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Exertional Rhabdomyolysis Induced Acute Kidney Injury: A Case Report and Literature Review

Yu Zhang

Department of Geriatric, The Second Hospital of Tianjin Medical University, Tianjin, China
Email: zhangyupandanew@sina.com

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Abstract

Background: The exRML (exertional rhabdomyolysis) is a pathophysiologic condition of skeletal muscle cell damage and breakdown associated with high intensity or prolonged exercise, normal exercise under extreme circumstances, or sudden and excessive skeletal muscle contraction. It may manifest from the increase in CK (creatine kinase) or MYO (myoglobin), a protein that can cause life-threatening injury to the kidney (AKI, acute kidney injury), and may or may not be associated with myoglobinuria. Here, we presented a case of exRML with AKI, and then reviewed the related reports. Vigorous hydration, sodium bicarbonate and furosemide are key treatments. **Aim:** To examine an elderly patient with exRML induced AKI and the key treatment process. **Case summary:** A 61-year-old man left our hospital without permission after his admission and has been walking for almost 30 kms with no water and food intake, then was diagnosed exRML and exRML induced AKI with an obvious elevation of CK, MYO and decrease of eGFR (estimated glomerular filtration rate) after coming back, and was treated with vigorous hydration, loop diuresis, sodium bicarbonate, prostaglandin and Shenkang injection. After vigorous resuscitation, the patient's renal function, CK and MYO returned normal. **Conclusions:** The exRML can cause serious complications such as AKI and death. Delayed diagnosis can be critical; therefore, manner of time should be taken to achieve a favorable prognosis.

Keywords

Exertional Rhabdomyolysis, Serum Creatine Kinase, Myoglobin, Acute Kidney Injury

1. Introduction

The rhabdomyolysis (RM) is the breakdown of muscle tissue with subsequent dispersion of intracellular contents into the extracellular environment and systemic circulation [1]. It could be either exertional or non-exertional causes for RM. Non-exertional causes include drugs, toxin exposure, dyselectrolytemia, and local muscle damage due to trauma or ischemia with or without compartment syndrome, infection, hypothyroidism and other metabolic diseases, inflammatory diseases, dermatomyositis, neuropsychiatric disorders, and cardiac diseases can also induce such damage. The exRML is a pathophysiologic condition of skeletal muscle cell damage and breakdown which is associated with high intensity or prolonged exercise, normal exercise under extreme circumstances, or a sudden excessive skeletal muscle contraction. ExRML may manifest from an increase in CK or MYO, a protein that can cause life-threatening injury to the kidney (AKI), furthermore may or may not be associated with myoglobinuria [2]. In order to diagnose exRML, there must be an elevation in CK greater than or equal to five times the baseline in association with muscle damage caused by exertion through an exercise or sporting activity. A decade ago, exRML was rarely reported and mostly reported with marathon runners and military recruit trainees. It is likely that exRML has always been underreported in the literature as it is abnormal to seek medical care; however, this condition may also be on the rise with the increased popularity of high intensity exercise classes and high intensity workouts. This article presented a case of exRML with AKI, and relevant literatures will be reviewed.

2. Case Report

A 61-year-old man, weighed at 65 kilograms, was admitted to our hospital at 21:00 on September 25, 2018 with a chief complain of "A progressive hypomnesia for 7 days and dizziness for 2 days". He had the history of cognitive dysfunction and alcoholism (800 - 1500 g daily drinking of liquor). He was confirmed that he was missing in the hospital from 9:30 am on September 28 and was found about 30 kilometers away from the hospital at 4:30 am on September 30. During the period of disappearance, he had no rest, no water or food intake. He seemed wilted with the decreased skin elasticity, slightly sunken eye socket, and being dehydrated. The patient was diagnosed with AKI due to exRML with his urging CK, MYO and decrease of eGFR. After treated with vigorous resuscitation, loop diuresis, sodium bicarbonate, prostaglandin and Shenkang injection, the patient's renal function, CK and MYO returned normal. His clinical features, laboratory tests, daily intake, urine output and fluid replacement conditions were shown in **Table 1**, **Table 2** and **Table 3**.

