Secretion of Creatine Kinase MB Isoenzyme by an Immature Teratoma with Predominant Rhabdomyosarcomatous Elements

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A 37-year-old man with metastatic immature (malignant) teratoma with prominent rhabdomyosarcomatous elements had markedly increased activity of creatine kinase (EC 2.7.3.2) MB in serum. There was no electrocardiographic evidence of infarction or ischemia, and autopsy revealed no myocardial infarction, significant coronary atherosclerosis, myocarditis, or invasion of the heart by tumor. A high proportion of the creatine kinase activity in a homogenate of the tumor was attributable to the MB isozyme. Persistent increases of creatine kinase-MB and an unusually high MB isoenzyme activity, out of proportion to total creatine kinase activity, may indicate a nonmyocardial origin of this isoenzyme.

Additional Keyphrases: cancer - tumor marker - lactate dehydrogenase - erythrocytes

An increase in the activity of the MB isoenzyme of creatine kinase (CK; EC 2.7.3.2) is considered to be highly specific for acute myocardial infarction. However, increases of CK-MB have also been reported in various noncardiac disorders, most notably diseases involving skeletal muscle (1, 2). Infrequently, increases of CK-MB have been associated with malignant neoplasms (3-8). The occurrence of increased CK-MB in patients with cancer is of considerable importance because, in these severely ill patients, concurrent conditions may produce signs, symptoms, or patterns of lactate dehydrogenase (LD; EC 1.1.1.27) isoenzymes that suggest myocardial infarction. Here, we report a case of recurrent metastatic immature (malignant) teratoma associated with increased serum CK-MB activity. CK-MB activity was demonstrated in a homogenate of the tumor, and there was no evidence of myocardial infarction.

Case Report

A 35-year-old man presented with a mass in the left anterior mediastinum that had been discovered on a routine chest roentgenogram performed as part of a pre-employment physical examination. Thoracotomy revealed that a 9-cm tumor mass had invaded the left upper lobe of the lung and encased the left phrenic nerve. The tumor was adherent to the ascending aorta, the pericardium, and the second and third left ribs. The left upper lobe and left phrenic nerve were resected along with the tumor.

Histologically, the tumor consisted of predominantly rhabdomyoblasts and undifferentiated spindle cells. Malignant cartilage, bone, nerve, and epithelial components were also identified. The diagnosis was immature (malignant) teratoma.

Postoperatively, the patient received chemotherapy with adriamycin, cisplatinum, VP-16, and bleomycin. He did well for two years after surgery, with no evidence of recurrence by clinical exam and computerized tomography (CT) scan. However, after two years, the patient developed lower back pain after slipping on ice. CT scans revealed a mass in the left thoracic wall, a left paraspinous mass, and a mass in the left acetabulum. He received radiation to the spine as well as chemotherapy with VP-16 and cisplatinum.

Three months later, 10 days after receiving doses of chemotherapeutic drugs, the patient became pancytopenic. He developed massive gastrointestinal bleeding, requiring multiple units of packed erythrocytes, fresh frozen plasma, and platelets. He developed cardiac dysrhythmias, which included supraventricular tachycardia and multifocal atrial tachycardia. Activities of total CK and total LD in his serum were increased, as were the CK-MB and LD-1 isoenzymes (Table 1), but there was no electrocardiographic evidence of infarction or ischemia. The patient died of sepsis a short time later.

Autopsy revealed a 6 × 4 × 1-cm tumor mass in the left chest wall. Tumor was also present in the adjacent diaphragm, visceral pleura, and pericardial remnant as well as the first four lumbar vertebrae. Histologically the tumor consisted predominantly of rhabdomyoblasts. It had not infiltrated or encroached upon the heart, and there was no evidence of myocardial infarction, significant coronary atherosclerosis, or myocarditis.

Materials and Methods

CK-MB was measured by an immunoextraction assay ("imack-MB"; International Immunoassay Laboratories, Santa Clara, CA 95054). This assay is calibrated in "equivalent units" (EU) per liter, 1 EU being equal to 5 IU enzyme activity units (U) of CK activity in this laboratory (9). Therefore, the percentage of CK-MB activity by the imack-MB is calculated as the CK-MB activity (EU/L) divided by the total CK (U/L) times 500%.

On selected samples, we also determined CK isoenzymes by agarose gel electrophoresis (Paragon CK; Beckman Instruments, Brea, CA 92621), being careful to avoid mistaking an atypical isoenzyme for CK-MB when interpreting the electrophoresis gels. To measure total CK and total LD we used the DACOS discrete analyzer and DAB reagents (Coulter Electronics, Hialeah, FL 33012). LD-1 was measured by immunoprecipitation (Isomune-LD; Roche Diagnostics, Nutley, NJ 07110).

