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Macro-Ck type 2 syndrome in prostate adenocarcinoma: Case report and review article

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ABSTRACT

A 67-year-old male had prostate adenocarcinoma with liver, bone metastases, iliac lymph nodes invasion ever receive hormone and chemotherapy. He was presented to our emergency department with acute onset of mild dizziness and shortness of breath. Elevated CK (1477 U/L) and elevated CK-MB (1602 U/L) was noticed. Electrocardiogram was unremarkable for myocardial ischemia. CK-isoenzyme lab test (electrophoresis) was obtained, which revealed macro CK type 2 accounting for 6.2% of total CK. Type 2 macro CK syndrome was impressed. The falsely elevated CK-MB and macro CK type 2 in serum may be associated with the patient's worsening metastatic disease.

1. Introduction

Elevated serum levels of creatine kinase (CK) is most often linked with the diagnosis of acute coronary syndrome (ACS); while other differential diagnoses, such as hyperthyroidism, connective tissue disorders, and acute kidney injury should also be taken into consideration.[1] One lesser known phenomenon is the macro-CK syndrome, in which the serum CK would be falsely elevated due to the increase of CK macroenzymes.[2] From the biochemical point of view, the macroenzymes are referred to as complexes formed by their corresponding enzymes with abnormally high molecular masses. It takes more time to remove these macroenzymes from human bodies than usual enzymes. The clinical importance of macroenzymes is that they could lead to laboratory errors of enzyme activity in blood samples.[2] Here, we present a case of metastatic castration-resistant prostate cancer (mCRPC) with macro-CK syndrome.

2. Case presentation

This 67-year-old male patient with past history of hypertension, first came to our hospital due to difficult in voiding for 3 months. He underwent transurethral resection of the prostate (TURP) and the pathologic report revealed prostate adenocarcinoma Gleason score 4 + 5 (Grade Group 5). Liver, bone and lymph node metastases and rectal invasion was confirmed by abdominal computed tomography (CT) (Fig. 1) and bone scan (Fig. 2). Meanwhile, his Prostate-Specific Antigen (PSA) was 2.43 and hormone therapy (Leuprorelin Acetate subcutaneous injection) and upfront chemotherapy (Docetaxel Dose 75 mg/m2, Total 130mg, three weekly) were initiated after diagnosis. CT revealed progression of liver metastases together with worsening bone pain despite PSA rised only from 0.039 ng/ml to 0.200 ng/ml at 9 months from primary treatment. mCRPC was impressed and Enzalutamide was added for cancer control. PSA level soon decreased to 0.059 ng/ml one month later but increased to 0.349 soon. He came to our emergency department for sudden onset of dizziness and mild respiratory distress 6 months later. 12-lead Electrocardiogram (ECG) showed no evidence of myocardial ischemia (no ST-segment elevation, no ST-segment depression, no T-wave inversion). Laboratory test showed elevated CK (1477 U/L), elevated CK-MB (1602 U/L) but only mild elevation of Troponin-T (17 ng/L, on the reference range of 2012 New Zeeland Guideline for Troponin-T). No evidence of myocardial ischemia on repeated ECG 5 hours later and the patient's symptoms resolved. Repeated lab test, however, revealed marked elevation of CK (2136 U/L) and elevated CK-MB (2296 U/L). Cardiologist was consulted. CK-isoenzyme lab test (electrophoresis) was obtained and the report (SPIFE Touch - Helena Laboratories) showed macro CK type 2 accounting for 6.2% of total CK

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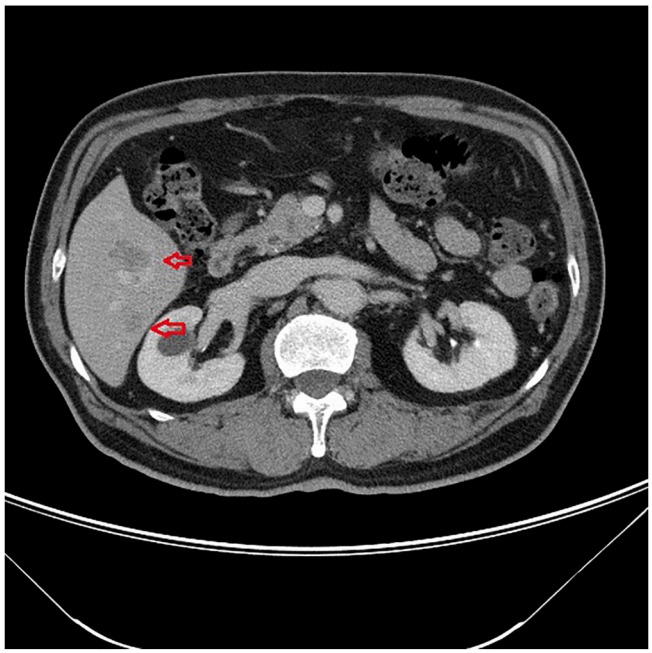

