

Hypothyroidism and Drug-Related Rhabdomyolysis and Acute Kidney Injury

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Abstract

Case Report

Rhabdomyolysis (RM) due to hypothyroidism is known, but acute kidney injury (AKI) due to hypothyroidism related RM is rare and potentially life-threatening. In our first case, a 80-year-old man presented with RM and AKI. He was diagnosed as severe hypothyroidism related RM and AKI. Second case was a 27-year-old woman presented with drug(combination of flurbiprofen/ thiocolchicoside and amoxicillin/ clavulanic acid) related RM and severe AKI. When we analyze the literature in detail, there are published cases of RM-AKI associated with hypothyroidism. In addition, there was no knowledge of the flurbiprofen/ thiocolchicoside and amoxicillin/ clavulanic acid associated RM and AKI. In patients presenting with RM and AKI, physicians should consider hypothyroidism and drug use.

Keywords: Hypothyroidism, rhabdomyolysis, acute kidney injury, flurbiprofen/ thiocolchicoside, amoxicillin/ clavulanic acid.

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INTRODUCTION

Muscle cells contains muscle enzymes [creatine phosphokinase (CK), lactate dehydrogenase (LHD)], glutamic oxaloacetic transaminase (AST), heme pigment including myoglobin, electrolytes (potassium, phosphorus) and purines. RM is characterized by skeletal muscle destruction and the release of muscle cell content into the circulation[1, 2]. The etiology of RM is classified according to traumatic and non-traumatic causes. Causes include injury, strenuous exercise, toxins, infections, hyperthermia, side effects of certain drugs, metabolic abnormalities, electrolyte disturbances and hypothyroidism [3, 4]. RM usually presents with markedly elevated CK levels, muscle pain, extremity weakness, swelling and myoglobinuria. The RM spectrum varies from asymptomatic serum muscle enzyme elevation to life-threatening electrolyte imbalance and AKI requiring renal replacement therapy[5]. Among patients with RM, 13- 50% develop AKI [6].

Our first case presented to us with terminal complications of hypothyroidism. He was diagnosed with hypothyroidism for the first time with these complications. RM-AKI complication due to hypothyroidism developed. In our second patient flurbiprofen/ thiocolchicoside and amoxicillin/ clavulanic acid were used and AKI developed in the

15th day. We report cases of RM-AKI occurring in two interesting and different reasons.

CASE PRESENTATIONS

Case 1: A 80-year-old man with dwarfism and mental retardation was relatively healthy up to 3 months ago. His psychological problems started after cataract surgery. He has had constipation for years. He was rarely taking bisacodyl + sennoside medication to dissolve constipation. A week ago, he had weakness and muscle pains and oral food intake decreased. During this time, the amount of urine started to decrease. Two days ago his consciousness began to deteriorate. He was brought to our emergency department. His history did not include trauma, kidney disease, chronic illness and uncontrolled serum glucose, infection and viral exanthema, severe exercise, medication (such as statin, herbal medicine), and toxin use. Physical examination findings were as follows; pulse rate: 100/ min, blood pressure: 80/50 mmHg, fever: 37.5 °C. There was no sign of goitre on the neck. Systemic edema (facial, periorbital, leg, foot) was detected. In laboratory investigations; Urea: 184.1 mg/ dL, creatinine (Cre): 3.11 mg/ dL, Sodium (Na): 151 mmol/ L, potassium (K): 7.3 mmol/ L, AST: 80 U/ L, LDH: 427 U/ L, CK: 1094 U/ L, White Blood Cell (WBC): 6.9*10³/ mm³, Hemoglobin (HGB): 9.6%, platelet (PLT): 145.000/ mm³, myoglobin: 1801.5 ng/

mL, C-reactive protein (CRP)): 7.6 mg/ L, ph: 7.13, pCO₂: 29.5 mm/ Hg, HCO₃: 8.9 mmol/ L. Urine Na level and urine fractional Na excretion were high (46 mEq/ L, 2%, respectively). We focused on RM-AKI.

