CASE REPORT

Title

Case Report: Rhabdomyolysis and Acute Kidney Injury Requiring Dialysis

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Background: Acute kidney injury (AKI) with myoglobinuria is the most serious complication of rhabdomyolysis, and can be life-threatening. Acute kidney injury as a complication of rhabdomyolysis is representing about 7 to 10% of all cases of AKI in the United State.^{1,2}

Case Illustration: A 42-year-old man was found with decreased consciousness and strangulated 3 hours before hospital admission. He consumed detergent as a suicide attempt five and one days before hospitalization. The patients have a history of paranoid schizophrenia and hypertension, and had been taking antipsychotic drug risperidone for 2 years irregularly. On physical examination, the patient was not alert with the Glasgow Coma Scale (GCS) of 3, attention and orientation were inadequate and vital signs were stable. Excoriation and hematoma around the neck and ronchi on the lung was found upon examination. Initial laboratory examination showed high leukocytes, low potassium, high alanine aminotransferase, and aspartate aminotransferase, initial creatinine was 1.639 mg/dL then increased to 6.8 mg/dL at the 4th day of care and 9.7 mg/dL on the 6th day with high serum uric acid and low serum calcium. The bicarbonate level in the blood gas analysis is 20.5. Erythrocytes and albumin were found in urinalysis. HCV serology was positive. On cervical x-ray examination showed swelling of the retropharyngeal soft tissue. Chest X-ray showed cardiomegaly and there were infiltrates in the right lung. Kidney ultrasonography showed no abnormality. The patient was diagnosed with acute kidney injury, rhabdomyolysis, paranoid schizophrenia, pneumonia, hypertension, soft tissue injury of the neck after attempted suicide by hanging, and hypocalcemia. The patient received intravenous hydration with

KN2 at 1000 mL daily, antipsychotic drugs, slow-release potassium supplementation, ceftriaxone, and ramipril. The intravenous fluid rate was increased to 1500 mL daily after urine volume decreases on the second day of hospitalization with persistent hyperkalemia. Intermittent conventional hemodialysis was done on the fourth day of hospitalization for 2 sessions. Total 24 hours urine volume was 1000 mL on day 6 of care. Creatinine and creatine kinase (CK) continued to improve without hemodialysis. After 24 days of hospitalization, he was discharged, with a creatinine level of 1.6 mg/dL and CK 299 IU/L.

Discussion: Patients with AKI due to rhabdomyolysis who receive supportive therapy earlier have better outcomes. Therapy initiation includes prompt volume repletion with a target urine output of approximately 3 ml per kilogram of body weight per hour. In patients who develop oliguria, the administration of intravenous fluids is limited due to volume expansion and pulmonary edema. In these cases, renal replacement therapy is indicated. Intermittent hemodialysis has added benefit to correct volume overload and pulmonary edema. Bicarbonates used to induce urinary alkalization.

Conclusion: Acute kidney injury is the most serious complication of rhabdomyolysis. Fluid overload and electrolyte imbalance need renal replacement therapy.

Keyword: Rhabdomyolysis, AKI, Hemodialysis

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Background

Rhabdomyolysis is a syndrome characterized by the breakdown of skeletal muscle and leakage of intracellular myocyte contents, such as creatine phosphokinase (CPK) and myoglobin into the interstitial space and plasma resulting in AKI.¹ Acute kidney injury associated with myoglobinuria is a serious complication of rhabdomyolysis and can be life-threatening, representing about 7 to 10% of all cases of AKI in the United State. The reported incidence ranges from 13% to 50, but there was no data on AKI due to rhabdomyolysis in Indonesia. Patients with rhabdomyolysis usually present with a clinical picture of volume depletion that is due to the sequestration of water in injured muscles.^{3,4}

Case Illustration

A 42-year-old man was found to be strangled and have decreased consciousness 3 hours before hospital admission. One and five days before admission he ingested detergent mixed with a glass of water due to a suicide attempt and then threw up 3 times. He denied a history of trauma or injury. There were no other symptoms such as coughing, tightness, chest pain or dizziness.