Fig. 1. CT axial view showed several low attenuation lesions at liver, up to 2.5cm with irregular margin, biopsy proved liver metastases (arrow).

(CK-Total 2136 U/L, CK-BB 87.2%, CK-MB 0%, CK-MM 6.6%) (Fig. 3). Subsequent follow up in cardiovascular ward revealed no typical chest pain or dynamic ECG changes despite elevated CK. Color doppler echocardiography showed normal left ventricle systolic wall motion and 54% left ventricle ejection fraction. Macro-CK secondary to prostate cancer was impressed. The patient still expired three months later due to progression of liver metastases causing hepatic failure.

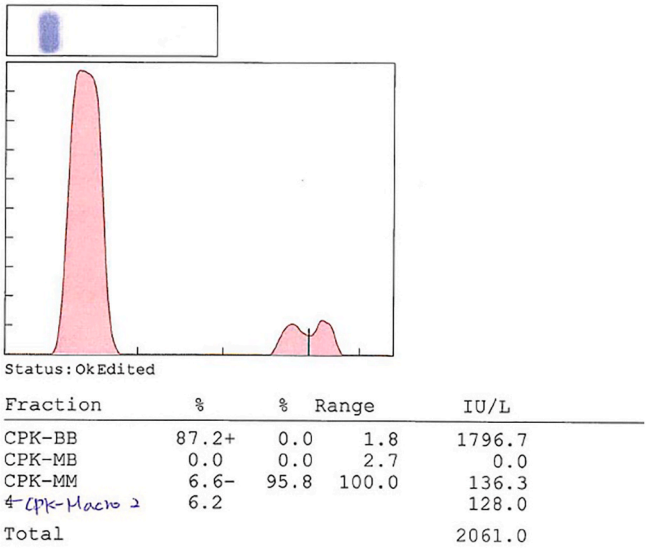

Fig. 3. CK-isoenzyme lab test (electrophoresis): macro CK type 2 accounting for 6.2% of total CK (CK-Total 2136 U/L, CK-BB 87.2%, CK-MB 0%, CK-MM 6.6%).

3. Discussion

Creatine kinase is an important muscle enzymes being released by several tissues and cells, such as striated muscle, heart tissue, brain, smooth muscle of gastrointestinal tract and urinary bladder. Creatine kinase may exist in the form of dimer, octamer, or macromolecule complex. Dimers of creatine kinase inside the cytoplasm include the well-known CK-BB, CK-MB and CK-MM. Another isoenzyme, CK-Mt, exists within the intermembrane space of mitochondria and can be observed as dimers or octamers.[1]

