respiratory symptoms with chills and intense shivering that was described as the worst she ever experienced. She had coughing episodes but denied sputum production and was treated with amoxicillin-clavulanate. She noticed decreased urine output but when she became anuric with more weakness presented herself to the ED. She has no history of trauma, statin use, alcohol, or recreational drug use. She has no personal or family history of muscle disorder. About four months earlier, she had normal electrolytes including creatinine. Physical examination on admission noted a well-developed black woman who is obese with a body mass index (BMI) of 46.89 kg/m² and weighing 131.7 kg. Vital signs include blood pressure (BP) of 121/71 mmHg, pulse 85 beats per minute, respirations 15 breaths per minute, temperature 36.2°C. The patient had no lymphadenopathy, Gottron papules, heliotrope rash, or skin lesions. Her first and second heart sounds were normal without murmurs and gallops. Lung examination was unremarkable without any adventitious sounds. Abdomen was soft with normal bowel sounds, no hepatosplenomegaly, or abdominal masses, and her urinary bladder was not palpable.

She had no joint effusions and her small, medium, and large size joints were not swollen but she displayed lower extremity quadriceps muscle weakness. Neurological

examination was otherwise unremarkable. Chest X-ray showed infiltrate in the right lower lobe suggestive of pneumonia/pneumonitis and she was treated with Ceftriaxone 2 g intravenously daily and Azithromycin 500 mg orally on day one, followed by 250 mg for additional four days even though no organism was ever identified. Serum electrolytes were noted with sodium of 130 meq/L (136–145), potassium 4.5 meq/L (3.5–5.1), chloride 101 meq/L (98–107), bicarbonate 17 (21–31), calcium 6.4 mg/dL (8.6–10.3), phosphate level of 9.5 mg/dL (2.8–4.5 mg/dL), blood urea nitrogen (BUN) 36 mg/dL (7–25), and creatinine 5.52 mg/dL (0.81–1.21 mg/L). Urinalysis was unremarkable except for large hemoglobin with red blood cell (RBC) of 409/hpf, urine protein >100 mg/dL, and large amount of myoglobin. Urine culture was negative. Additional testing included urine sodium of 70 mmol/L with osmolality of 168 mOsm/kg. Total creatinine kinase was significantly elevated at 208,736 (nl 26–192 uL). Troponin 2.2 ng/mL (nl 0–0.4 ng/mL), phosphate was elevated at 9.5 mg/dL (0.8–4.5 mg/dL), and toxicology screen was negative for prescribed or illicit drugs. Additional studies include negative thyroid panel, antinuclear antibodies (ANA), extractable nuclear antigen (ENA) panel, cytoplasmic and peripheral antineutrophil cytoplasmic autoantibody (C-ANCA and P-ANCA, respectively), complement levels, serum and urine protein electrophoresis, myeloperoxidase, proteinase-3 IgG antibody, antigen-B IgG antibody, mitochondrial antibody panel, and smooth muscle antibody panel. A nasopharyngeal specimen was tested for various pathogens using the multiplex nested polymerase chain reaction assay (Film Array Respiratory Panel, BioFire Diagnostics Inc, Salt Lake City, Utah, USA) and was negative for infections including COVID-19 [polymerase chain reaction (PCR) and IgG], *Human immunodeficiency virus* (HIV), *Cytomegalovirus* (CMV), *Methicillin-resistant Staphylococcus aureus* (MRSA), *Herpes simplex virus infection* (HSV), *Mycoplasma*, *Epstein-Barr virus* (EBV), *Legionella*, *Adenovirus*, *Human metapneumovirus*, *Rhinovirus*, *Enterovirus*, *Influenza strains*, *Parainfluenza strains*, *Respiratory syncytial virus* (RSV), *Bordetella*, *Chlamydia*, and other *Coronavirus strains*. A diagnosis of non-traumatic rhabdomyolysis caused by pneumonia/pneumonitis was made and she was started on intravenous hydration with half-isotonic saline (0.45% or 77 mmol/L sodium with 75 mmol/L sodium bicarbonate). Hemodialysis was started daily for three days and every other day thereafter. Diagnostic musculoskeletal biopsy was not done since it is not helpful in the presence of acute rhabdomyolysis. Subsequent biopsy of the left kidney revealed acute tubular injury with myoglobin casts, consistent with acute myoglobinuric renal failure.

