Misdiagnosis of Acute Myocardial Infarction*

VILDAN MANZO, M.D., TSIEH SUN, M.D., and YORK Y. LIEN, Ph.D.

Department of Laboratories, North Shore University Hospital-Cornell University Medical College, Manhasset, NY 11030

ABSTRACT

A total of 979 cardiac profiles were reviewed. Seventeen cases were found to have elevated CK-BB by electrophoresis and were misidentified by the immunoinhibition/immunoprecipitation technique as elevated creatine phosphokinase (CK-MB). Eleven of the 17 cases also had elevated lactate dehydrogenase (LD) LD-5/LD-1 ratio; five cases were motor vehicle accident (MVA), four cases were prostatic carcinoma (PC), and one case each of breast carcinoma and coronary heart disease. One case of PC and one of MVA with a preliminary clinical diagnosis of acute myocardial infarction (AMI) were presented. Our findings underscore the importance of electrophoretic confirmation of the presence of CK-MB when detected by a quantitative technique. Clinicians should consider the possibilities of PC or other cancers when elevated “CK-MB” is present in conjunction with a raised LD-5/LD-1 ratio in patients who fail to show clear-cut clinical evidence of AMI. The mechanism of elevated CK-BB and LD-5/LD-1 ratio in PC patients are discussed.

Introduction

Creatine phosphokinase (CK) and lactate dehydrogenase (LD) isoenzymes are usually included in the cardiac profile for the diagnosis of acute myocardial infarction (AMI) in most clinical laboratories. However, when the MB fraction of CK is quantified by an immunoinhibition/immunoprecipitation technique, a misdiagnosis of AMI may occur when CK-BB is elevated. In our prospective study of a large series of cardiac profiles, incorrect identification of CK-MB by the immunoinhibition/immunoprecipitation technique was not infrequently detected by electrophoretic confirmation testing. This paper presents various conditions in which false-positive CK-MB may be reported and the related changes in LD isoenzymes.

Materials and Methods

A series of 979 specimens submitted for cardiac profile testing were examined.
A total CK and LD were determined by spectrophotometric techniques as used in the SMAC system.* When CK and/or LD were elevated, corresponding isoenzymes were analyzed. The CK isoenzymes were quantified by an immunoinhibition/immunoprecipitation technique, Isomune CK† and by electrophoresis.‡ The LD isoenzyme analysis was performed by electrophoresis.‡

After false-positive CK-MB results were found in cases of prostatic carcinoma (PC), additional sera from patients with benign and malignant prostatic diseases were also collected for CK and LD isoenzyme studies. Twenty two normal sera were used as controls.

Results

Among the 979 specimens examined, false-positive CK-MB results were detected in 17 specimens, which were confirmed to be CK-BB by electrophoresis. Eleven of the 17 specimens also had elevated LD-5/LD-1 ratio. Among the 11 cases, there were four cases of PC, five cases of motor vehicle accidents (MVA), and one each of breast carcinoma and coronary heart disease. One case of lung carcinoma and three cases of lymphoma had elevated CK-BB but not LD-5/LD-1 ratio.

Further studies of patients with prostatic diseases revealed that 10 of 16 PC cases had significantly increased levels of CK-BB, ranging from five to 66 percent in their sera. The detection of CK-BB in four of 13 cases of benign prostatic hypertrophy (BPH) was within the two percent level. The difference between these two groups was statistically significant (P < 0.05). When a cut-off point of one was used for the LD-5/LD-1 ratio, 10 of 16 PC cases and none of BPH cases were positive. The difference between these two groups was statistically highly significant (P < 0.01).

Case Reports

Two cases illustrate false-positive CK-MB results found in a case of PC and a case of MVA.

Case 1

A 92-year-old white male presented with a chief complaint of chest pain and shortness of breath of two days' duration. The patient was admitted to the medical intensive care unit to rule out acute myocardial infarction.

The patient had transurethral resection of the prostate 18 years ago. One month prior to admission, he was admitted to another hospital because of congestive heart failure and found to have metastatic prostatic carcinoma.

On admission, the cardiac examination showed II-III/VI systolic murmur at apex. Chest roentgenograph revealed bilateral middle and lower lobe interstitial infiltration. Electrocardiogram demonstrated an ST depression in V4-6. Cardiac enzymes showed a total CK of 167 U/L (reference range 0 to 225 U per L), LD 1,038 U per L (reference range 60 to 200 U per L), aspartate transaminase 128 U per L (reference range 0 to 45 U per L), and alanine transaminase 48 U per L (reference range 0 to 45 U per L). Quantitation of CK-MB by an immuno-inhibition technique showed 16 U per L (reference range 0 to 10 U per L). However, CK isoenzyme study by electrophoresis revealed absence of the CK-MB band and presence of the CK-BB band (10 percent). The LD isoenzyme study by electrophoresis showed elevation of LD-5/LD-1 ratio, 3.3 (normal ratio: less than 0.3).

On the third hospital day, the patient no longer had chest pain, and his EKG returned to normal. Since the patient had a history of metastatic prostatic carcinoma, a serum prostatic acid phosphatase was performed; its value was 13.50 U/L (reference range 0 to 1.2 U per L).

Quantitation of CK-MB by an immuno-inhibition technique showed 16 U per L (reference range 0 to 10 U per L). However, CK isoenzyme study by electrophoresis revealed absence of the CK-MB band and presence of the CK-BB band (10 percent). The LD isoenzyme study by electrophoresis showed elevation of LD-5/LD-1 ratio, 3.3 (normal ratio: less than 0.3).

