Extremely High CK-MB Levels Exceeding Total CK Levels in A Patient with Chest Pain：A Case Report

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Abstract

An 82-year-old man presented with left chest pain and was found to have an elevated creatine kinase MB (CK-MB) value greatly exceeding the total creatine kinase (CK) activity. Subsequent electrophoresis showed that creatine kinase MM (CK-MM) accounted for 100% of the total CK activity. Eventually, the patient was diagnosed with prostatic adenocarcinoma (stage D). His elevated CK-MB was most likely due to the presence of macro CK. It is important to be aware of different causes of CK isoenzyme elevation. When the patient's condition is not compatible with myocardial infarction, malignancy must be considered. (J Intern Med Taiwan 2003;14: 243-247)

Key Words：Creatine kinase, Creatine kinase MB, Acute myocardial infarction, Prostatic adenocarcinoma

Introduction

Commonly available tests to assess cardiac injury include creatine kinase (CK) and CK isoenzymes. The latter include CK-BB, which predominates in brain, prostate, gut, lung, bladder, uterus, placenta, and thyroid, and CK-MM, found in skeletal and cardiac muscle. CK-MB is present, to various degrees, in heart muscle (25% to 46% of CK activity) and also to a minor degree in skeletal muscle (<5%)1.Classically, an increase in the myocardial-specific enzyme CK-MB is considered the hallmark of acute myocardial infarction, and increased levels are frequently interpreted by the clinician as objective evidence of myocardial cell damage. However, increased CK-MB may be found in the absence of myocardial injury, notably when macro

creatine kinase or CK-BB is present in the plasma. These forms of the enzyme interfere with the immunoinhibition methods normally used in emergency room laboratories to measure CK-MB.

We present a patient with extremely high levels of CK-MB and discuss the approach to diagnosis, laboratory methods for the determination of CK-MB, and technical reasons for false positive elevations of CK-MB.

Case Report

An 82-year-old man came to the emergency department because of left chest pain of one day's duration. Myocardial ischemia was initially considered. The pain was unrelated to external pressure or movement, did not radiate to the jaw or back, and was not relieved by rest. The patient had noted nausea and poor appetite a few days earlier. He denied cough, fever, wheezing, dyspnea, hemoptysis, or weight loss.

He complained of nocturia (6 to 7/night), urinary frequency, and decreased caliber of the urine stream for several days. He also noted right flank soreness for a month. There was no history of urinary urgency. He had had a transurethral resection of the prostate gland (TURP) for benign prostatic hypertrophy at the age of 73.

He did not use alcohol, tobacco, or illegal drugs. There was no history of diabetes mellitus, hypertension, hyperlipoproteinemia, asthma, or chest trauma.

The patient's temperature in the emergency department was 37.4 ℃, the pulse was 104, the respiratory rate was 20, and the blood pressure was 142/61 mmHg. There were no skin lesions or lymphadenopathy. The head and neck were normal. The carotid pulses were full without bruits. The lungs were clear. The heart, abdomen, arms and legs were normal. There was punch tenderness of the right costovertebral angle.

The results of hematologic and other blood tests are shown in Table 1. The CK level was 964 U/L, the CK-MB level was 1205 U/L, and the aspartate aminotransferase level was 80 U/L. Serial enzyme values are shown in Figure 1.

An electrocardiogram showed a sinus tachycardia at a rate of 100 per minute. A chest radiograph revealed a configuration suggestive of hypertensive cardiovascular disease. A radiograph of the abdomen showed paralytic ileus and osteophytes of the lower thoracic and lumbar spine. Abdominal sonography revealed right hydronephrosis. The patient was admitted to the hospital because of right hydronephrosis, unexplained chest pain, and the extremely high levels of CK-MB. Electrophoresis revealed that CK-MM accounted for 100% of the total CK activity. An intravenous pyelogram showed right hydronephrosis and hydroureter to the right vesicoureteral junction. The prostate specific antigen was 821.1 ng/ml. Prostate sonography showed a heterogenous gland with an uneven capsule. A urodynamic

study revealed a low uroflow rate and the presence of residual urine. A bone scan revealed multiple foci of increased uptake in the skull, cervical and thoracolumbar spine, pelvis, ribs, sternum, scapulae, and femora. Based on these findings, the patient was operated on for prostate cancer and underwent TURP and bilateral orchiectomy for stage D adenocarcinoma of the prostate.

Discussion

CK activity is greatest in striated muscle, brain, and heart tissue. The active form of CK is a dimer composed of two subunits, so that only three different pairs of subunits can exist: BB, MB, and MM 1. CK activity may also be found in a macromolecular form called macro CK. It is often found transiently in up to 6% of patients, but only a small proportion of these have abnormal total CK activities. Macro CK exists in two forms, types 1 and 2. Type 1 is usually a complex of CK-BB and IgG, but other complexes have been described, such as CK-MM with IgA. Type 2 is an oligomeric mitochondrial CK with a reported prevalence between 0.5% and 2.6% 1.