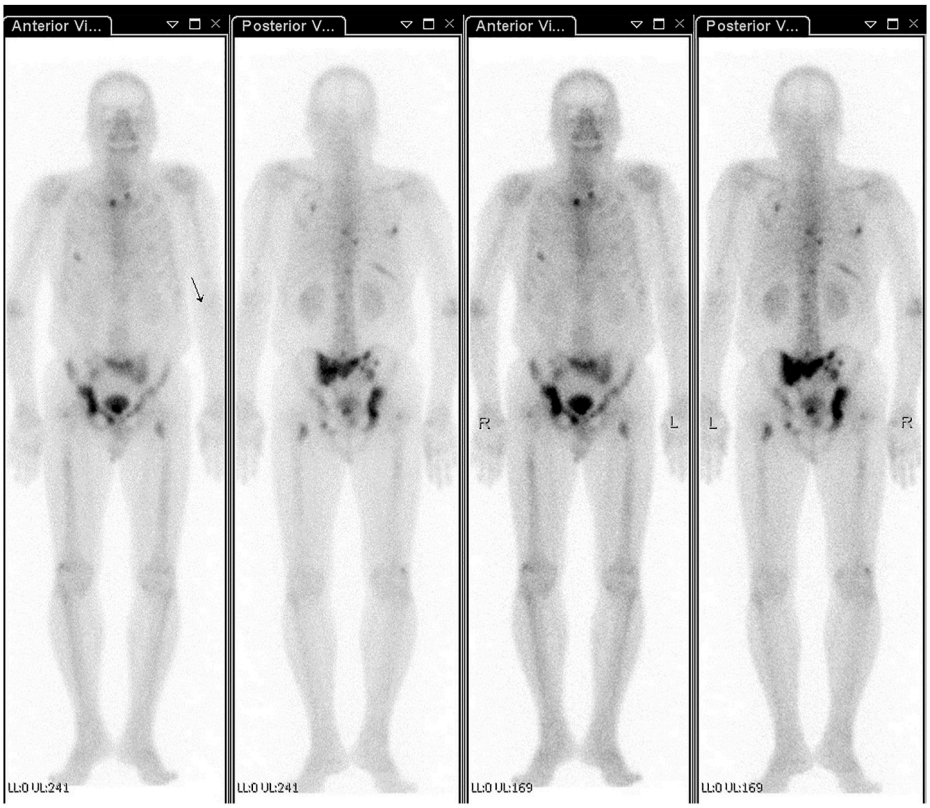

Fig. 2. Bone scan revealed multiple bone metastases at pelvic, sacrum and spin.

Occasionally, CK can be found in a macromolecular form (macro-CK) with two different types. Macro-CK type 1 consists of immunoglobulin and CK dimer, usually IgG and CK-BB; while macro-CK type 2 consists of oligomeric mitochondrial CK. Both types of macro-CKs are rare in prevalence.

The current measurement of CK is mostly based on its catalytic function converting creatine phosphate (CrP) to creatine (Cr).[3] As for CK isoenzyme detection, the most commonly used method is immunoinhibition.[3] This technique utilizes the anti-CK-M antibody, which selectively inhibits the M component of CK dimers in CK-MB and CK-MM. The remaining activities are all from B component. Considering no CK-BB or macro-CK in serum, the total activity of CK-MB can be calculated by multiplying the remaining activity by 2.[4] In our patient, a series of lab tests all showed higher levels of CK-MB than total CK, which indicated calculating errors with CK-MB measurement. The possible explanation of this was the presence of macro-CK molecules. These high-molecular complexes have reduced clearance and could not be inhibited by the anti-CK-M antibodies.[4] Since the assumption of CK-MB measurement (non-existence of CK-BB or marco-CK in the serum) was not met, the calculated CK-MB activity would be falsely elevated, causing diagnostic pitfalls.

Other methods can be used to avoid this situation. Electrophoresis appeared to be a preferred technique for detecting macro-CK existence (Fig. 3). With electrophoresis, we can separate the CK family into different bands on the agarose gel.[4] From the anode side, the first band found is CK-BB, followed by CK-MB and CK-MM. With the presence of macro-CK, type 1 complex will lie between CK-MB and CK-MM, whereas type 2 complex will be cathodal to MM.[2]

In previous studies, the prevalence of macro CK type 2 has been reported to be from 0.5 to 3.7% and cancer and liver disease.[1] Three case reports discussing about macro CK type 2 in metastatic prostate cancer were record.[3–5] The pathophysiology of marco CK type-2 existence in these conditions was not fully studied. One hypothesis is that the rich content of mitochondrial CK in liver will be released by dying and regenerating cells in liver disease and metastatic liver tumor.

In conclusion, creatine kinase level higher than normal limit is not always an indicator of coronary artery disease or connective tissue disease. Also, electrophoresis is the method of choice for detecting the composition of CK isoenzymes on account of false elevation of CK-MB level in the existence of macro CK with the immunoinhibition method. In the scenario of macro CK type 2, associated comorbidities such as liver cirrhosis and metastases should be included in clinical decision making.

Declaration of competing interest

No competing financial interests exist.

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