3. Discussion

The RM is caused by the breakdown and necrosis of a muscle tissue, which cause the release of intracellular contents into blood stream. There are many causes of RM, but the central pathophysiology of RM is the destruction of the sarcolem-

mal membrane and release of intracellular components into the systemic circulation [3]. RM was firstly reported in 1881 [4], and were elaborated on the specific performances until the World War II London Big Bang campaign in 1941 [5] [6]. In previous studies they have showed that acquired causes such as trauma and exertion, hypoxic injury, infections, alcoholism, hyperthermia, drugs and toxins are the independent risk factors of RM [7] [8]. Genetic abnormality like enzyme deficiencies (for carbohydrate or lipid metabolism) and myopathies also lead to the RM. Recently, more studies indicate that the prevalence of RM in black race is higher than that within the white race, because blacks are more likely to have an autosomal dominant genetic disease, sickle cell disease, which was characterized as chronic hemolytic anemia [9]. The exRML or exercise-induced RM is a special type of RM, which has been reported in cases with excessive unaccustomed exercise in several scenarios including military training, physical education class, mountaineering, supervised, unsupervised strenuous training, and marathon running [10], which is caused by the breakdown of skeletal muscle cells after intense or unaccustomed exercise. Release of intracellular contents ensues, including but not limited to CK, MYO, electrolytes, and proteases. While exRML is typically viewed as a pathologic condition, baseline and post-exercise CK levels can vary widely in asymptomatic individuals, with post-exercise elevations in CK (*i.e.*: hyperCKemia) being a normal physiologic response in some individuals [6] [7] [8]. Pathologic ER most commonly manifests as severe muscle pain with or without swelling, weakness, and myoglobinuria. Medical management of individuals with exRML is largely supportive, but if severe and or unrecognized, ER may lead to AKI, metabolic acidosis, electrolyte abnormalities, arrhythmias, compartment syndrome, and rarely death.

Table 1. Clinical features.

date	clinical features				
	mental state	skin	lips	eye socket	colors of urine
September 30 (1st day)	wilted	dry	dry	slightly sunk	dark black
October 1 (2nd day)	sober	normal	normal	normal	deep yellow
October 2 (3rd day)	sober	normal	normal	normal	deep yellow
October 3 (4th day)	sober	normal	normal	normal	yellow
October 6 (8th day)	sober	normal	normal	normal	clear

Table 2. Laboratory tests.

date	Hb (g/L)	HCT (%)	Na (mmol/L)	K (mmol/L)	CO_2CP	CK (U/L)	CK-MB (U/L)	BUN	Crea	UA	Scr	MYO	U-pH
8 am Sep. 25	128	37.8	142.0	3.7	26.0	47.0	3.0	5.0	61.6	537.5	115.3		6.0
9 am Sep. 30	131	38.4	143.0	4.2	18.8	3916.5	81.3	19.5	578.9	978.6	12.3	>400	

Continued

14 pm Sep. 30												≤5.0
20 pm Sep. 30			141.4	3.5	26.0	3344.0	36.0	17.8	347.6	844.7	20.4	398.2	5.5
22 pm Sep. 30													5.5
6 am Oct. 1	118	34.2	142.0	3.4	29.1	1425.0	19.0	16.6	226.2	826.5	31.4	99.1	5.5
23 pm Oct. 1													6.0
6 am Oct. 2	114	34.0	139.4	3.5	30.7	956.0	7.0	10.5	104.6	611.0	67.9	50.1	6.0
7 am Oct. 3	109	33.0	143.1	4.8	24.1	500.1	21.2	7.0	83.0	446.9	85.6		6.0
7 am Oct. 4	103	313	141.2	4.5	27.9	260.0	3.0	4.0	68.3	346.0	104.0	28.1	6.0
7 am Oct. 6	105	31.9	141.7	4.2	24.6	99.9	17.1	6.1	70.9	344.4	100.2	15.4	6.0

Table 3. Daily output and fluid replacement therapy.

date	Daily total intake (ml)	Oral intake (ml)	fluid infusion (ml)	fluid infusion speed (ml/h)	$NaHCO_3$ (ml)	furosemide (mg)	daily urine (ml)	U-pH	rale in lung
Sep. 30	3980	200	3780	Bolus + 170 - 180	100	20	1600	≤5.0	slightly in left lung
Oct. 1	3950	600	3350	regular (100 - 120)	0	10	3400	5.5	(−)
Oct. 2	3650	1000	2650	regular (100 - 120)	0	10	2500	6.0	(−)
Oct. 3	2250	700	1550	regular (100 - 120)	0	0	1500	6.0	(−)
Oct. 4	3240	1600	1640	regular (100 - 120)	0	0	2800	6.0	(−)
Oct. 6	2150	850	1300	regular (100 - 120)	0	0	2000	6.0	(−)