Her response to hemodialysis along with changes in CK, myoglobin, BUN, and creatinine are shown graphically (Figure 1). A diagnosis of rhabdomyolysis caused by intense rigors was made. She was taken off dialysis after seven weeks and of significance is that

myoglobin in the urine cleared before serum myoglobin went back to normal range and her kidney function has remained within normal range since then.

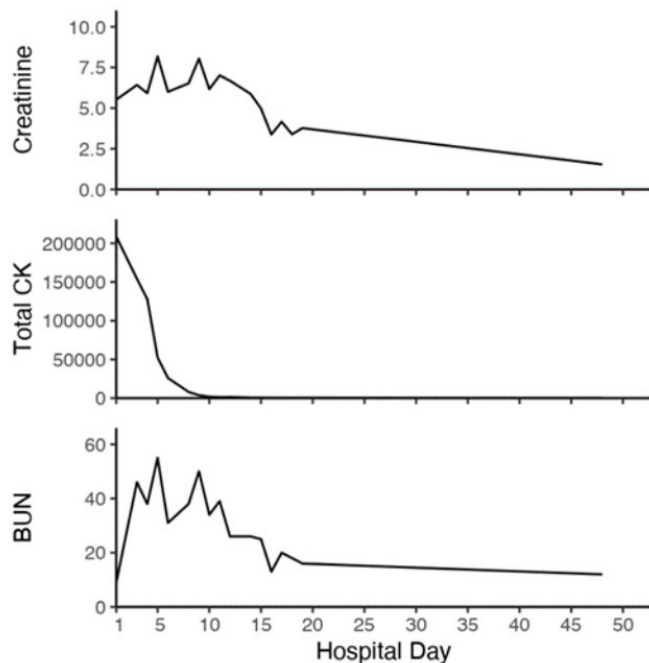


Figure 1: Rapid decline in creatinine kinase (CK) and progressive improvement in the renal function, serum creatinine, and blood urea nitrogen (BUN) with fluid support and hemodialysis.

DISCUSSION

Rhabdomyolysis is a syndrome characterized by damage to skeletal muscle leading to the secretion of creatinine kinase and myoglobin in the blood with consequent damage to the kidney. Acute increases in serum CK of 5× upper limit or levels of >1000 U/L along with increased serum and urine myoglobin are diagnostic [1–6]. There is no direct linear relationship between CK levels and patient outcomes in patients with rhabdomyolysis [2, 6]. The McMahon Score is a predictive value used to estimate kidney failure and mortality in patients older than 18 years old and with CK level of at least 5000 U/L within 72 hours of admission. It also aids in early recognition and intervention that may reduce morbidity and mortality [9]. It is based on eight variables: age, gender, admission serum creatinine, admission CK, calcium, phosphate, bicarbonate, and etiology not due to seizure, syncope, exercise, statin use, or myositis [11, 12]. A score less than 5 indicates a 3% risk while scores of 10 or greater indicate a 52% risk of renal damage requiring renal replacement therapy or death [11, 12]. Our patient had a McMahon Score of 13 which put her at significant risk and was reflected by a prolonged dialysis course.

Mechanism for rhabdomyolysis associated with acute kidney injury includes hypovolemia, myoglobin toxicity, metabolic acidosis, and uric acid precipitations. Skeletal muscles cell death leads to initial depletion of intracellular fluid and subsequent extracellular fluid sequestration with a consequent decrease in intravascular volume. The renin angiotensin aldosterone system (RAAS) is then activated leading to further dehydration [1].

The release of myoglobin which is the oxygen carrier protein of the muscle into the circulation exerts a cytotoxic effect. The released free iron from myoglobin breakdown in the kidney reacts with hydrogen peroxide generating radical oxygen species causing further damage to the kidney [13].

Myoglobin also may interact with Tamm-Horsfall protein in the distal tubules causing renal tubules obstruction and renal failure. Also with tissue destruction, uric acid is precipitated in the kidney in the presence of metabolic acidosis associated with kidney failure.

Rhabdomyolysis caused by infections may not be fully appreciated since muscle enzymes are not routinely ordered even in patients with mild renal insufficiency. Since muscle aches and weakness are not unusual with various infections an association with kidney damage is not often made and discolored urine may be attributed to urinary tract infections. The most common site of rhabdomyolysis caused by infections is in the pulmonary tract and the main organisms are Legionella, Streptococcus species, and viruses, especially influenza A [13, 14]. Rhabdomyolysis associated with infection causes lesser degree of muscle damage but more renal failure and the reason is not clear [15]. Rhabdomyolysis associated pneumonia is seen more often in men and the middle-aged population with alcohol use/abuse and smoking as significant risk factors.

