



A rare case of hypokalemia-induced rhabdomyolysis

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A 68-year-old male was complained of chest pain for two years and fatigue for one week. He was admitted to other hospitals two years ago because of severe chest pain. A diagnosis of acute non-ST segment elevation myocardial infarction (NSTEMI) was made. But the coronary angiography was refused by himself. After effective conservative treatment, he got better and discharged. A regular administration of aspirin, metoprolol and simvastatin was taken. No recurrent symptoms occurred. However, he felt fatigue and palpitation after 30-m walking one week ago without predisposing factors.

In the past history, he had hypertension, diabetes and hyperlipidemia for two years with irbesartan 150 mg or hydrochlorothiazide 12.5 mg per day, metoprolol 25 mg per day, simvastatin 20 mg per night and irregular oral metformin. Besides, he developed poliomyelitis for over 60 years with right lower extremity disabled and usually walked with a cane. About three weeks before admission, he caught a cold, and glycyrrhiza tablets were taken with a dose of four pills daily.

At admission, his temperature was 36.1 °C, blood pressure was 170/60 mmHg, and the pulse was 91 beats/min. No special signs had been found, except for left leg muscle strength level II and right leg muscle strength level I. He could not walk as usual. The patient's arterial blood gas analysis indicated metabolic alkalosis. His hemoglobin was 118 g/L. The serum creatine level was elevated to 164 μmol/L. Serum creatine kinase (sCK) was 598 U/L (range: 20–200 U/L), and myoglobin (MYO) was 331.6 μg/L (range: 28–72 μg/L), while creatine kinase-MB (CK-MB) was 6.93 U/L (range: 0–6.22 U/L) and hypersensitive myotroponin T (hs-cTnT) was 0.146 μg/L (range: 0–0.024 μg/L). Besides, serum potassium of 2.18 mmol/L was detected. At admis-

sion, the electrocardiogram was presented as sinus rhythm, bidirectional T waves on leads V₁–V₃ with inverted U wave on leads V₂–V₄. The heart rate was 93 beats/min, and the QTc interval was prolonged with 544 ms (Figure 1A). Based on these data, the initial diagnosis was made with an impression of acute coronary syndrome, hypokalemia and renal dysfunction.

However, this patient did not have any chest discomfort. The cardiac biomarkers were monitored continuously and the elevation of sCK and myoglobin MYO were more remarkable than hs-cTnT and CK-MB (Figure 2). No dynamic changes were shown among the following different ECGs (Figure 1). In addition, the echocardiography did not indicate any anomaly either. On the basis of these evidences, we preferred acute muscle injury rather than cardiac factors. After admission, diuretics, simvastatin and glycyrrhiza were all discontinued. By intravenous potassium substitution and fluid infusion, serum potassium was increased to normal within two days. Correspondingly, sCK decreased to normal within ten days (Figure 3). Moreover, in the ensuing ECG data, QTc interval was shortened obviously, u wave disappeared and T wave in V₁–V₃ leads became upright (Figure 4). After discharge, the patient was followed for over one year, and the level of CK, MYO and potassium remained normal ever since.

Besides, hormones were examined to further screen endocrine diseases. Apart from an increased aldosterone and cortisol, other hormone levels were normal. No typical clinical representation existed. The adrenal ultrasonography was also negative. Furthermore, hypokalemia did not recur during 1-year follow-up. Thus we exclude endocrine disorders.

Rhabdomyolysis is one syndrome characterized by muscle necrosis. According to the diagnosis,^[1] the level of sCK at presentation is usually at least four times more than the upper limit of normal. Consequently, rhabdomyolysis was established in this case.

