CASE REPORT

A case report of Asymptomatic hyperCKemia and literature review

Meng Luo[1], Xuerong Huang[2], Wenhui Wang[3], Qingjun He[4], Chunhong Zhou[5], Yingyu Lin[6], Chunxiao Fan[7], Jianbin Pi[8]

Abstract

The case report of a female with Asymptomatic hyperCKemia along with a literature review is presented. The objective of this report is to highlight an effective diagnosis and treatment option for Asymptomatic hyperCKemia patients, as well as to bring to attention a rare and benign cause of CK elevation, which can lead to diagnostic and therapeutic errors.

Keywords: Asymptomatic hyperCKemia; Rare disease.

DOI: https://doi.org/10.47391/JPMA.11448

Introduction

Asymptomatic hyperCKemia is a disease with significant clinical heterogeneity. The European union of Neurology has determined that the creatine kinase value of Asymptomatic hyperCKemia as 1.5 times higher than the upper limit of the normal value. This paper reports a young woman with elevated creatine kinase found by physical examination. After in-hospital examination and follow-up, the diagnosis of Asymptomatic hyperCKemia was confirmed. The pathogenesis of the disease is complex and the aetiology is diverse, so the author believes that it is extremely necessary to improve the ability of medical workers to identify and diagnose the disease and avoid missed diagnosis and misdiagnosis as far as possible to improve the prognosis of such patients.

Case Report

A 25-year-old female patient was admitted to the cardiology department of Foshan Hospital of Traditional Chinese Medicine in China on March 24, 2022, with complaints of CK elevation since one month and palpitations, dyspnoea, and fatigue since one day. On Feb. 26th 2022, she first noticed the abnormal result of hyperCKemia during a routine check up, where CK levels were found to be 491 U/L (reference range: 40-200 U/L) and CK-MB levels were 419 U/L (reference range: 0-24 U/L). For the last month，she had been receiving standard treatment, including coenzyme Q10 as the doctor considered that hyperCKemia might be associated with Myocarditis. However, there was no obvious change in hyperCKemia. On March 23rd, 2022, the patient underwent a five-item cardiac enzyme test at another hospital, which showed CK levels of 420 U/L, CK-MB levels of 502 U/L, and no abnormalities in troponin I (TNI) levels. The patient was admitted to our hospital for the treatment but denied any history of coronary artery disease, hypertension, diabetes, or allergic diseases. She had no family history of neuromuscular diseases, and she did not smoke or drink alcohol. She had a past medical history of anxiety neurosis. Over the last 4 months, from November 2nd 2021 to March 15th 2022, she had been taking quetiapine fumarate tablets (100mg tid), zaleplon tablets (5mg qd), escitalopram oxalate tablets (10mg qd) regularly.

Physical examination upon admission showed a body temperature of 36.4℃, heart rate of 75 beats/min, respiratory rate of 18 breaths/min, and blood pressure of 107/79mmHg on the left arm and 108/80mmHg on the right arm. The patient was conscious and responsive but exhibited mildly laboured breathing. No abnormality was found upon examination of the cervical vertebrae, chest,

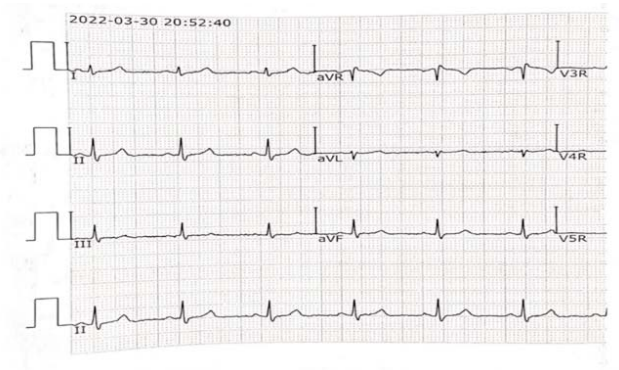

Figure-1: Electrocardiogram of patient.

[1,2,5,6,7]Department of Teaching and Research, Foshan Hospital of Traditional Chinese Medicine, China; [3,4,8]Department of Cardiology, Foshan Hospital of Traditional Chinese Medicine, China.

