The Significance of Creatine Kinase (CKBB) in Metastatic Cancer of the Prostate

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ABSTRACT

Alterations of serum creatine kinase isoenzymes were observed in five cases of prostatic carcinoma. Creatine kinase isoenzyme BB was found in the serum of two of three cases with metastases. Its presence in serum does not seem to be related to acid phosphatase activity but seems associated with extension of the tumor to other tissues. Preliminary studies on effusions from patients with malignant and non-malignant prostates showed that CK-BB was detectable only in cytology positive effusions. This finding suggests that CK-BB may be a tumor product rather than a result of a host response. The observation of CK-BB in a significant percentage of patients (two of three) with metastatic carcinoma of the prostate is of interest and suggests that CK-BB isoenzymes may have some predictive value in following patients with malignant disease.

Introduction

During the past several years, it has become apparent that certain cancers synthesize special protein moieties which circulate in the serum and which may be particularly helpful in detecting and staging certain tumors (table I). These biologic markers may also help identify early recurrence of the tumor and monitor the efficacy of various therapeutic modalities. The recent development of sensitive and specific methods to measure these proteins in the serum of patients with certain cancers makes it possible to use these tumor products as markers for the presence of neoplasm. The very recent report of an electrophoretically distinct form of serum galactosyltransferase (GT-II), predominately in patients with colorectal carcinoma, and a correlation with overall extent of tumor is of great interest.

In 1964, the enzyme creatine kinase (ATP: creatine phosphotransferase, EC 2.7.3.2) was added to the rapidly increasing group of enzymes which can appear in multiple molecular form. The soluble fractions obtained from different tissues generally show one to three electrophoretically distinguishable creatine kinase isoenzymes. In addition to the cytoplasmic creatine kinases, one additional form exists in mitochondria from
Several tissues have been observed with metastatic carcinoma of the prostate, whose serum contained markedly increased amounts of CK-BB isoenzyme. This report discusses the potential value of this tumor marker in the diagnosis and follow-up of patients with prostatic cancer.

Materials and Methods

The work of Eppenberger et al has shown that creatine kinase (CK) is a dimer. Each protomer may be of the muscle type (M) which is electrophoretically slow (at an alkaline pH) and moves on cellulose acetate electrophoresis toward the cathode or a brain type (B) which is the fast fraction and moves toward the anode. The hybrid MB isoenzyme exhibits electrophoretic migration on cellulose acetate corresponding to an intermediate position (figure 1). After separation, creatine kinase isoenzymes are located by a tetrazolium dye (NBT) after coupling the CK reaction with hexokinase and glucose-6-phosphate reactions. The hydrogen ions necessary for reduction of the NBT dye come from the reduction of NADP, in the presence of glucose, creatine phosphate, ADP and Mg2+. AMP is added in order to inhibit the adenylate kinase reaction.

An electrophoresis apparatus and cellulose acetate strips were used with the latter system according to the manufacturer’s instructions. Relative isoenzyme activities were then quantitated. A control specimen containing all three CK isoenzymes was determined with each electrophoretic run. Total creatine kinase activity was measured and assayed with a

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* Beckman Model 100 Microzone.
† Beckman Model 111 Microzone Computing Densitometer.
‡ Ortho Diagnostics.
Gilford Model 3400 Discrete Analyzer§ using CK reagents (cysteine hydrochloride-activated). Total acid phosphatase and prostatic acid phosphatase activity were determined using a p-nitrophenol phosphate substrate¶ and a fast parallel analyzer,** both in the presence and in the absence of 0.04 mol tartrate ion per l.

Results

In table II are shown the results of CK isoenzyme assays on serum from patients with biopsy proven prostatic cancer. Of the five patients studied, one (JK) had markedly elevated CK-BB fractions (figure 2) and demonstrated widespread metastases (lung, bone) at autopsy. Two other patients (CB and EL) demonstrated increased total CK (normal, 4 to 50 U per liter) and the absence of a definitive BB band. The remaining subjects (AA and RK) had borderline elevated total CK and in the case of patient (AA) the CK-BB fraction approximated 17 percent. The latter patient on autopsy showed extension of the carcinoma to bladder and rectum. Patients JK and AA did not have their brains examined for metastatic tumor. All of the subjects studied had elevated total acid phosphatase (normal, 0 to 9 U per liter) as well as prostatic acid phosphatase (normal, 0 to 4 U per liter). These findings were demonstrated in consecutive assays on all patients.