A week before hospitalization, the patient was worried that someone else would kill him. The patient had a history of paranoid schizophrenia and had been taking antipsychotic risperidone for 2 years irregularly. The doctor replaced risperidone with long-acting antipsychotic fluphenazine but he experienced acute dystonia and stopped taking the medicine. Two and a half years ago the patient suffered from anxiety and then received sertraline and clobazam. There was a history of auditory hallucinations and he often got angry and talked to himself seven years ago. He also had a history of hypertension since 1 year ago and the blood pressure was controlled with amlodipine 5 mg 1 time a day.

He has divorced from his wife 7 years ago. He lived with his 80-year-old mother and his 10-year old daughter. Informed consent was obtained from the patient.

On initial physical examination, he was unresponsive with a Glasgow Coma Scale 3, attention and orientation were inadequate. Initial blood pressure was 148/87 mmHg with a pulse rate 100 times per minute, and respiratory rate 20 times per minute. Oxygenation saturation was 100% in room air. Excoriation and hematoma coiled around the neck. Heart rate was regular without murmurs, and ronchi on lung examination and abdomen was soft without tenderness or organomegaly. A Foley catheter was inserted and 50 ml of tea-colored urine was obtained. On the second and third day of hospitalization, urine volume was only 300-350 cc in 24 hours (table 1)

Initial laboratory examination showed hemoglobin 14.5 g/dl, leukocyte 19690/ul, normal sodium, potassium 2.8 mEq/L, alanine aminotransferase 254.7 u/L, aspartate aminotransferase 106 U/L, ureum 13 mg/dl, creatinine 1.639 mg/dl, uric acid 13.2 mg/dl, calcium 7.7 mEq/L. Blood gas analysis showed bicarbonate was 20.5. Urinalysis showed cloudy, leukocytes 2-3/ filed of view, erythrocytes 10-12/ field of view, specific gravity 1.025, PH 5, albumin 2+, HCV serology was positive. HCV RNA and phosphate levels had not been done, and myoglobinuria reagent was not available. The cervical x-ray showed swelling of the retropharyngeal soft tissue. Chest X-ray showed cardiomegaly and infiltrates in the right lung. Kidney ultrasonography showed no abnormality.

The patient was diagnosed with acute kidney injury, rhabdomyolysis, paranoid schizophrenia, pneumonia, hypertension, soft tissue injury of the neck after attempted suicide by hanging, and hypocalcemia.

Figure 1. Laboratory examination: Ureum and Creatinin

Figure 2. Laboratory examination: Creatinine kinase

Initial treatments were intravenous hydration with 1000 mL KN2 for 24 hours and enteral nutrition via nasogastric tube. The patient was prescribed haloperidol 5 mg/day, risperidone 2 mg 2 times a day, slow-release potassium 600 mg 3 times a day, and antibiotic ceftriaxone 2 gram a day. The

Table 1. Laboratory and clinical examination

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 10	Day 14	Day 19	Day 23	Day 27
Ureum (mg/dl)	55		66	112	153		92	112	108	69	43	48
Creatinine (mg/dl)	1.6		6.8	9.7	12		8.9	9.7	7.9	2.7	1.8	1.6
eGFR (ml/min- ute/1.73 m ²)			9.1	5.9	4.6		6.9					
Potassium (mg/dl)	3.3		3.7		4.1		4.3					
CK			23426	22115	10041		1218		345	624	870	505
Urine Volume (cc/24 hours)	800	300	350	250	500	1000	2000	2500	3000	3000	3000	3000
Intravenous fluid (24 hours)	K2N 1000	K2N 1500	NaCl 2000	NaCl 500	NaCl 500	NaCl 500	NaCl 1000	NaCl 1500	NaCl 1500	NaCl 1500	NaCl 1500	NaCl 1500
Oral fluid (NGT)	500	500	1200	1200	1200	1200	1200	1500	1500	1500	1500	1500
Hemodialysis/ Ultra- filtration volume				V 1500		V 1500						

antihypertensive drug was ramipril 5 mg and amlodipine 10 mg once daily.

On the second and third days of treatment, the urine volume was 300-350 cc in 24 hours, therefore the amount of intravenous fluid was increased to 1500 cc in 24 hours, but the patient still experienced oliguria and hyperkalemia. Potassium supplementation was also stopped.