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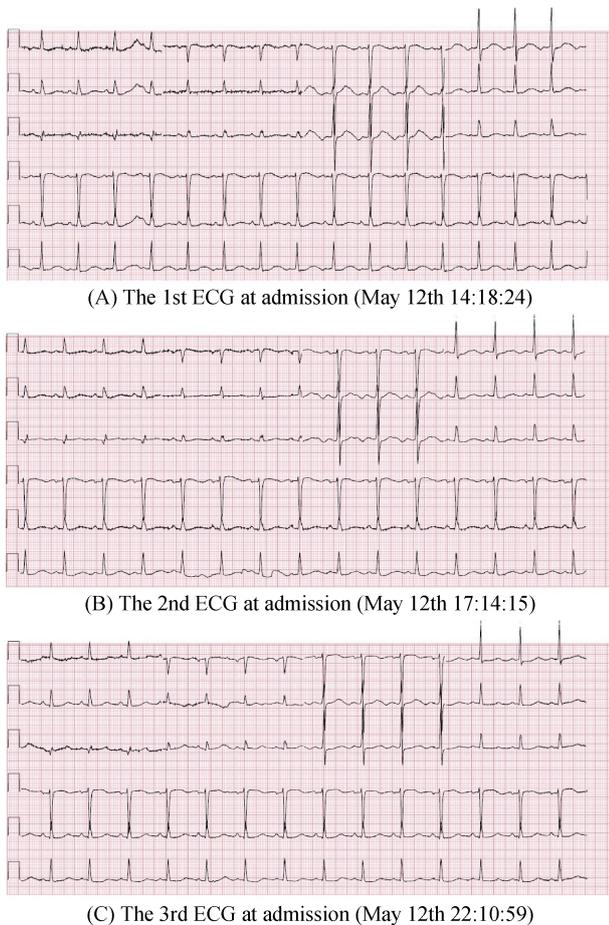


Figure 1. The first three ECGs at admission. As shown above, we did not see any obvious dynamic changes among the three ECGs. (A): The ECG was shown as sinus rhythm, bidirectional T waves on leads V1–V3 with inverted u wave on leads V2–V4. The heart rate was 93 beats/min, and the QTc interval was prolonged with 544 ms. (B): The morphology remained unchanged. The heart rate was 87 beats/min with QTc interval of 495 ms. (C): The heart rate was 87 beats/min with QTc interval of 563 ms.

As reported, both statins and hypokalemia can contribute to rhabdomyolysis. However, this patient has taken simvastatin 20 mg daily for over two years. The U.S. Food and Drug Administration (FDA) published the recommendation^[2] in 2011 that simvastatin 20 mg daily is relatively safe as only 0.02% patients in 20 mg group developed myopathy or rhabdomyolysis. Similarly, recently another large-sample case-control study^[3] demonstrated that only 0.0045% person per year develops myopathy or rhabdomyolysis after taking simvastatin 20 mg daily for four years. Moreover, it is found that the risk seems to be higher in the first year of administration and then decreases afterwards. As for this patient, his onset of fatigue and muscle injury just happened one week before admission, inconsistent with his medication regimen. Above all, although oral statins could result in

rhabdomyolysis, the dose of 20 mg daily is so small that it is less likely to develop rhabdomyolysis.

Thus, hypokalemia is considered as the main reason for rhabdomyolysis in this case. During muscle contraction, potassium will be released from the intracellular to extracellular space. This is to mediate vasodilation and promote blood flow to contracting muscle. In state of hypokalemia, this stimulus is lost, the blood flow of myocytes decreases significantly and arterioles may constrict, leading to muscular ischemia and the subsequent cascade of myocyte destruction.^[4] Afterwards, the depression of glycolytic enzyme function and stimulation of lipid activity result in the accumulation of free fatty acids (FFA) within muscle cells. High concentrations of FFA will prompt pump dysfunction (Na/K-ATPase, Ca²⁺-ATPase pump), increase permeability of the cell membrane and thus raise the intracellular calcium concentration. The increased intracellular calcium level soon sensitizes the downstream pathways, activates calcium-dependent proteases and phospholipases, and then destroys myofibrillar, cytoskeletal and membrane proteins, leading to muscle necrosis and intracellular sCK and MYO released into blood circulation.^[5,6]

In terms of hypokalemia, two underlying causes should be taken into account. Firstly, we consider that diuretics may play a role. As the patient took Irbesartan/hydrochlorothiazide tablets 162.5 mg daily before, the serum potassium was lost a lot from urine. Hydrochlorothiazide will inhibit the absorption of sodium iron from distal tubule and proximal tubule, further enhance the activity of renal outer medullary potassium channel and H/K-ATPase, which leads to hypokalemia. However, his long-term medication course for two years could hardly explain the newly-onset symptoms. Besides, due to the potassium-sparing effects by irbesartan, the incidence of hypokalemia induced by irbesartan/hydrochlorothiazide is reported only 0.3%–0.6%.^[7,8]