Tumor (from the left chest wall) and ileopectus muscle (used as a negative control) tissues obtained at autopsy were frozen in liquid nitrogen and stored at -70 °C overnight. The tissues were thawed in a 37 °C water bath and homogenized in DACOS diluent. After centrifuging, we analyzed the supernates for total and isoenzyme activity of CK and LD. The protein content of the supernates was determined by using the cerebrospinal fluid protein packs in the aca III (Du Pont, Wilmington, DE 19898).
Table 1. Enzyme and Isoenzyme Activities in the Patient's Serum and Tissue Homogenates

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum CK, U/L</th>
<th>EU/L</th>
<th>%</th>
<th>LD-1, U/L</th>
<th>Electrolyophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MM, %</td>
</tr>
<tr>
<td>Autopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td>3.35</td>
<td>0.36</td>
<td>54</td>
<td>3.23</td>
<td>0.57</td>
</tr>
<tr>
<td>Muscle</td>
<td>17.5</td>
<td>0</td>
<td>0</td>
<td>3.73</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*Final admission. *U/mg of total protein. *EU/mg of total protein.

Discussion

In this case, the source of the increased serum CK-MB was the tumor, as was evidenced by the high proportion of CK-MB activity in the tumor homogenate as well as the absence of any other apparent source. There is no doubt that the substance detected was in fact CK-MB. The immunoextraction assay used has been shown to be free from interferences by CK-BB, mitochondrial CK, and adenylate kinase (EC 2.7.4.3) (10); further, the presence of CK-MB was confirmed by electrophoresis. Although the CK-MB percentage of total CK activity appears to be higher by the immunoextraction assay than by electrophoresis, this finding is consistent with previous correlations performed in this laboratory (9).

Increased serum CK-MB has been associated with rhabdomyosarcoma (3), mixed mesodermal tumor with a predominant rhabdomyosarcomatous component (4), small cell carcinoma of the lung (5, 6), poorly differentiated colon carcinoma (7), and prostatic carcinoma (8). However, CK-MB was demonstrated in tumor homogenate in only two of those six cases cited (5, 7). MM, MB, and BB isoenzymes were all present in the tumor homogenate of one small-cell carcinoma (5), whereas no MB and only a small percentage of BB were present in the tumor homogenate of the other small-cell carcinoma (6); the source of the increased serum CK-MB in the latter case remains obscure. Only MB and MM isoenzymes were demonstrated in the tumor homogenate of the colon carcinoma (7). Tumor homogenates were not studied in the three remaining cases. Interestingly, in the case of the colon carcinoma (7) and the case reported here, CK-BB was detected in the serum but not in the tumor homogenate. Bone marrow has been shown to contain CK-BB; therefore the presence of CK-BB in the serum of patients with metastatic cancer may be due to the release of the isoenzyme from the marrow when it is invaded by cancer rather than secretion of CK-BB by the tumor itself (11). Another pertinent observation is that detectable concentrations of CK-BB in serum are relatively common in all critically ill patients, presumably because the blood–brain barrier is in some way compromised (11).

Secretion of CK-MB by immature teratoma has not, to our knowledge, been reported previously. On the other hand, this immature teratoma, the mixed mesodermal tumor (4), and the rhabdomyosarcoma (3) are related in that all three tumors were composed of predominantly rhabdomyosarcomatous elements. The increased CK-MB in diseases such as polymyositis and dermatomyositis has been attributed to production of this isoenzyme by regenerating skeletal muscle fibers, presumably by some alteration in gene expression (2). It seems reasonable to suppose that a similar alteration in gene expression occurs in neoplastic muscle cells.

The major clinical importance of neoplastic production of CK-MB is that it may lead to an erroneous diagnosis of myocardial infarction. Clues to the nonmyocardial origin of CK-MB in this case were the persistent increase of CK-MB and the extremely high proportion of the MB isoenzyme in relation to the total CK. During the course of myocardial infarction, CK-MB peaks in 12–20 h, and returns to normal in two to three days (12). But in this patient's case, CK-MB remained increased for well over a week. In human heart, MB isoenzyme accounts for 14–42% of total CK activity (13). Therefore, a diagnosis of myocardial infarction should be suspect when CK-MB activity accounts for >42% of the total CK activity, as in this case.

Another potential source of confusion in this case was the increased LD-1. LD-1 represented a relatively small proportion of total LD activity in the tumor homogenate, and therefore it is unlikely that LD-1 secretion by the tumor could account for the increase of LD-1 in the serum. However, increased LD-1 is commonly seen in megaloblastic anemia (14). This patient's pancytopenia from chemotherapy is a likely explanation for the increased LD-1. The massive transfusions that the patient received also probably contributed to the concentration of LD-1 in his serum. LD-1, which accounts for a large fraction of the LD activity in erythrocytes, leaks out of these cells during the preparation and storage of blood products, such that serum LD-1 may be increased after a transfusion.

References

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