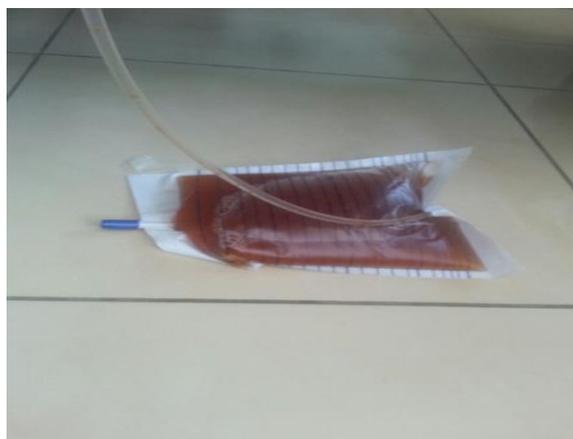


Fig-1: Dark urine of case 1

Hormone profile was; Free T₃ (FT₃): 1.06 pg/ml, Free T₄ (FT₄) = 0.44 ng/ ML, thyroid stimulating hormone (TSH) > 150 mIU/ L. In addition, the patient had high titer thyroid peroxidase (TPOAb) 1: 6,400 and anti-thyroglobulin antibody (TgAb) 1: 6,400 antibodies. Based on these findings, the patient was diagnosed with hypothyroidism associated with Hashimoto's thyroiditis. Low dose levothyroxine was given oral form (50 mc/day) from the nasogastric tube. Hemodialysis was planned when he did not respond to conservative treatment. While the hemodialysis preparation was being designed (such as providing hemodialysis vascular access), the patient underwent a cardiac arrest and died.

Case 2: A 27-year-old woman presented with sore throat, weakness and muscle ache for 15 days. Flurbiprofen/ thiocolchicoside and amoxicillin/ clavulanic acid tablets were given orally. Then diarrhea and menstrual irregularity started. Diarrhea lasted 2 days. During this period, she experienced darkening of his urine. Oral intake decreased, weight loss and fatigue added and she admitted to emergency department. She was hospitalized in Internal Medicine Unit and hydration and supportive treatments were started. The urine amount decreased (400 ml/ day) during this follow-up. On the 3rd day of hospitalization, metabolic acidosis was found in blood gas analysis. Her history did not include trauma, kidney disease, chronic disease, and uncontrolled blood sugar, infection, and viral exanthema, referral, severe exercise, medication (such as statin, herbal medicine), and use of toxins. Examination was; pulse rate: 60/ min, blood pressure 160/90 mmHg, fever 37 °C. Abdomen was mildly distant. Mild pretibial edema was detected. In laboratory investigations; urea: 383.3 mg/ dL, cre: 28.1 mg/ dL, Na: 142 mmol/ L, K: 6.4 mmol/ L, AST: 57 U/ L, LDH: 718 U/ L, CK: 2663 U/ L, myoglobin : 2760 ng/ mL, ph: 7.18, HCO₃: 9.8 mmol/ L. Cardiac enzyme

Parenteral hydration, bicarbonate, furosemide therapies were started. Urine was red in dark red (Figure 1) and urine analysis showed blood reaction with dipstick test but no RBC in microscopy.

elevation was not supported by ECG and it was commented as the effects of rhabdomyolysis. We thought RM- AKI. We transferred the patient to the Nephrology department. Parenteral hydration, bicarbonate, furosemide treatments were continued. Her urine was in deep red and urine analysis showed blood reaction with dipstick test, but microscopic examination did not show erythrocyte. She had severe metabolic acidosis and hypervolemia. Hemodialysis was performed for 3 consecutive days. RM reasons were evaluated for her. In the Black Sea region of Turkey hantavirus and leptospirosis infections are commonly seen. Microscopic agglutination test for leptospirosis, antibodies to Hanta (IgG, IgM) were found to be normal. Other virus infection analyzes were found negative. The patient had no upper and lower respiratory tract infections. There's a history of diarrhea before. The gaita test was clear. Three sessions of hemodialysis were performed. Renal functions and other biochemical data improved during the follow-up period. Urine output was provided. General condition stabilized. She was discharged with healing.

DISCUSSION

Rhabdomyolysis is associated with a variety of reasons. The pathogenesis of rhabdomyolysis is related to direct sarcolemic injury (such as trauma) or depletion of ATP in myocytes and leads to irregular leakage of calcium ions into cells [7]. Sarcoplasmic calcium is strictly regulated by energy-dependent ion pumps such as Na⁺/ K⁺ATPase and Ca²⁺ATPase in sarcolemma. These pumps keep calcium levels in resting muscle low, but allow actin-myosin binding and increase in calcium levels when muscle contraction is required. Regardless of the underlying mechanism, muscle injury increases sarcoplasmic calcium and causes persistent contraction. Finally, there is muscle fiber necrosis after activation of the cell protease. Then, potassium, phosphate,

myoglobin, CK and uric acid are released out of the cell into the systemic circulation [5].

