

Review

Elevation of myocardial creatine kinase in absence of myocardial injury (Case report with literature review)

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Macro enzymes are high molecular mass complexes that consist of normal serum enzymes and protein-immunoglobulins. Creatine kinase (CK) is a muscle enzyme that has three isoenzymes. Two types of macro CK have been described; Macro CK type 1 and macro CK type 2. We report a case where cardiac enzymes were persistently elevated in the absence of myocardial injury. The false elevation was secondary to the presence of macro CK type 1 yielding aberrantly increased CK-MB. Our patient lacked clinical as well as electrocardiographic (EKG) changes to validate myocardial ischemia. Apperception of diagnosing falsely elevated cardiac markers is imperative to avoid unnecessary procedures

Key words: Macro CK, ischemia, myocardial infraction.

INTRODUCTION

The use of cardiac markers in the evaluation of myocardial injury is invaluable. However, interpretation of this data ought to be viewed in concert with the clinical picture and the electrocardiogram. Failure to acknowledge the significance of the conjunctive criteria of myocardial injury may lead the physician astray and may result in potentially unnecessary investigations. In our patient persistent elevation of CK was secondary to Macro enzymes CK type 1. Macro enzymes are high molecular mass complexes that consist of normal serum enzymes and protein-immunoglobulins. We report the presentation, work up in addition to literature review of the subject.

CASE PRESENTATION

We report a case of an 80-year-old African American female with a past medical history significant for coronary artery disease (with stent placement), moderate mitral valve regurgitation, diabetes mellitus, hypertension, and

dyslipidemia. The patient presented to our medical center complaining of shortness of breath and was subsequently found to be in congestive heart failure.

Her physical exam on admission was positive for bilateral rales, with an apical pansystolic murmur radiating to the axilla, an S3 gallop, jugular venous distension and bilateral pitting edema. The chest X-ray showed cardiomegaly with bilateral congestion. The patient's symptoms ameliorated after treatments with diuretics and vasodilators. The EKG showed a normal sinus rhythm at 87 beats per minute, with a left anterior fascicular block and non specific ST changes in the lateral leads that were present on a prior EKG. Admission labs showed: an elevated Brain natriuretic peptide (BNP) of 1200 pg/ml, as well as an elevated Creatine Kinase (482 IU/L) and CK-MB (132.9 IU/L) (The normal values in our laboratory using a Beckman Coulter Synchron are: CK <195 IU/L and CKMB < 9.5 IU/L) with a normal cardiac troponin I (0.02 ng/ml) (The cardiac troponin was measured using Siemens Healthcare Diagnostics, with a normal value lower than 0.05 ng/ml). Repeated measurement (The CK and CK-MB were measured at eight hour intervals) showed an increase of the CK and CK-MB (841 and 359 IU/L respectively), with normal levels of cardiac troponin I (< 0.05 ng/ml). The serum TSH was normal along with all other laboratory values.

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The 2-D echocardiogram showed: left ventricular hypertrophy with an ejection fraction of 35% (via fractional shortening) with global hypokinesia, Moderate Mitral regurgitation (vena contracta width of 0.2cm, regurgitant jet of 15% of left atrium area and a small central regurgitant jet area of 3 cm²), trace aortic insufficiency and mild tricuspid regurgitation (central jet area of 0.4 cm², the jet density was soft and parabolic and a hepatic vein flow that has systolic dominance). A Subsequent cardiac catheterization showed patent stents in the left anterior descending LAD and the right coronary arteries RCA.

We suspected a false elevation of the CK-MB due to the discrepancy between the laboratory findings and the clinical picture. Utilizing CK isoenzyme electrophoresis revealed Macro CK type 1 with an elevation of the CK-MM fraction and a normal CK-MB. We concluded that the erroneously elevated CK-MB was secondary to the presence of macro enzymes in the patient's serum. The clinical picture discrediting ischemia by the electrocardiogram and cardiac catheterization findings led us to further investigation. Thus, physicians should perceive the notion that erroneously elevated CK-MB is plausible secondary to the presence of macro enzymes.

DISCUSSION AND LITERATURE REVIEW

Despite the specificity of CK-MB, the aforementioned case serves to show that it can be misleading. This case is unique in that the patient underwent multiple tests in addition to a cardiac catheterization, all of which did not explain the elevated CK-MB. Furthermore, review of the literature on published CK-MB cases shows that the enzyme is minimally elevated, in comparison to this patient which had a CK-MB of 359 IU/L. Moreover, the CK-MB increased from 132.9 IU/L to 359 IU/L within 24 h of admission, while the cardiac troponins were within a normal range on serial tests. This rise further increased our suspicion of the presence of coronary artery disease.

The measurements of CK-utilizes an immunoinhibition method: the sample is incubated in the CK-MB reagent which includes the anti-CK-M antibody. The activity of the noninhibited CK-B is then determined using the following series of reactions:

ADP + Creatine Phosphate (via CK) → Creatine + ATP

ATP + Glucose (via HK) → ADP + Glucose-6-Phosphate

G-6-P + NAD⁺ (via G6PDH) → 6-Phosphogluconate + NADH + H⁺

CK-B catalyzes the reversible phosphorylation of ADP (adenosine diphosphate), in the presence of creatine phosphate, to form ATP (adenosine triphosphate) and creatine. The auxiliary enzyme hexokinase (HK) catalyzes the phosphorylation of glucose by the ATP

format, to produce ADP and glucose-6-phosphate (G-6-P) is oxidized to 6-phosphogluconate with the concomitant production of NADH. The rate of NADH formation, measured at 340 nm, is directly proportional to serum CK-B activity.