The clinical manifestation varies widely depending on the extent and severity of muscle damage ranging from an asymptomatic increase in the serum levels of enzymes released from muscle cells, e.g., CK, LDH, AST, to worrisome conditions associated with severe intravascular volume depletion, metabolic acidosis, multiple electrolyte abnormalities (hyperkalemia, hyperphosphatemia, and hypocalcemia), and AKI [11]. AKI is one of the most serious complications with incidence and mortality of 13% - 50% and 20% - 50%, respectively [12]. The risk factors include advanced age (>70 years old), dehydration, blood uric acid ≥ 6 mg/dl (356.88 umol/L), hyperosmotic diabetic coma and exertional exercise [13]. The characteristic clinical manifestation of AKI is in dark brown or tea-like colored urine [14]. In this case, the patient left hospital and had been walking all the time during the period of disappearance for almost 44 hours, 30 kms without any rest and intake, indicated an exertional exercise. When he returned, he appeared to be wilted and weakness with dry skin, dry

lips, sunken eye socket, dark black urine, as well as dehydration. The exertional walk may cause muscle damaged with increased CK and MYO, thus blocked renal tubules. The elevated creatinine, serum uric acid, decreased creatinine clearance rate and metabolic acidosis were confirmed the AKI. The specific physiological process of AKI induced by the exertional exercise in this case was shown in Figure 1.

In current of exRML, markers such as serum CK and MYO can increase four to five times in the normal value. Additionally, serum lactate dehydrogenase (S-LDH) and aspartate transaminase (AST) can be doubled compared to their normal levels. The most used marker is the CK, which has replaced MB as the preferred marker for the identification of ER since MB is rapidly eliminated from bloodstream with a maximum peak at 24 - 36 hours after exercise and recovered to the basal states at a rate of 40% per day if it was got well treated, and a rise in CK five times the upper-limit normal values (5 × 200 IU/L) or CK exceeding 5000 IU/L is required and more recently a criteria of diagnosis was set at 1000 UI/L after a systematic review around RM definition. And CK would return to baseline levels at 48 - 72 hours with effective treatment [15]. The CK level was 47.0 U/L when the patient was admitted and urge to 3916.5 U/L after coming back (almost 80times compared to the normal), when he was got well treated, the level gradually declined from 3344.0 U/L to 99.9 U/L.

The other important tests to request include serum MYO, urinalysis (to check for myoglobinuria), and a full metabolic panel include serum creatinine and electrolytes. Under physiological conditions, MYO binds to globin. When the RM occurs, muscle cells are destroyed massively, a large amount of MYO are released into bloodstream, resulting MYO level rapidly increasing, when the MYO

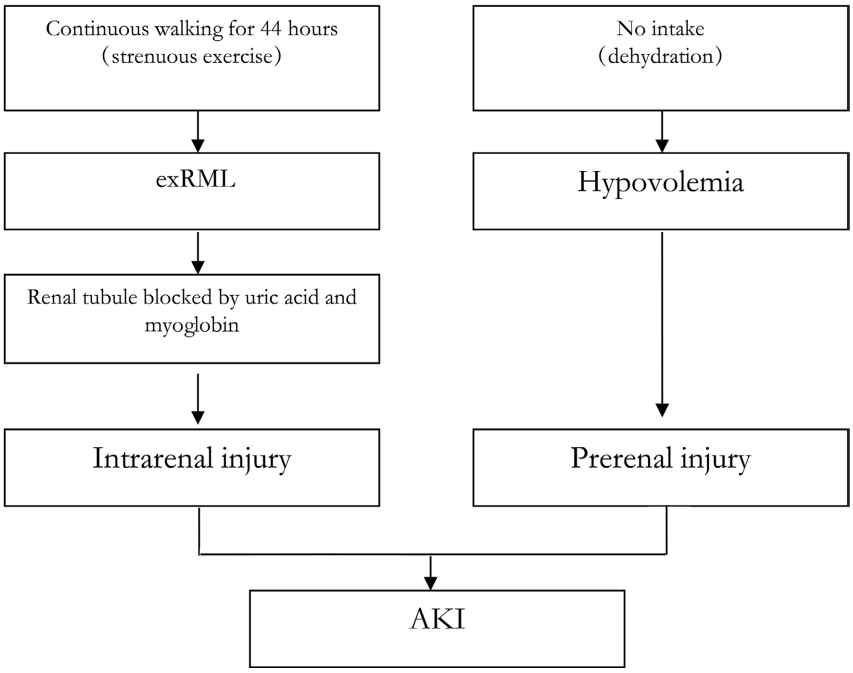

Figure 1. The physiological process of AKI in this case.