Current Affiliation (Authors-1,2,5,6,7): Department of Teaching and Research, The Eighth Clinical Medical College of Guangzhou University of Chinese Medicine, China

Current Affiliation (Authors-3,4,8): Department of Cardiology, The Eighth Clinical Medical College of Guangzhou University of Chinese Medicine, China

Correspondence: Jianbin Pi. **Email:** jianbipi@163.com

ORCID ID: 0009-0009-1327-1372

Submission complete: 08-01-2024 **First Revision received:** 15-03-2024

Acceptance: 30-10-2024 **Last Revision received:** 29-10-2024

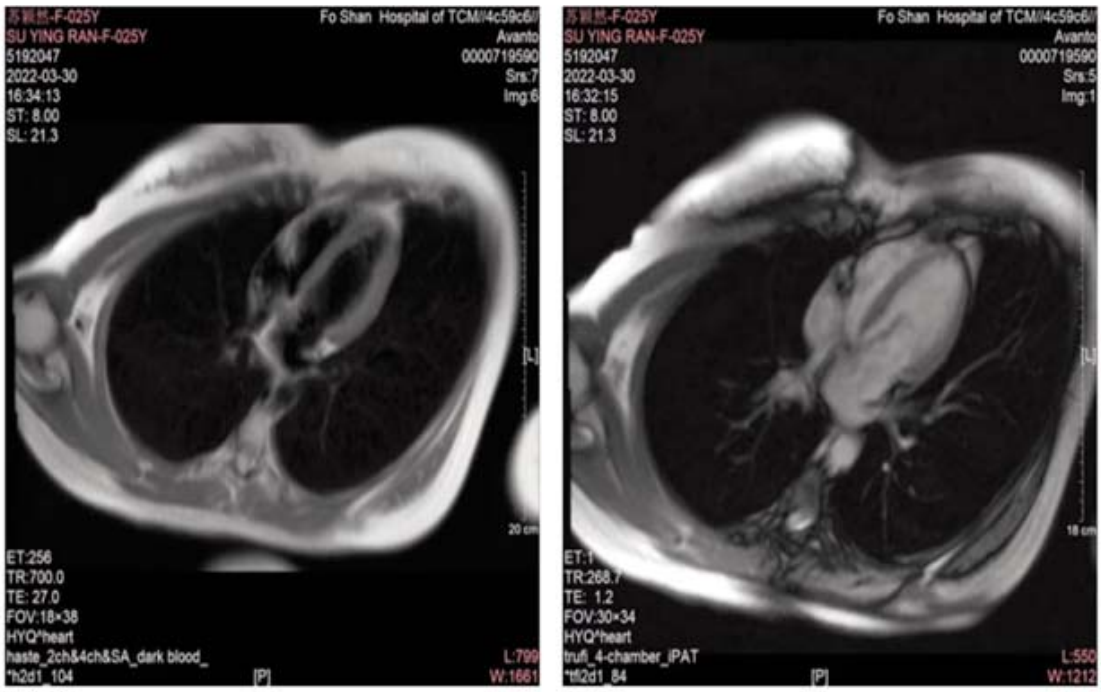

Figure-2: Cardiac Nuclear Magnetic Resonance Imaging of patient.