Macro enzymes are high molecular mass complexes that consist of normal serum enzymes and protein-immunoglobulins. Several types of macroenzymes have been reported, including macro creatine kinase (CK), macro lactate dehydrogenase (LDH), macro amylase, and macro aspartate transaminase (AST). They can be found in healthy individuals, but some cases are associated with malignancies and autoimmune disorders (Galasso et al., 1993). The presence of macroenzymes should be suspected when the elevated enzyme levels do not correspond with the clinical presentation.

Creatine kinase has three typical isoenzymes which are dimers of M and B chains that exist in three combinations: CK-MM (skeletal muscle), CK-MB (myocardium) and CK-BB (brain) (Bessman and Carpenter, 1985). These enzymes are cytosolic enzymes that help in the transfer of high energy phosphates in and out of mitochondria, thus helping in regeneration of cellular ATP. Each of these enzymes has a molecular weight of 80 kDa while the two atypical macro CK variants have a higher molecular weight of over 200 kDa which results in different electrophoretic and chromatographic mobility (Struk and Sanders, 1990; Wu et al., 1983).

Macro CK type 1 is CK (CK-MM or CK-BB) -Ig complex (Ruiz Ginés et al., 2006) and electrophoretically. It is the so-called anodal macro CK (migrates between CK-MM and CK-MB, but can still migrate to the position of either CK-MM or CK-MB according to the type of immunoglobulin complex (CK-IgG in the earlier and CK-IgA in the latter) (Tozawa, 1989), the most common combination is CK-BB with IgG. Macro CK type 2 is the so called cathodic macro CK which migrates cathodally to CK-MM and it represent oligomers of mitochondrial CK (Tozawa, 1989). On Gel filtration chromatography normal CK elutes coincidentally with albumin whereas macro CK elutes earlier. The two atypical types of macro CK (type 1 and type 2) can give false elevations of the CK-MB isoenzyme (Ruiz Ginés et al., 2006).

The presence of CK and CK isoenzymes in different tissues was previously described from biopsies taken from surgical patients. In one study, a total of 38 biopsies were obtained from 19 different tissues. After homogenization and centrifugation many tissues showed high CK catalytic concentrations. The highest specific activities were found in skeletal muscle (2400 U/g), brain (530 U/g), and myocardium (460 U/g). The separate isoenzyme activities were estimated by electrophoretic, anion-exchange chromatographic, immunoinhibiting, and radioimmunological methods. CK-BB was present in all tissues and, in fact, was the only cytoplasmic CK isoenzyme in 16 of the 19 tissues examined. The other isoenzyme CK-MM, was the major isoenzyme of skeletal

muscle and myocardium and was in addition observed in placenta, in trace amounts. Finally the results showed that CK-MB was present in high catalytic concentrations in myocardium (20% of total CK) and in low catalytic concentrations in skeletal muscle (1.1% of total CK) (Urdal et al., 1983).

Macro CK as a reason for high CK values has been known since 1979 (Strobel et al., 2003). The estimated prevalence of macro CK type 1 is 0.9-1.2% (Struk and Sanders, 1990), and is more common in older subjects and females (Struk and Sanders, 1990) but still it was detected even in apparently healthy individuals (Whelan and Malkus, 1983) and in pediatrics (Wu et al., 1983). Macro enzyme elevation has been reported in a 13-month-old baby with Kawasaki disease. In this case Kawasaki induced muscle tissue involvement that led to the presence of macro CK (Inoue et al., 1999).

Macro CK type 1 may arise as an immune autoreactivity phenomenon as a result of release of self antigens during cellular damage or due to molecular mimicry (Holmbergh and Coutinho, 1985; Guilbert et al., 1982).

Moreover, it has been reported more commonly with cardiovascular disease and myositis (Wu et al., 1983), however, sampling bias may be of concern in that setting. Other associations include autoimmune disorders, neoplasms, and hypothyroidism.

Furthermore the CK-antibody subclass may point to specific underlying diseases for example the incidence of CK-IgG but not CK-IgA complexes showed particular association with ulcerative colitis (Tozawa, 1989).

Macro CK type 2 prevalence is estimated to be 0.5-3.7% (Struk and Sanders, 1990), and is more common in patients with underlying malignancy, such as colonic carcinoma, and liver disease (Struk and Sanders, 1990; Laureys et al., 1991).

The diagnosis of macro CK is usually made by CK electrophoresis, immunoinhibition, and chromatographic techniques (Struk and Sanders, 1990). Macro CK usually causes small elevation (<500 IU/l) in CK or a high CK_{MB}/CK ratio without an elevation of the total CK. There have been reports of CK levels that exceed 12000 IU/l in the setting of macro CK. However, several of these patients were found to suffer from co-existent polymyositis (Laureys et al., 1991).

CONCLUSION

The diagnosis of acute coronary syndrome relies on history, EKG and cardiac markers. The cardiac markers are very helpful in aiding physicians in making a diagnosis of coronary artery disease. Physicians should be aware that these lab values could be invaluable when used appropriately. The utility of these markers should be used in conjunction with the clinical and EKG findings. The aforementioned case outlines the importance of recognizing false elevated cardiac markers in the absence of any pathology.

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