Discussion

Evidence is accumulating that serum CK-BB is detectable or increased in a wide variety of clinical circumstances, even with techniques that are less sensitive than RIA, CK-BB has been reported in renal failure,8 Reye’s syndrome,18 malignant hyperthermia,1 myopathy,12 neuropathy,12 pregnancy and the peripartum period.14

In prostatic carcinoma, CK-BB was found in the serum of two of five cases. The observation of CK-BB in a significant percentage of patients with highly invasive carcinoma of prostate (metastatic) is of interest and, along with the report of Feld and Witte,6 suggests that CK-BB

<table>
<thead>
<tr>
<th>Patient</th>
<th>ACP-T</th>
<th>ACP-P</th>
<th>Total CK</th>
<th>CKMM</th>
<th>CKMB</th>
<th>CKBB</th>
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<tbody>
<tr>
<td>JK§</td>
<td>86</td>
<td>69</td>
<td>480</td>
<td>0</td>
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<td>100</td>
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<tr>
<td>CB (lung)</td>
<td>29</td>
<td>22</td>
<td>97</td>
<td>100</td>
<td>0</td>
<td>0</td>
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<tr>
<td>EL (bone)</td>
<td>12</td>
<td>7</td>
<td>129</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AA (bladder, rectum)</td>
<td>33</td>
<td>25</td>
<td>64</td>
<td>83</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>RK</td>
<td>14</td>
<td>5</td>
<td>52</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Total acid phosphatase (EC 3.1.3.2)
†Prostatic acid phosphatase
§Distant metastases
isoenzymes may have some predictive value in studying patients with neoplastic diseases. These findings suggest a correlation of serum CK-BB with extent of cancer. Some patients with both circumscribed and extensive prostatic carcinoma also demonstrated no detectable serum CK-BB. This finding may be related to differences in the biology of the tumor or response of the host rather than extent of the disease. Alternatively the inability to detect CK-BB in some patients with prostatic carcinoma may reflect the presence of an inhibitor. Indeed, the presence of a CK inhibitor has recently been detected in the serum of a patient with Reye’s Syndrome and Bruns has reported low apparent creatine kinase activity and prolonged lag phases in serum of patients with metastatic disease.

Hoag has studied prostatic tumor homogenates and shown an increased proportion of CK-BB. Several of these cases demonstrated CK-BB in the serum. Preliminary studies on effusions from patients with malignant and non-malignant prostates showed that CK-BB is detectable only in cytology positive effusions (Table III). This finding suggests that CK-BB may be a tumor product rather than a result of host response.

The presence of CK-BB in serum of patients with prostatic cancer and in the tissue homogenates and effusions from patients with malignant disease suggests some degree of specificity that may be of eventual use in diagnosis and treatment of patients with metastatic prostatic disease. Various cancerous tissues and metastatic malignancies demonstrate unusual isoenzymic modifications. Aldolase B (liver type) is decreased in hepatoma; aldolase A (muscle type) is decreased in spleen reticulosarcoma. The “M” type lactate dehydrogenase predominates in cancerous tissues and an “H” type has been found in some hepatomas. Several metastatic prostatic tumors have been shown to exhibit an increased serum and tissue level of CK-BB. A common feature of these modifications is their fetal-like pattern which may be an expression of dedifferentiation at a molecular level, characterized by the repression of synthesis of the most specific form of the tissue enzyme.

References

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**TABLE III**

<table>
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<th>Type</th>
<th>Serum CK-BB</th>
<th>Effusion CK-BB</th>
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<tbody>
<tr>
<td>Benign disease (4)*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology positive (1)*</td>
<td>100</td>
<td>2+</td>
</tr>
<tr>
<td>Cytology negative (4)*</td>
<td>0</td>
<td>0</td>
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*Number of patients studied.
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