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False-Positive Elevation of Creatine Kinase MB Mass Concentrations Caused by Macromolecules in a Patient who Underwent Nephrectomy for Renal Cell Carcinoma

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Creatine kinase MB isoform (CK-MB) is a biochemical marker that is used to evaluate patients with suspected acute myocardial infarction. Rapid immunoassays to measure CK-MB mass concentration use various monoclonal anti-CK-MB antibodies, and these have been reported to be highly sensitive, specific, and free of interference [1].

Here, we report the first case of a false-positive CK-MB result (as determined by a mass assay) from a patient who underwent nephrectomy for renal cell carcinoma. A 78-yr-old man was admitted to the Urology department of Ilsan Paik Hospital in Goyang, Korea, for partial nephrectomy for the treatment of renal cell carcinoma. He developed dyspnea and tachycardia at three days after the surgery. The electrocardiogram revealed atrial fibrillation. CK-MB mass concentrations, CK activity, and N-terminal B-type natriuretic peptide (NT-pro-BNP) levels increased to 10.44 μg/L (reference range, <6.8 μg/L), 1,533 U/L (<171 U/L), and 15,927 ng/L (526 ng/L), respectively. However, the troponin I level was normal (Fig. 1). Acute myocardial infarction was suspected because CK-MB mass concentrations were increased; however, the results of the transthoracic echocardiogram and cardiac angiography were unremarkable.

During the week following admission, the patient's CK-MB mass concentration using CK-MB VIDAS test (Vidas-Biomerieux, Marcy-l'Etoile, France) increased to more than 300 μg/L. With sample dilutions, the results were not linear. Following heterophilic blocking tube (HBT) (Scantibodies Laboratory, Santee, CA, USA) treatment, no changes in CK-MB mass concentrations were observed. With Elecsys Creatine Kinase MB reagent (Roche Diagnostics, GmbH, Mannheim, Germany), the CK-MB mass concentration was found to be 6 μg/L (reference range, <6.73 μg/L). CK electrophoresis with a SPIFE CK Vis Isoenzyme Kit (Helena Laboratories, Beaumont, TX, USA) revealed only a creatine kinase MM isoform (CK-MM) band. 98.3% of the CK-MB mass concentration was decreased by polyethylene glycol (PEG) precipitation [2]. These results raised the possibility of the presence of macro-CK.

Macromolecules have been reported to have little to no influence on CK-MB mass assays [3]. Mass assays have previously been reported to be an effective method to exclude macro-CK interference in a CK-MB activity assay [4, 5]. However, our case demonstrated that macromolecules could falsely elevate CK-MB mass concentration, persisting for a minimum of four weeks.

It is particularly important to distinguish macro-CK from CK-MB to avoid unnecessary invasive procedures in patients with symptoms mimicking acute coronary syndrome. Our patient underwent relatively expensive and invasive procedures such as

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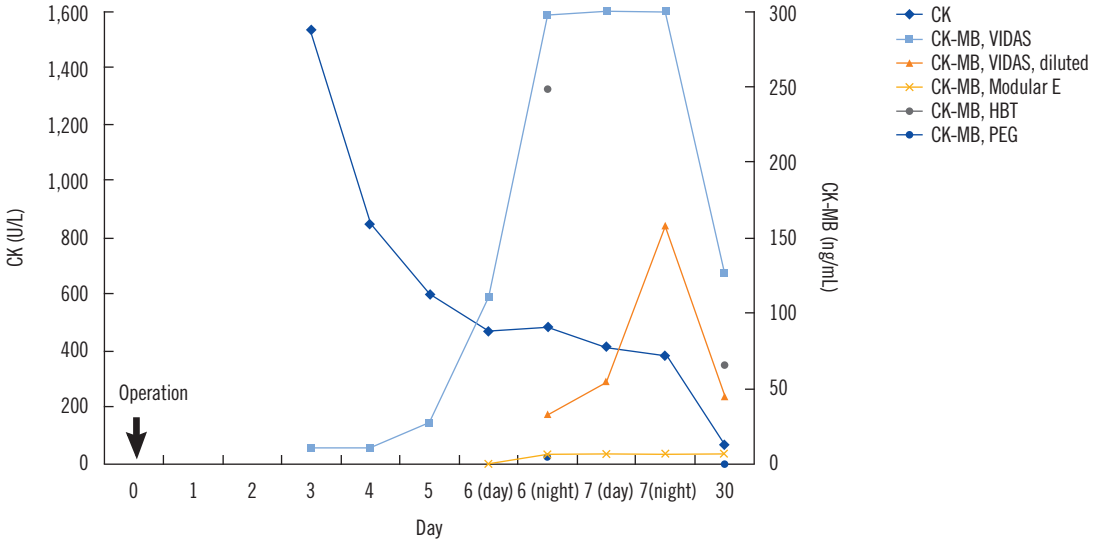