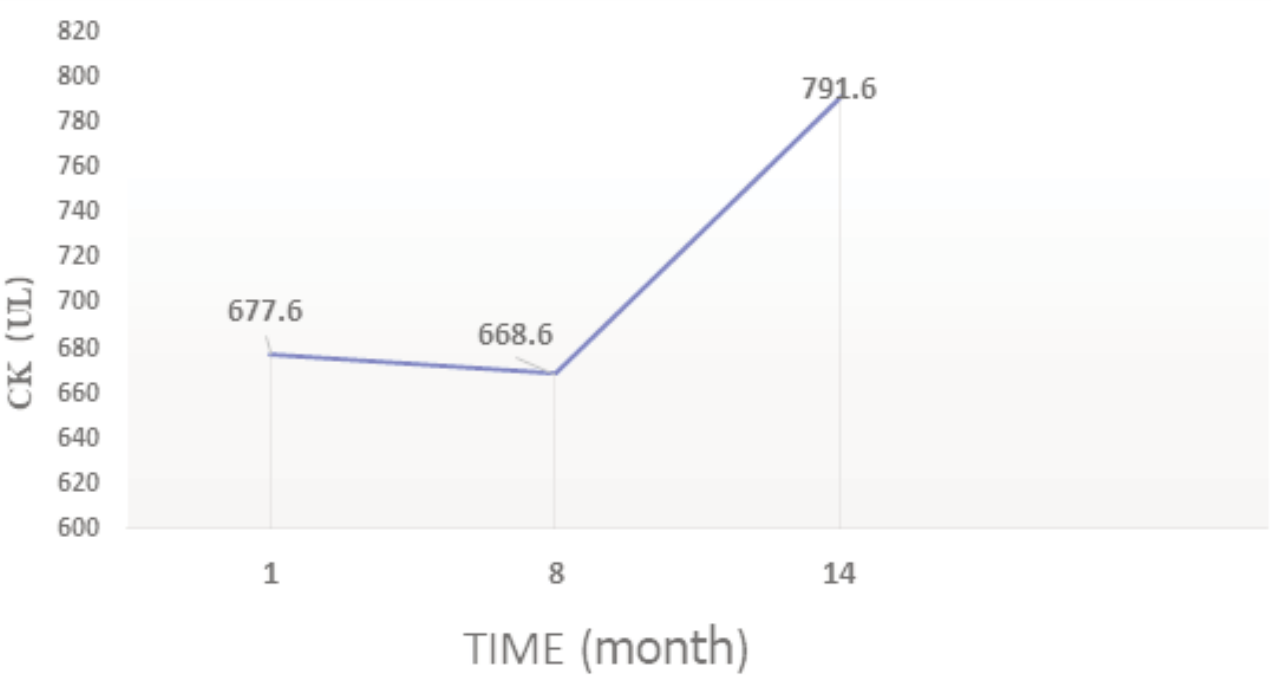

Figure-4: The table presents the laboratory test results for CK-MB at month 1, month 8 and month 14 after the patients were discharged from the hospital.

and abdomen. No significant abnormalities were detected upon neurological examination.

No significant abnormalities were detected in kidney function tests, coagulation function tests, erythrocyte sedimentation rate (ESR), glycated haemoglobin, female tumour screening tests, infectious disease screening tests, rheumatologic disease tests or autoimmune disease tests. No abnormalities in ECG (Figure 1), cardiac ultrasound, cardiac MRI (Figure 2). Lab work results showed a CK level of 393.2 U/L and a CK-MB level of 784.7 U/L. A four quantitative items for myocardial infarction (TNT, CTnI, Myo, CK-MB) showed a CK-MB level of 1.1 ng/ml, which

Figure 3: Electromyography results of both lower extremities.

Measurement of nerve conduction velocity.									
Nerve name	**From-TO**	**Nerve conduction velocity (m/s)**		**Stimulus**	**Record**	**Latent time (ms)**		**Induced action potential amplitude (μV)**	
		Left	**Right**			**Left**	**Right**	**Left**	**Right**
Tibial nerve-motion	Popliteal fossa-Ankle	52	51.2	Ankle	Exallucis	3.19	7.88	19900	17800
				Popliteal fossa	Extensor hallucis Longus	10.5	10.3	17300	16500
				Popliteal fossa	Gastrocnemius		4.23		12400
Common peroneal nerve-motion	Under the fibulae-Ankle	52.3	54.1	Ankle	Extensor hallucis brevis	3.95	3.29	9000	108500
				Under the fibulae	Extensor hallucis brevis	9.69	9.21	9000	9800
Superficial peroneal nerve - sensation	Middle posterior leg-upper lateral malleolus	53.1	50	Middle posterior leg	upper lateral malleolus	2.5	2.71	29	25.6
Sural nerve - sensation	Lower lateral lower leg-posterior lateral malleolus	50	55.1	Lower lateral lower leg	posterior lateral malleolus	3.23	3.38	33	30.2
F wave of peroneal nerve	Occurrence rate %	100	100		The average latent time	42.9	41.7		
F wave of Common peroneal nerve	Occurrence rate %	60	85		The average latent time	41.3	39.6		

fell within the normal reference range of less than 5.8 ng/ml. Liver function tests or hormone tests were also negative. No muscle damage was observed in the muscles of both lower limbs (Figure 3). A cranial MRI at another hospital also showed no abnormalities. As the patient was not in any discomfort, she refused to undergo the muscle biopsy. The initial diagnosis was CK elevation of an unknown origin, possibly asymptomatic hyperCKemia. The patient was treated with quetiapine to nourish the myocardium, fluids, and supportive care. The symptoms improved after treatment, and the patient was discharged from the hospital. Up to the 14th month after discharge, follow-up examinations were conducted on two occasions which showed that the CK value remained elevated (Figure 4). The patient did not experience any muscle pain or weakness during her treatment course.

Discussion

Creatine kinase (CK) is a dimeric enzyme whose role is to catalyse the reversible transfer of high-energy phosphate bonds between creatine and ATP. It is important for muscle contraction, regeneration of ATP, and intracellular energy transport.CK consists of three isozymes, CK-MB, which is mainly found in cardiac muscle, CK-MM, which is mainly distributed in skeletal and cardiac muscle, and CK-BB, which is a brain-type isozyme found mainly in brain, prostate, intestine, and lung tissues and is almost absent in serum. The common causes of elevated CK are cardiac disease, neurological disease, common muscle lesions, tumours, and drug-induced disease. The European Federation of Neurological Societies defines asymptomatic hyper-CKemia as a 1.5-fold increase in serum creatine kinase above the upper limit of normal, with the following criteria:

no clinical, neurophysiological or histopathological neuromuscular disease identified, no family history of neuromyopathy, no cardiac-related disease, normal thyroid function, no history of intramuscular injections, no history of CK-elevating drug use, and exclusion of dystrophinopathy.[1]