Hypothyroidism may present with muscular findings such as myalgia, proximal muscle weakness and cramping. Hypothyroidism is a cause of non-traumatic RM. The exact cause of RM in hypothyroidism has not been fully elucidated; however, it is accepted that thyroxine deficiency suppresses glycogenolysis, mitochondrial oxidation and the transformation of triglycerides into an energy source. This causes muscle dysfunction. The same situation results in muscle injury and even RM in oxidative stress conditions [8]. RM-induced AKI caused by hypothyroidism is relatively rare [9]. In the first case, CK level was measured to be higher than the normal limit. Biochemical analysis was accompanied by hyperkalemia, uremia, and metabolic acidosis. There was no pathology in urinary system ultrasound. Myoglobin was very high in serum. The positive blood reaction of urine with dipstick test, but the absence of erythrocyte microscopic examination was also considered RM-AKI. For the etiologic reasons of RM, detailed history was taken from the relatives of the patients and additional examinations were performed. In our case, there was no previous hypothyroidism and no drug use. He did not see a doctor before, because he did not have a chronic disease. He only had cataract surgery on her both eyes three months ago. After the operation, he completely lost his sight. As a result, the patient had psychological problems such as anxiety. Deep hypothyroidism was found in his hormone profile. Thyroid autoantibodies and ultrasonography were in favor of Hashimoto's thyroiditis. In our country, only oral levothyroxine is available. The incidence of the disease is high, especially in middle and older women [10]. It is rare to find an old man with chronic autoimmune thyroiditis. Usually the use of lipid-lowering drugs, alcohol, exercise or chronic renal failure can be found as a triggering factor. In our case, there was no trigger factor and Hashimoto was the cause of hypothyroidism. Here RM had no other triggering factor except hypothyroidism. Prakash et al. found that thyroid hormones and CK levels in patients with hypothyroidism had an inverse ratio in serum. In their study, it was concluded that the detection of serum CK levels may be extremely valuable in screening patients with hypothyroidism [11]. These findings were consistent with the results of our case. Therefore, RM and AKI tables were linked to hypothyroidism. The patient's cataracts and psychological problems were probably related to the terminal complications of hypothyroidism. The patient was given bicarbonate and prophylactic antibiotics. Retrospective analysis has shown that early aggressive fluid replacement with saline is useful in minimizing AKI formation. After saline treatment, starting with alkaline agents (bicarbonate) and forced diuresis (mannitol or furosemide) within 6 hours has been reported to minimize the risk of AKI. The goal is to minimize the

accumulation of intratubular heme pigment and to act as a free radical scavenger, thereby minimizing cell damage [12-17]. Because of hypotension, our patient could not tolerate hemodialysis. He did not respond to resuscitation and died. Probably hyperkalemia was the cause of cardiac arrest.

In the second case, CK level was also high. Biochemical analysis accompanied uremia, metabolic acidosis. Myoglobin was very high in serum. The positive blood reaction of urine with dipstick test, but the absence of erythrocyte microscopic examination was also considered RM-AKI. For the etiologic reasons of RM, detailed history was taken from the patient and additional examinations were performed. There was no prior drug use. She had taken combination of flurbiprofen/ thiocolchicoside and amoxicillin/ clavulanic acid. There was no other pathological condition in the medical history other than these drug combinations. Thyroid hormone levels were normal. No viral or bacterial infection that could cause rhabdomyolysis was found. There was no apparent elevation in WBC or CRP. There was no pathology in urinary system ultrasound.

Flurbiprofen inhibits the synthesis of prostaglandins by at least 2 cyclooxygenase isoenzymes, cyclooxygenase-1 (COX-1) and -2 (COX-2). It may inhibit chemotaxis, may alter lymphocyte activity, decrease proinflammatory cytokine activity, and may inhibit neutrophil aggregation. Adverse effects of flurbiprofen are edema, fluid retention, abdominal pain with cramps, diarrhea etc [18].

Thiocolchicoside is widely used as a muscle relaxant. The primary side effects of thiocolchicoside are nausea, somnolence, allergy and vasovagal reaction [19]. Epileptic seizures following thiocolchicoside ingestion have been reported in a few cases [20].

Amoxicillin binds to penicillin-binding proteins, thus inhibiting final transpeptidation of peptidoglycan synthesis in bacterial cell walls; addition of clavulanate inhibits beta-lactamase-producing bacteria. It is a semisynthetic antibiotic with a broad spectrum of bactericidal activity, including gram-negative and gram-positive microorganisms. Adverse effects are diaper rash, mycosis, nausea, rash, vomiting, loose stool, candidiasis, vaginitis etc [21].

The cause of rhabdomyolysis was the combination of drugs that she had taken. In the literature a case of simvastatin-induced rhabdomyolysis has been exacerbated by the use of amoxicillin/ clavulanic, but it was not as severe as our case, and there was no need for hemodialysis. Renal function improved with medical treatment [22].

Thiocolchicoside side effects include rhabdomyolysis but there is no renal failure [23].

Rhabdomyolysis with venlafaxine and amoxicillin/clavulanic interaction has been reported [24].

In the second patient the urine output could not be achieved by conservative treatment such as fluid resuscitation, bicarbonate, force diuresis and 3 days of sequential hemodialysis was performed. There was urine output during follow-up. Renal values improved and she was discharged with healing.

As a result, AKI due to muscle destruction may occur rarely on the basis of hypothyroidism. In cases with these two severe complications, physicians should add hypothyroidism to the differential diagnosis list. In addition, the drug should be selected according to the indication of the patient when writing the medication, otherwise it may cost the patient's life with complications.

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