Fig. 1. Biochemical results of the patient. CK-MB mass concentrations and CK activity increased at three days after the surgery. However, troponin I level were normal, and the results of the transthoracic echocardiogram and cardiac angiography were unremarkable. During the week following admission, the patient's CK-MB mass concentration using CK-MB VIDAS test (Vidas-Biomerieux, Marcy-l'Etoile, France) increased to more than 300 μg/L, but the CK-MB mass concentrations with sample dilutions were not linear. 98.3% of the CK-MB mass concentration decreased by PEG precipitation. CK-MB mass concentrations using another immunoenzymatic reagent (Elecsys Creatine Kinase MB, Roche Diagnostics, GmbH, Mannheim, Germany) was within reference range.
Abbreviations: CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; HBT, heterophilic blocking tube; PEG, polyethylene glycol.

transthoracic echocardiography and coronary angiography. Thus, macroenzyme forms should be considered when the CK-MB result does not correspond with other cardiac markers or dilution test results, even when a mass assay is performed.

In our case, electrophoresis did not reveal any specific macro-CK band. During electrophoresis, macro-CK type 1 usually migrates between CK-MM and CK-MB but may also migrate at the position of CK-MM (CK-IgA complexes) [6]. Macro-CK type 1 is a complex form of one of the CK isoenzymes (CK-BB) and immunoglobulin (anti-CK-BB). This formation is not caused by an abnormal CK isoenzyme structure, but rather is the result of an antigen and autoantibody reaction. The binding site resides in either the Fab or $F(ab')_2$ fragment of the immunoglobulin molecule [6]. Gel filtration chromatography (GFC) is a confirmative test, but because of the lack of adequate sample volume, we were unable to perform GFC. The lack of GFC was a limitation in our study.

In our case, the discrepancy of results between two reagents would be explained by the specificity of the antibodies used in each assay format. The Roche test uses two monoclonal antibodies that specifically recognize the MB dimer. It is a chemiluminescence sandwich immunoassay using two monoclonal antibodies directed against human CK-MB (a biotinylated monoclonal anti-CK-MB antibody [mouse] and a monoclonal CK-MB-specific antibody [mouse] labeled with a ruthenium complex). The VIDAS CK-MB test is a sandwich immunoassay based on enzyme-linked fluorescence using one monoclonal and one polyclonal antibody (a monoclonal anti-CK-MB immunoglobulin [mouse] and an alkaline phosphatase-labeled anti-CK-MB polyclonal antibody Fab' fragment [goat]). The specific information of antibodies for anchoring the target antigen CK-MB is proprietary information of the manufacturer.

The macro-CK of our patient was thought to be formed from CK-MM and autoantibodies, which developed from muscle injury during the surgical procedure and malignant tumor, respectively. The macromolecule can interfere with CK-MB activity and the mass assay, causing false-positive results. Laboratory staff should always consider the possibility of the presence of macroenzyme forms in the following cases: 1) when a clinical feature does not correspond to the laboratory data, 2) when other cardiac markers such as troponin I do not correspond to the CK-MB results, and 3) when diluted samples do not produce linear results.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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