In this case, the patient was admitted to the hospital with elevated CK and CK-MB in cardiac work up. CK < CK-MB could be attributed to different detection methods.[2]

The patient with elevated CK-MB in the five point examination of cardiac function (TNI, Myo, BNP, CK-MB, D-Dimer) could be due to elevated CK iso-groups CK-BB and macro-CK and different molecules were excluded which could be cross reacting with CK. In contrast, the four quantitative items for myocardial infarction showed no abnormalities in CK-MB and negative results for troponin

and myoglobin, suggesting that elevated CK-MB could be excluded from being a cause of myocardial damage.

The patient had no significant abnormalities in cardiac MRI, electromyography, triple A, tumour index and rheumatic autoimmune disease markers. She reported of having a negative cranial MRI examination at an outside hospital. The patient had been taking Quetiapine Fumarate Tablets, Zaleplon, and Escitalopram Oxalate regularly for anxiety. AS there are many reports of drug-induced CK elevation, the advantages and disadvantages of prescribing these drugs should be weighed in clinical practice.[3] A few cases have reported[4] the elevation of CK due to ingestion of antipsychotic drugs. However, this patient was regularly monitored and had normal blood drug levels during the course of anxiolytics. The anxiolytics were discontinued due to the elevated muscle enzymes, which did not decline even at a later stage which excluded drug-induced elevation of muscle enzymes.

The exact mechanism of asymptomatic hyper-CKemia is still unclear, but it has been reported that it may be related to an increase in serum CK levels due to mutations in the caveolin-3 gene, which usually presents a familial aggregation with calf hypertrophy.[5] The increased level of CK after exercise is associated with different exercise styles, intensities and training levels, and prolonged intense exercise leads to damage and destruction of myocytes, resulting in an abnormal increase in CK.[6] In some cases, repeated intramuscular injections can also cause hypercalcaemia, which is restored or close to normal after conventional treatment, and this is a short-term increase in CK.[7] Therefore, clinically, when treating patients with elevated CK without obvious symptoms, a detailed medical history should be taken to exclude related diseases.

Large sample studies have shown an incidence of asymptomatic hypercalcaemia of approximately 0.71%,[8] and subjects with asymptomatic hypercalcaemia have a greater risk of hypertension than normal individuals. This could be due to relatively high tissue creatine kinase activity, resulting in greater ATP buffering capacity, which generates and maintains high blood pressure levels.[9] It has also been reported that girls with elevated CK levels may be carriers of Duchenne/Becker muscular dystrophy (DMD/BMD), and require long term follow-up.[10] Such patients often experience muscle pain, weakness, and other discomforts. Combining the past medical history and symptoms of the patient in this case, and the electromyography suggesting no signs of myogenic damage, myogenic-related diseases are not considered for the time being. There are no local reports on the need for aggressive enzyme-lowering therapy.

In routine tests, elevated CK may be associated with the diagnosis of rhabdomyolysis (CK-MM), myocardial infarction (CK-MB) or pancreatitis (amylase). Asymptomatic hyper-CKemia is a group of diseases with significant clinical heterogeneity. Healthcare professionals should carefully screen such patients, maintain close follow-up, review CK indicators regularly, and analyse them in combination with clinical manifestations and further laboratory tests. Understanding the causes of elevated CK helps to make a differential clinical diagnosis, determine further tests, and ultimately clarify the diagnosis and treatment to avoid misdiagnosis and missed diagnoses.

Conclusion

The patient had a history of depression and had been off medication for a week prior to admission. The patient's serum drug concentration was normal, and there was no family or personal history. The relevant examinations (biochemical indicators and imaging studies) at admission did not reveal any obvious abnormalities. After the patient was discharged, we followed up with the patient for 14 months, her CK level remained elevated in the blood, with no symptoms of discomfort. Therefore, the patient's extremely high CK level was considered to be Asymptomatic hyperCKemia.

Abbreviation

CK: creatine kinase; ULN: upper limit of normal; BNP: B-type natriuretic peptide; CK-MB: creatine kinase MB isoenzyme; ATP: adenosine triphosphate; TNT: TroponinT; CTnI: Cardiac troponinI; Myo: Myoglobin.

Consent for publication: Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: No funding received.

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AUTHORS' CONTRIBUTIONS:
ML, XH: Concept and design.
WW, QH: Data analysis, interpretation and revision.
CZ, YL, CF: Data acquisition.
JP: Revision and final approval.
All authors agreed to be accountable for all aspects of the work.