Ethnic characterizations have been noted in the literature. Young black males with BMI of greater than 40 kg/m³ are at further risk of rhabdomyolysis perhaps because of inherent larger muscle mass [3]. Non-traumatic rhabdomyolysis has also been noted in black soldiers with sickle cell trait in US Military but black women do not have similar risk [8]. Our patient is unique and is a middle-aged black woman with high BMI, elevated CK level of over 200,000 uL that was associated with pneumonitis and intense shivering.

A potential, but rarely documented, exertional cause of myoglobinuria is intense shivering associated with infection. In an effort to combat an infection, the body induces a fever by increasing its thermoregulatory set point within the hypothalamus. Specifically, the preoptic area (POA) receives thermosensory information and relays signals to effector organs that elicit shivering and thermogenesis to increase the body's temperature to its new goal point [9, 16–19].

It is our hypothesis that these intense sustained muscular contractions in our patient caused depletion of local energy stores and loss of cell membrane integrity, which mimics conditions in exertional rhabdomyolysis [20, 21].

CONCLUSION

We conclude that intense shivering can cause muscle damage and renal dysfunction similar to that seen in other exertional etiologies of rhabdomyolysis. This case report suggests that this should be considered in the differential diagnosis of rhabdomyolysis and renal failure.

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Author Contributions

Emily Bliss – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Shahnaz D Vellani – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Caleb Spencer – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Douglas Federman – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related

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Guarantor of Submission

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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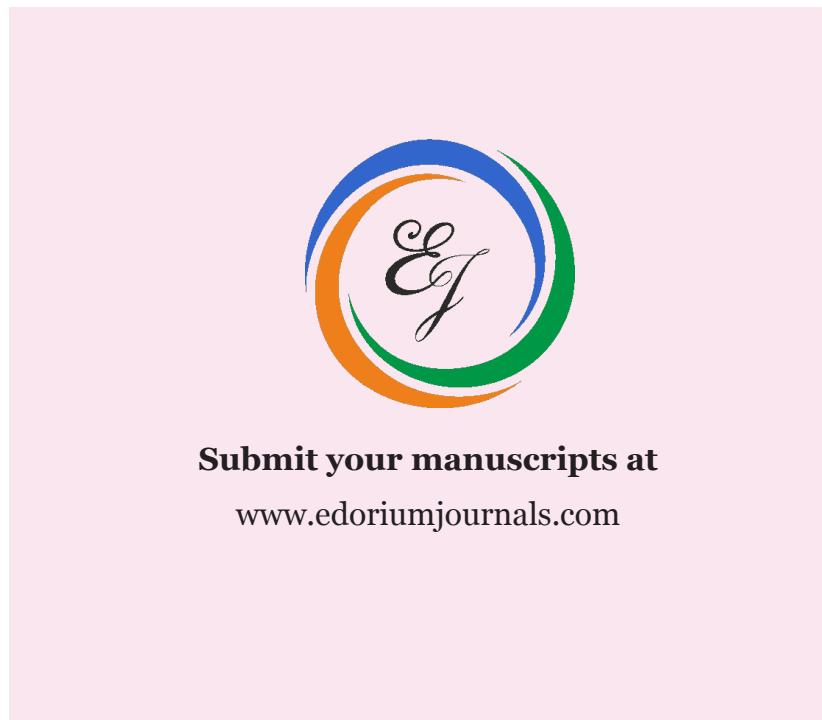
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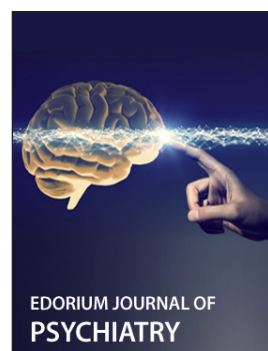
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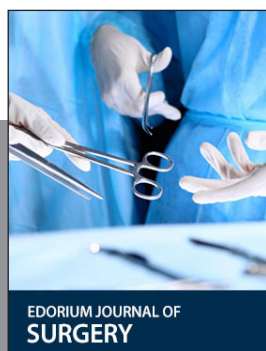
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