level is greater than 0.5 - 1.5 mg/dl, which beyond the ability of binding, MYO is discharged via the urine forming myoglobinuria, therefore the urine becomes tea-colored or dark black, representing the amount of damaged muscle tissue > 200 g. Meanwhile, excessive MYO blocked the renal tubules, caused AKI. Furthermore, the blocked renal tubules prevent MYO from being excreted from urine, leading to increase in plasma MYO levels [16]. In this case, as the CK level raising in MYO, it gradually increased with the performance of dark black urine, when it had got fluid replacement therapy, when MYO gradually decreased, and the urine turned to normal.

Uric acid, the end product of purine metabolism, is excreted predominantly by the proximal tubules. Abnormal serum levels of uric acid are due to alterations in production or excretion. Renal excretion of uric acid consists of four steps: (1) glomerular filtration, (2) presecretory reabsorption, (3) secretion and (4) postsecretory reabsorption. Almost all of the urate is filtered through the glomerulus, with most of the filtered urate (99%) being reabsorbed in the early S1 segment of the proximal tubule (presecretory reabsorption). This is followed by tubular secretion in the S2 segment of the proximal tubule that returns approximately 50% of the filtered urate into the tubular lumen. However, the majority (40%) of the secreted urate undergoes postsecretory reabsorption that occurs predominately in the last segment (S3) of the proximal tubule. Hyperuricemia along with other electrolyte abnormalities like hyperkalemia, hypocalcemia, and hyperphosphatemia leads to AKI due to acute uric acid nephropathy which is associated with significant morbidity. Acute hyperuricemia plays a major role in the pathogenesis of uric acid nephropathy. Supersaturation of urine and precipitation of uric acid crystals cause intraluminal obstruction of the distal nephron. This in turn leads to dilatation, inflammation, and obstruction of the proximal tubules. Acute uric acid nephropathy should be suspected in high risk patients who develop oliguric AKI with significantly elevated serum uric acid concentration of more than 10 - 15 mg/dL and presence of copious uric acid crystals in the urinary sediment [17]. In 2012, the organization of kidney disease in order to improve global outcomes (KDIGO) defined AKI as serum which creatinine increased by ≥26.5 umol/L (0.3 mg/dl) within 48 hours, or serum creatinine increased more than 1.5 times than normal within 7 days, or urine output <0.5 ml/kg/h, lasting for more than 6 hours, therefor AKI is divided into three grades, in accordance with the degree of serum creatinine and urine output [18]. In this case, the patient's urine output decreased, who accompanied with dark black urine, not only related to pre-renal hypo perfusion, but also related to the RM. According to the AKI grading criteria of KDIGO, the patient was stage 3, as the acute inflammation in kidney and local vessels, and the key treatment was anti-inflammatory.

Prostaglandin injection is a prostaglandin E1 preparation, which is a very potential vasodilator drug. It can directly expand the glomerular artery and increase the renal blood by directly acting on the glomerular arterial smooth muscle cells and mesangial cells. Additionally, it can inhibit the activity of renin an-

giotensin aldosterone system (RASS), by reducing the resistance of the efferent arterioles, intraglomerular pressure, to improve the renal hyper perfusion, high pressure, high filtration, thereby preventing renal ischemia and renal hemodynamics. Alprostadil can also inhibits platelet aggregation and immune complex formation, dilates micro vessel, to reduce hypercoagulability and prevent thrombosis in the glomerulus; furthermore, it can inhibits the antibody production and inflammatory, which has antioxidation to protect vascular endothelial cells and anti-fibrosis, thereby alleviating the inflammatory response of the kidneys and to protect the renal parenchyma [19]. Shenkang injection has the effect of lowering adverse rise of energy and dispelling turbidness by supplementing qi to activate circulation. Modern research shows that Shenkang injection has the effects in dilating blood vessels, regulating blood lipids, to reduce blood viscosity, platelet and red blood cell aggregation, thereby increasing renal blood infusion, to reduce glomerular capillary pressure and this improve hypercoagulability in glomerulus to protect the kidneys [20]. Combination with vigorous hydration, we used prostaglandin injection (20 mg/d) and Shenkang injection (100 ml/d) were used to reverse the inflammatory injury of AKI in this case.