The three major techniques for measuring CK isoenzymes are electrophoresis, ion-exchange chromatography, and immunologic methods. Electrophoresis is generally considered the most specific means of identifying the isoenzymes, but the presence of atypical macro-CK isoenzymes can lead to inaccurate results 2,3. Immunoinhibition is simpler and faster than immunoprecipitation and is more commonly used. In this method anti-CK-M antibody is used to inhibit both M subunits of CK-MM and the single M subunit of CK-MB, allowing determination of the enzyme activity of B subunits. Then the CK-MB value is computed by a doubling of the activity of the B subunits. If this is the technique used by a clinical laboratory to detect CK-MB, it must assume the absence of CK-BB or macro CK from the tested serum 1. This is a potential source of a false positive CK-MB. An elevated CK-BB may spuriously double the CK-MB. Furthermore, macro CK is not inhibited by antibodies to either CK-M or CK-B and thus can also cause spuriously high CK-MB values when using the immunoinhibition method 4,5. Electrophoresis of CK enzymes may be the best way to resolve problems with immunoinhibition 6.

The equipment used in our hospital for electrophoresis is the Rapid ElectroPhoresis unit (Rep R , Cat. No. 3078) from Helena Laboratories (Beaumont, Texas, USA). The Rep R is a totally automated electrophoresis system designed for high-volume and through-put analysis. The on-board computer controls sample application onto agarose gels, electrophoresis at various programmable voltages and currents, substrate application and incubation, drying, and precision densitometry 7.

The falsely elevated CK-MB in our patient was not related to CK-BB because electrophoresis revealed only CK-MM. Was CK-MM therefore the cause of his

falsely elevated CK-MB? Another possibility is macro CK (type 1 or 2), which may be difficult to differentiate from CK-MM on electrophoresis alone 8. In one electrophoretic system, the macro CK might appear to be distinct from CK-MM, while in another system, macro CK might migrate along with the CK-MM and easily be mistaken for it 9. We suspect this was the case in our patient and that he in fact had macro CK. We would need a suitable electrophoretic method that clearly demonstrates this unusual isoenzyme to confirm our impression 9.

Macro CK comigrating electrophorectically with creatine CK-MM can easily be unmasked by including an immunoprecipitation step before electrophoresis 8,10. The MM isoenzyme is removed first by precipitation with M-subunit-specific antibodies 10. Stein showed that detection of macro CK type 2 or exact identification of electrophoretic bands is only possible if two independent methods are applied in combination (e.g., electrophoresis and immunoinhibition or heat inactivation and activation) 11.

Macroenzymes are serum enzymes that have a higher molecular mass than the corresponding enzymes normally found in serum under physiologic or pathophysiologic conditions 12. There are many reports of prostatic cancer or other cancers with elevated CK-BB 2,4,13,14 or the presence of macro CK 10,12,15,16,17. Clinicians should consider the possibility of prostatic carcinoma or other cancers when elevated CK-MB is present in patients who fail to show clear-cut clinical evidence of AMI 18. At many hospitals, assays for both CK-MB and cardiac troponins are routinely ordered for all patients with acute chest pain. The assay for CK-MB is inexpensive, and serial measurements permit detection of reinfarction. Hence, CK-MB measurement is unlikely to disappear completely from diagnostic strategies for acute chest pain 13. The explanation for an increase in CK-MB, however, should be consistent with the clinical diagnosis and not simply equated to myocardial necrosis. We suggest that elevated CK-MB levels not consistent with the patient's condition be evaluated with electrophoresis, or better yet, with an immunoprecipitation step before electrophoresis. Immunoinhibition is the method of choice because of (a) the ease and rapidity of performance with automated instruments, (b) greater sensitivity than electrophoresis or a column procedure, (c) smaller sample size, and (d) lower cost per test 14.

Recognition that macroenzymes are one possible cause of elevated serum enzymes may help physicians avoid unnecessary invasive or costly procedures to investigate the abnormal enzyme levels 12. If macro CK is identified, underlying malignancy should be considered.

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肌酸激酉每同功酉每 MB 型(CK-MB)異常高且超過肌酸激酉每(CK)的胸痛病人：一病例報告

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摘　要

一位八十二歲男性主述胸痛，被發現肌酸激酉每 MB 型(CK-MB)異常升高，且超過肌酸激酉每(CK)值。肌酸激酉每同功酉每的電泳分析顯示爲百分之百的肌酸激酉每 MM 型(CK-MM)。這種現象可能是因爲出現了巨型肌酸激酉每(macro CK)，而導致檢驗時 MB 型的肌酸激酉每異常上升。巨型肌酸激酉每常與惡性疾病相關，最後這位病人被診斷出是 D 期攝護腺癌。因此了解造成肌酸激酉每同功酉每異常變化的原因相當重要，當發現此激酉每上升情況不符合常見的心肌梗塞時，惡性腫瘤必須列入鑑別診斷。

Table 1. Hematologic and biochemical values

Variable	Value
Hemoglobin (gm/dL)	10.6
Hematocrit (%)	31.5
MCV (fL)	88.7
White-cell count (per mm3)	6080
Neutrophils (%)	74.5
Platelet count (per mm3)	397k
Glucose (AC) (mg/dL)	101
Albumin (gm/dL)	2.6

ALT (U/L)	54/14
Bilirubin (T/D) (mg/dL)	0.4/0.1
Alkaline phosphatase (U/L)	280
BUN (mg/dL)	16
Creatine (mg/dL)	0.8
K (meq/L)	3.5
Na (meq/L)	137
Cl (meq/L)	106