On the third hospital day, the patient no longer had chest pain, and his EKG returned to normal. Since the patient had a history of metastatic prostatic carcinoma, a serum prostatic acid phosphatase was performed; its value was 13.50 U/L (reference range 0 to 1.2 U per L).

During the hospital stay, the patient had another episode of chest pain. A chest x-ray at that time showed features of pneumonia. The patient was successfully treated with antibiotics and discharged eight days after admission.

Case 2

A 61-year-old white male was admitted to the hospital because of trauma owing to a motor vehicle accident.

---

* Technicon, Terrytown, NY.
† Roche Diagnostics, Nutley, NJ.
‡ Corning, Palo Alto, CA.
His past medical history was unremarkable except for an old myocardial infarction and hypertension. Physical examination on admission showed stable vital signs and tenderness along the left chest wall. His chest x-ray showed multiple rib fractures. The electrocardiogram was significant for a left bundle branch block. The features of an echocardiogram were consistent with an old inferior wall myocardial infarct. The laboratory test results were within normal limits except for the cardiac profile which revealed CK of 4,674 U per L, LD 472 U per L, aspartate aminotransferase (AST) 472 U per L and alanine aminotransferase (ALT) 162 U per L. CK-MB, as determined by an immuno-inhibition technique, was 28 U per L. However, electrophoresis demonstrated three percent CK-MB and six percent CK-BB band. In addition, LD isoenzymes showed elevation of LD-5/LD-1.

The patient's hospital course was uneventful and he was discharged five days after admission.

Discussion

Our study underscores the importance of electrophoretic confirmation of the presence of CK-MB when detected by a quantitative technique. Since electrophoresis is time-consuming, many clinical laboratories adopt the immunoinhibition/immunoprecipitation technique to quantify CK-MB.\(^{20}\) This technique is supposed to be highly specific for CK-MB and, indeed, several articles claimed that CK-BB did not interfere with the result of CK-MB; however, no patients’ sera with high CK-BB were included in those studies.\(^ {2,3}\) According to the manufacturer’s instruction, when total CK is greater than 400 U per L, CK-MB can be higher than the cut-off point of 12 U per L. In those cases, 3.5 percent of total CK becomes the cut-off point for CK-MB. Thus, high levels of CK-MB can be detected when total CK is very high. The manufacturer does not point out what the false-positive CK-MB represents. Our finding is that when CK-BB is elevated, such as in cases of PC, MVA and other tumors, the quantitative results will be mistaken as elevated CK-MB and the case misdiagnosed as AMI.\(^ {4,15}\) The simultaneous LD isoenzyme determination may challenge the diagnosis of AMI. However, LD isoenzymes can be normal in early AMI, and an elevation of LD-5 may be misinterpreted as hepatic congestion after AMI.\(^ {16}\)

It is interesting to observe in our study that, in most cases with false-positive CK-MB (11/17), LD-5/LD-1 ratio is also elevated. Although MVA apparently differs from AMI clinically, under certain circumstances, AMI must be ruled out as the predisposing factor of MVA. In cancer patients who are mostly elderly and frequently have chest pain and electrocardiographic changes, the distinction between cancers and AMI is obviously very important.\(^ {15}\)

Elevation of CK-BB has been reported in a great variety of neoplasms, especially in prostatic cancer.\(^ {4,9,14,15,16}\) The CK-BB is high in metastatic PC and in malignant pleural effusion; therefore, this isoenzyme is apparently derived from the tumor rather than the invaded tissue.\(^ {7,9,14}\) In fact, normal prostate tissue contains a high concentration of CK-BB.\(^ {18,19}\) In our study, serum CK-BB is significantly higher in cases of PC than those of BPH. Other studies have showed that CK-BB is elevated mainly in patients with metastatic PC, while changes in cases of BPH have not been studied.\(^ {5,6,10,16}\) In tissue analysis, there is no significant difference in the concentration of CK-BB between PC and BPH.\(^ {12}\)

This discrepancy may be explained by the fact that CK-BB is not released from normal tissue but from tumor tissue, especially when there is necrosis or metastasis.\(^ {1}\) One study showed that irradiation of normal tissue containing CK-BB did not raise serum CK-BB level, but radiotherapy to tumor tissue containing CK-BB resulted in high serum CK-BB.\(^ {12}\) This finding may support our explanation for the difference in CK-BB levels between PC and BPH cases.
The mechanism of elevated LD-5/LD-1 ratio in tumor tissue and the patient’s serum is related to the difference in the metabolic pathway between normal and tumor tissues. Tissues in which aerobic pathway predominates show a preponderance of LD-1. Neoplastic tissues usually shift toward anaerobic glycolytic pathway; therefore, the slow isoenzyme, LD-5, predominates. The sensitivity of using these isoenzymes as diagnostic markers for PC is controversial. One study showed that when both CK isoenzyme and prostatic acid phosphatase (PAP) were performed by radioimmunoassay, the former detected more cases of PC than that of the latter. Other authors found that the positive rate of CK-BB in cancer patients was too low to be a useful marker. The general consensus is that CK-BB is good only for the diagnosis of PC in stage D. The sensitivity of serum LD-5/LD-1 ratio for the diagnosis of PC is unclear, because there have been only a few reports concerning serum LD isoenzyme levels in cases of PC.

While not advocating the use of CK and LD isoenzymes as routine tests for the diagnosis of PC, clinicians should consider the possibility of PC when elevated “CK-MB” is present in conjunction with a raised LD-5/LD-1 ratio in patients who fail to show strong clinical evidence of AMI.

References