Clinical measures can be instituted in the emergency department to prevent RM in order to induce AKI in this situation. Early and vigorous hydration should begin as soon as possible with the placement of two intravenous (IV) access lines; at least one being large bore. In other studies, infusion of an isotonic saline fluid bolus of 25 ml/kg over 2 hours and continued at 1 to 2 L/h is recommended if the patient had no history of congestive heart failure. The goals of hydration are to ensure adequate renal perfusion and increase urine flow [21]. In this case, the calculation method of hydration: calculating the patient's blood volume to make a preliminary judgment in accordance to the his Hb. Hct and urine have specific gravity (USG). However, the patient had no significant changes in Hb and HCT, and there was elevation in PRO, urine RBC, WBC and USG after return, result it was inaccurate to assess the volume capacity according to USG. Therefore, to calculate the blood-volume in accordance to the daily physiological needs with 30 - 40 ml/kg/24 h, the cumulative loss (ml) = (30 - 40 ml) * 65 kg * (44 h/24 h) = 3575 - 4767 ml (mean 4100 ml), it was estimated to supply until normal level in 2 - 3 days (about 1366 - 2050 ml/day) be adding with the daily physiological needs about 1950 - 2600 ml (mean 2275 ml), so the patient's total daily intake is about 4000ml per day on the first 3 days. According to the principle of hydration, the patient got 1500 ml 0.9% normal saline within 2hs, and then the correction speed was controlled between 140 ml/h - 180 ml/h with closely monitored, including renal function, creatinine clearance rate, USG (roughly represents patients' fluid loading status), and patients' lung signs (whether there was small wet rile, or whether the range of rale was enlarged). After 72 h resuscitation, the patient's renal function returned to be normal.

Alkalinisation with sodium bicarbonate was recommended. So we calculated the consumption of $NaHCO_3$: $NaHCO_3$ (g) in accordance with CO_2CP = {target CO_2CP-actual CO_2CP} * KG * 0.3 * 84 by considering CO_2CP = 24 as the target

value and being calculated that about 5.24 g $NaHCO_3$ (5% sodium bicarbonate $NaHCO_3$ about 105 ml). The patient was given 5% sodium bicarbonate about 100 ml to correct acidosis, then the CO_2CP was up to 26.0.

Loop diuretics are recommended to be used by as comparing to none. Furosemide, a loop diuretic, can reduce the oxygen consumption of the medullary tubules, to temporarily increase glomerular plasma flow, but does not increase glomerular filtration rate. Experiments have also shown that furosemide can prevent reabsorption of electrolyte, by reducing hypoxic damage of the renal medulla in a perfused rat kidney *in vitro* [22]. Sodium bicarbonate reduces the precipitation of protein and uric acid in the renal tubules by alkalizing the urine, then protecting the kidney function [23]. In this case, the patient's urine rapidly turned deep yellow and then faint yellow after vigorous hydration of isotonic crystalloid fluid, intravenous sodium bicarbonate to correct acidosis, furosemide to diuretic, and prostaglandil which combined with Shenkang injection to protect the kidney circulation. The creatinine clearance rate was restored from 12.3 ml/min/1.73 m^2 to 100.2 ml/min/1.73 m^2, which returned to normal without hemodialysis, the whole treatment process was within 120 hours.

4. Conclusion

exRML seems to be underestimated, and it is essential to screen patients who present with muscle soreness and/or dark urine after heavy endurance events to avoid any further complications like AKI. When exRML happens, vigorous fluid resuscitations, loop diuresis, sodium and bicarbonate are necessary, and sometimes renal replacement therapy is used in patients with severe AKI.

Disclosure Statement

The content has not been published or submitted for publication elsewhere. The studies involving human participants were reviewed and approved by the Ethical Committee of the Second Hospital of Tianjin Medical University. The patients/participants provided their written informed consent to participate in this study.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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