Intermittent conventional hemodialysis was applied on the fourth-day of care. Temporary catheter double-lumen was inserted. The patient was dialyzed for 2 sessions with ultrafiltration volume of 1000 mL, blood flow 180 mL/hours, and dialysate flow 500 ml/hours. the urine volume reached 1000 ml in 24 hours on the sixth day of hospitalization. The last dialysis session was on the 6th day of hospitalization. Creatinine and CK continued to decrease without dialysis. After 24 days of hospitalization, the patient was discharged, with lab results of creatinine 1.6 mg/dL and CK was 299 IU/L. The patient was advised to remain properly hydrated, avoid nephrotoxic drugs, and periodic kidney function evaluation.

Discussion

Rhabdomyolysis is a syndrome characterized by the breakdown of skeletal muscle and leakage of intracellular myocyte contents, such as CPK and myoglobin into the interstitial space and plasma resulting in AKI. Acute kidney injury as a complication of rhabdomyolysis is quite common. The reported incidence ranges from 13% to approximately 50%. It is the cause of renal failure in 5-25% of all cases of renal failure in hospitalized patients.^{1,2}

Rhabdomyolysis usually presents with elevated CPK levels, muscle pain, limb weakness and swelling, and myoglobinuria.⁵ Initial creatinine kinase level in this patient was 23426 mg/dL on day 3rd and 22115 mg/dL on the 4th day. In this

case, the diagnosis of rhabdomyolysis was based on CK levels. Phosphate data are not available and urine myoglobin cannot be performed because reagents are not available. Laboratory findings include urine dipstick positive for blood in the absence of urinary erythrocytes, myoglobinuria, granular casts, epithelial cells in the sediment, and elevated muscle enzymes levels in the serum such as CK, LDH, and aspartate and alanine aminotransferases (AST, ALT), besides elevated serum phosphate and potassium serum levels and initially low serum calcium concentration.^{6,7} In this case, aspartate and alanine aminotransferases increased and erythrocytes and albumin were present in urinalysis.

Causes of rhabdomyolysis usually result in the destruction of muscle cells and the release of intracellular contents into extracellular fluid or circulation. When cells are subjected to mechanical stress, there is an influx of sodium and calcium into the cell, which causes several pathologic processes due to the excess of calcium. Excessive intracellular calcium results in persistent contraction of the myofibers, depletion of adenosine triphosphate (ATP), production of free radicals, activation of vasoactive molecules, release of proteases, and cell death. Afterward, neutrophils invade and amplify the damage with the release of proteases and production of free radicals, and inflammatory myolytic reaction develops. Myoglobin released from lysis of muscular cells does not have a specific binding protein, and it is freely filtered by the glomeruli. Casts are produced after filtration of myoglobin through the glomerular basement membrane that caused brown urine. Water reabsorption causes a rise of myoglobin concentration, and in the presence of acid urine, myoglobin precipitates and forms obstructive casts. Moreover, myoglobin can, through the heme fraction, induce the release of free iron, which catalyzes free radical production and further enhances ischemic tubule damage. In the absence of hypovolemia and acid urine, myoglobin has a less nephrotoxic effect. Another factor that can exacerbate tubular obstruction is the disseminated intravascular coagu-

lopathy associated with rhabdomyolysis due to the activation of the coagulation cascade by the substances released from damaged muscle cells. Acute kidney injury in rhabdomyolysis caused by vasoconstriction, tubular obstruction and tubular injury and hypovolemia.⁸⁻¹² Moreover, cases of AKI and rhabdomyolysis have been described in patients using haloperidol and other neuroleptics, presenting as a neuroleptic malignant syndrome.¹³

Figure 3. Pathophysiology acute kidney injury due to rhabdomyolysis.¹⁴

Elevated serum CK level is enough to establish the diagnosis of rhabdomyolysis. Five times higher than the normal CK level confirm the diagnosis of rhabdomyolysis. The maximum CK level is usually reached during the first 24 hours in 70% of the cases. Magnetic resonance image (MRI) is the method of choice to evaluate the distribution and extension of the affected muscles. Rhabdomyolysis can also be diagnosed with a muscle biopsy. The histopathologic findings usually include loss of cell nucleus and muscular striae with the absence of inflammatory cells.^{13,15-17}