Secondly, glycyrrhiza should be taken into account. Recent studies suggest that glycyrrhiza can induce hypokalemia and muscle weakness, even life-threatening rhabdomyolysis.^[9,10] The main component of glycyrrhiza is glycyrrhizic acid,^[11] which plays an important role in the mechanism of glycyrrhiza-related pseudo-hyperaldosteronism. Glycyrrhizic acid is hydrolyzed into glycyrrhetic acid by oral ingestion and then inhibits the activity of 11- β -hydroxysteroid dehydrogenase (11- β -HSD), prevents the transformation of cortisol to cortisone. Glycyrrhizic acid can also directly bind to mineralocorticoid receptor or suppress 5- β -reductase activity and therefore slow down the hepatic metabolism of aldosterone, resulting in pseudo-hyperaldosteronism, which manifests as hypokalemia, hyperten-

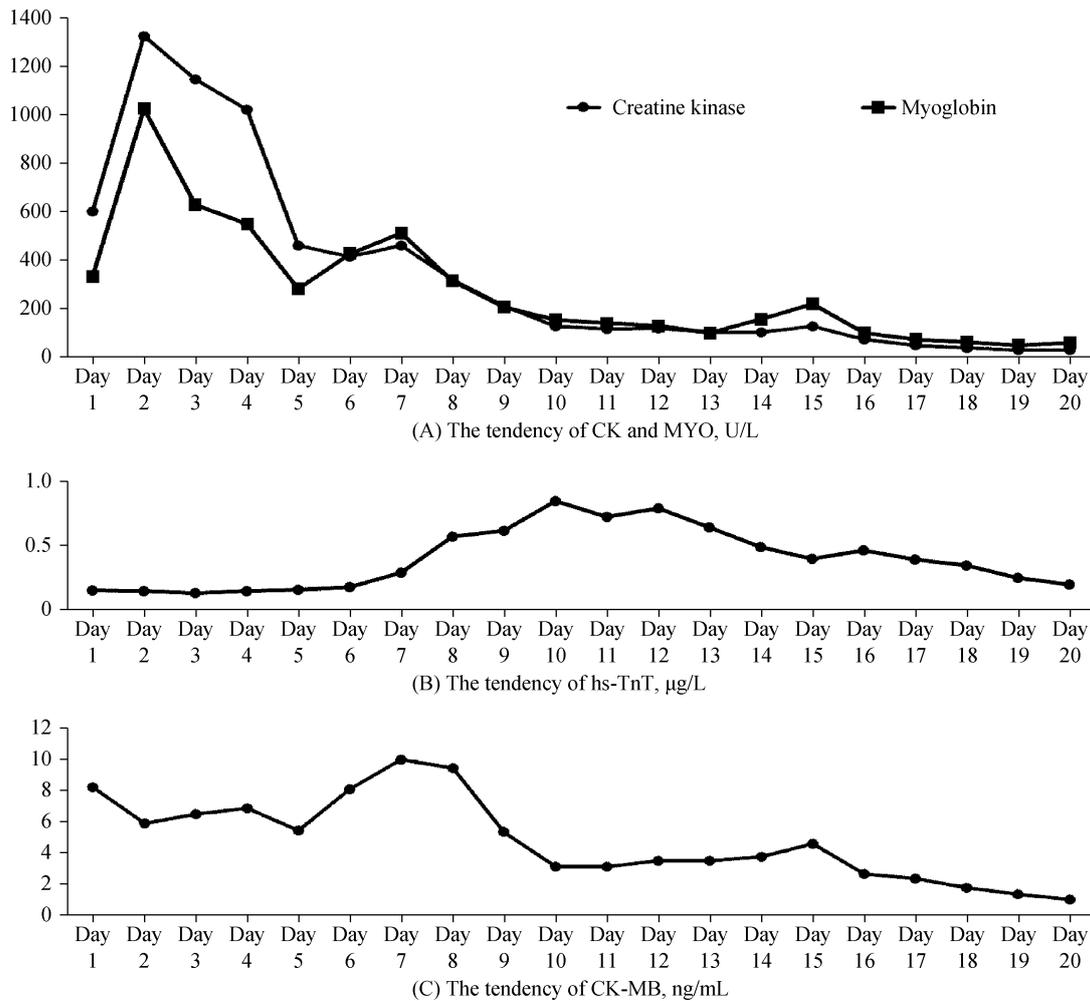


Figure 2. The variation of the biomarkers of myocardial injury after admission. (A): The serum CK and MYO concentration significantly increased at admission and then decreased evidently after rapid potassium supplement; (B & C): The level of hs-TnT and CK-MB raised slowly and did not reach the peak in 48 h, of which the trend was not in keep with the typical changes among AMI patients. AMI: acute myocardial infarction. CK-MB: creatine kinase-MB; MYO: myoglobin.