The risk of AKI in rhabdomyolysis is usually low when CPK levels at admission are less than 15,000 to 20,000 U per liter although AKI may be associated with CPK values as low as 5,000 U per liter, usually occurs when coexisting conditions such as sepsis, dehydration, and acidosis are present.⁵ The severity of the disease ranges from asymptomatic elevations in serum CPK to life-threatening electrolyte abnormalities and AKI requiring renal replacement therapy (RRT). The AKI can be severe enough to result in complete loss of renal function leading to end-stage renal disease.⁵ In this case initial creatinine level was 1.639 mg/dL, creatinine increased 6.8 mg/dL on 3th and 9.7 mg/dL on the 4th day.

Patients with rhabdomyolysis that are associated with AKI usually present with a clinical picture of volume depletion that is due to the sequestration of water in injured muscles, pigmented granular casts, reddish-brown urine supernatant, and markedly raised serum CPK. The electrolyte abnormalities that can occur with rhabdomyolysis include hyperkalemia, hyperphosphatemia, hyperuricemia, high anion-gap metabolic acidosis, and hypermagnesemia mainly.^{5,9-10}

Patients with rhabdomyolysis must receive early and prompt treatment. Initial therapy includes volume repletion with normal saline promptly at a rate of approximately 400 ml per hour (200 to 1000 ml per hour depending on the setting

and severity), with target urine output of approximately 3 ml per kilogram of body weight per hour. In a randomized, prospective trial of fluid repletion with ringer's lactate as compared with normal saline in patients with rhabdomyolysis attributed to doxylamine intoxication, 28 patients were randomly assigned to receive one of the solutions. In this study administration of diuretic increased urine volume and decreased myoglobin precipitation, although statistically not significant.¹⁵⁻¹⁸ In this case, our patient developed oliguria, and therefore administration of intravenous fluids is limited due to volume expansion and pulmonary edema.

Bicarbonates can be used to induce urinary alkalization and mannitol to prevent renal failure in patients with rhabdomyolysis. Alkalization of urine can be attempted to reduce the formation of myoglobin casts in renal tubules and prevent Tamm-Horsfall myoglobin precipitation, inhibits the reduction-oxidation cycling of myoglobin and lipid peroxidation, metmyoglobin induces vasoconstriction only in acidic medium. In an experimental study, the association of saline solution, sodium bicarbonate, and mannitol were more effective than hypertonic saline dextran in decreasing oxidant injury in rhabdomyolysis. If CPK exceeds 5,000 IU/L it is advisable to institute aggressive venous hydration, prophylactic bicarbonate, and mannitol. Brown et al performed a study with 2,083 patients with post-traumatic rhabdomyolysis in intensive care unit and concluded that the administration of bicarbonate and mannitol should be reevaluated since they did not prevent renal failure (creatinine > 2.0 mg/dL), dialysis, or mortality in patients with CK levels greater than 5,000 U/L.¹⁸⁻²¹

Renal replacement therapy is considered if resistant hyperkalemia of more than 6.5 mmol per liter, oliguria (<0.5 ml of urine per kilogram per hour for 12 hours), anuria, volume overload, and/or resistant metabolic acidosis (pH <7.1) occurred. In this case, renal replacement therapy was indicated because of oliguria. Intermittent hemodialysis has benefits to correct volume overload and pulmonary edema. Our patient was dialyzed for 2 sessions of 3 hours, with ultrafiltration volume of 1000 mL, blood flow 180 mL/hours and dialysate flow 500 ml/hours. Conventional hemodialysis with high flux filters does not remove myoglobin effectively. The use of highly permeable membranes in continuous venovenous hemofiltration could be a promising treatment because allows for large molecules such as myoglobin to be filtered by convective clearance and helps remove myoglobin. Large pore membranes increase the clearance of solutes with molecular weights in the range of 20–50 kDa, such as immunoglobulin light chains, cytokines, and myoglobin (17.8 kDa).²¹⁻²⁵

Limitations of this case report were lack of ability to generalize, no possibility to establish a cause-effect relationship. **Conclusion:** Acute kidney injury is the most serious complication of rhabdomyolysis. Fluid overload and imbalance electrolyte need renal replacement therapy.

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