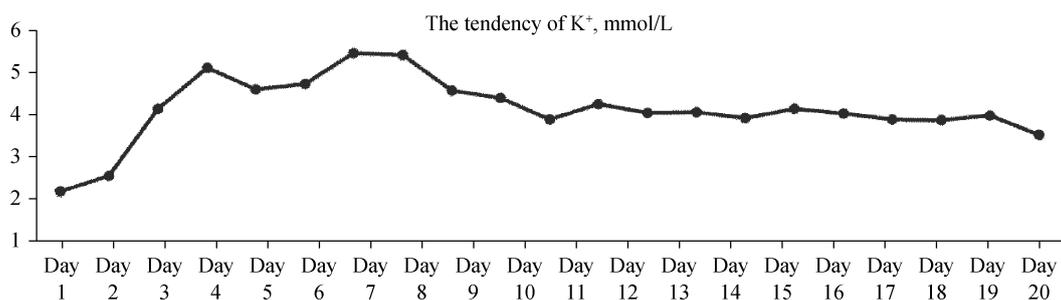


Figure 3. The variation of serum potassium level after admission and rapid complement. With the increasing of K⁺ level, the level of CK and MYO decreased correspondingly and reached normal. CK-MB: creatine kinase-MB; MYO: myoglobin.

sion and metabolic alkalosis. Because of these metabolic pathways, the elevated cortisol and aldosterone level in our case can be well explained. Cessation of glycyrrhiza intake,

combined with adequate potassium replacement will reverse the side effects. Based on U.S. FDA announcement,^[12] current estimates for intake of licorice extract are recom-

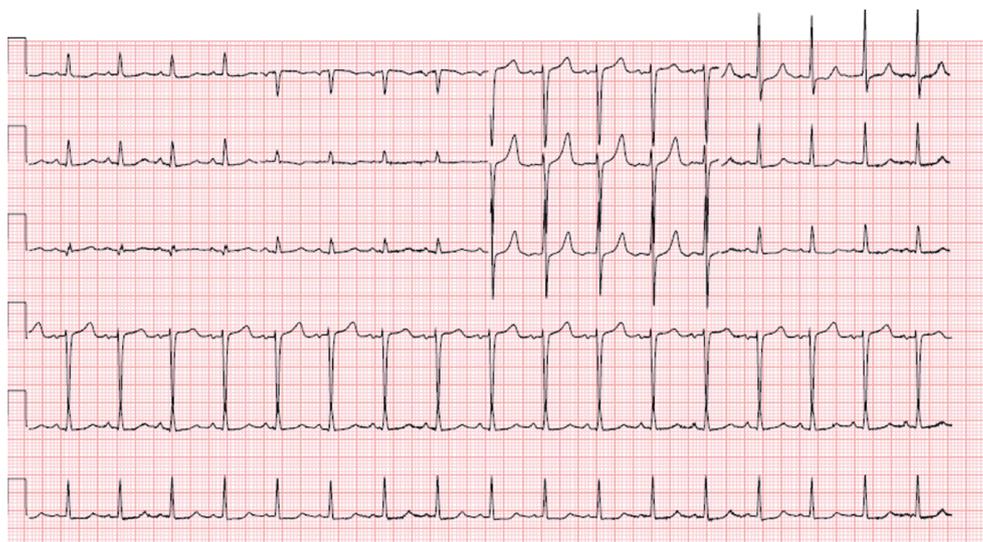


Figure 4. The ECG manifestation after serum potassium level returned to normal. As shown above, when serum potassium level returned to 4.14 mmol/L, the ECG was shown as sinus rhythm, upright T waves on leads V1-V4. The u wave disappeared. At this time the heart rate was 104 bpm, and the QTc interval shortened to 473 ms.

mended in the range of 1.6–215 mg per day. Comparatively, the patient just took relatively large amount of glycyrrhiza regularly (450–560 mg per day) for three weeks before admission. We think that glycyrrhiza is likely to be the key factor for the new onset of hypokalemia and rhabdomyolysis in this case.

At last, although the patient had poliomyelitis, no relationships between poliomyelitis and rhabdomyolysis have been reported yet.

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