Transient Increase in Serum Creatine Kinase Isoenzyme BB Activity after Prostatectomy in a Patient with Massive Benign Prostatic Hyperplasia

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The activity of creatine kinase isoenzyme BB (CK-BB) in serum is rarely abnormally high (i.e., detectable). An increase in immunoreactive CK-BB or CK-BB activity in patients with prostatic disease has been proposed as an indication of prostatic adenocarcinoma. Here we report the case of an elderly man with massive benign prostatic hyperplasia but no clinical or pathological evidence of prostatic adenocarcinoma, whose serum CK-BB activity was found by agarose gel electrophoresis to be 1 U/L (normal: 0%), 10% of his total CK activity. Serum CK-BB activity was further increased to 16 U/L (20% of total CK activity) 1 h after prostatectomy, but became undetectable by the second day after the operation. The findings suggest that: (a) the source of the serum CK-BB activity was the enlarged prostate gland; (b) abnormally high CK-BB activity in serum of men with prostatic disease does not necessarily indicate the presence of prostatic adenocarcinoma; and (c) myocardial injury could be erroneously diagnosed postoperatively in prostatectomy patients if CK isoenzyme methods are used that do not consistently separate "heart-specific" CK-MB from CK-BB.

Determination of serum creatine kinase (EC 2.7.3.2) isoenzymes is widely used as a diagnostic test, primarily because creatine kinase isoenzyme MB (CK-MB) activity in serum increases after an acute myocardial infarct (1). Creatine kinase isoenzyme BB (CK-BB) has also been reported to be increased in the serum of patients with various conditions, including gastric, pulmonary, and prostatic tumors (2–7). Recently, Silverman et al. (7) found increased serum CK-BB by radioimmunoassay in 15 of 17 patients with untreated prostatic carcinoma; nine of the 15 patients' sera also showed above-normal CK-BB activity on agarose gel electrophoresis. In contrast, only six of 75 patients with benign prostatic hypertrophy showed above-normal immunoreactive CK-BB in their sera. On this basis, they proposed that increased serum immunoreactive CK-BB and CK-BB activity in patients with prostatic disease may be useful as a tumor-associated "marker" for prostatic carcinoma.

Here we report a patient with massive benign prostatic hyperplasia, whose serum showed CK-BB activity by agarose-gel electrophoresis. In addition, a further transient increase in CK-BB activity just after prostatectomy was followed by its decrease to non-detectable (normal) activity. The implications of the case for interpretation of serum CK-BB activity in patients with prostatic disease and for selection of CK isoenzyme methodologies are discussed.

Clinical History

An 83-year-old man presented with a one-year history of intermittent grossly visible, total, painless hematuria. After four days of massive hematuria with passage of clots, he was admitted to The Johns Hopkins Hospital. At this time his hematocrit was 17. His prostate was so markedly enlarged as to prevent cystoscopy. Serum (prostatic) acid phosphatase (EC 3.1.3.2) activity, as measured with the thymolphthalein-substrate method (8), was normal on two occasions. Suprapubic cystostomy showed the bladder mucosa to be normal, and the source of bleeding was identified to be the large intravesical prostate. Twelve days later, a retropubic prostatectomy was performed. The resected prostate weighed 290 g and, microscopically, hyperplasia and focal infarcts with associated squamous metaplasia could be seen. No carcinoma was found. Because of the patient's age, serial specimens of serum were collected for total CK and CK isoenzyme assay, although there was no clinical or electrocardiographic evidence of acute myocardial injury.

Methods

Blood for serum was collected by venipuncture, and the separated serum was stored at 4 °C until CK and CK isoenzyme determinations. Total CK activity was measured at 30 °C by use of a 12-min fluorimetric kinetic assay (Statzyme CPK-1; Worthington Biochemical Corp., Freehold, NJ 07728) based upon the Rosalki–Oliver method (9, 10), with a centrifugal analyzer (Centrifichem; Union Carbide Corp., Rye, NY 10680). The upper limit of normal for total CK in our laboratory is 50 U/L. Isoenzymes were determined with the Creatine Phosphokinase (CPK) Isoenzyme Reagent Kit (Beckman Instruments, Inc., Fullerton, CA 92634). The kit procedure involves agarose gel electrophoresis followed by incubation of the gel with overlay paper wetted with reconstituted reagent containing the constituents for coupling conversion of creatine phosphate to creatine with hexokinase (EC 2.7.1.1) and glucose-6-phosphate dehydrogenase (EC 1.1.1.49) for NADH production. Relative percentages of the CK isoenzymes were determined by fluorometric scanning of the overlay paper. Detected CK-MB activity is normally 4 U/L or less; CK-BB is normally undetectable (11). We used a reaction mixture lacking creatine phosphate to exclude non-enzymic reduction of NAD+ as a source of apparent enzyme activity.

Results

Table 1 summarizes the total CK and CK isoenzyme activities in serum during the interval of one day before to four days after prostatectomy. Total CK activity was 11 U/L the day before operation, and CK-BB activity of 1 U/L was detected by fluorometric scanning. The specimen drawn 1 h after prostatectomy had total CK activity of 80 U/L with CK-BB of 16 U/L, 20% of the total (Figure 1). Total CK activity had reached 108 U/L 18 h after operation but CK-BB had greatly

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Alternative designations for CK isoenzymes are: CK1 = CK-MM, CK2 = CK-MB, and CK3 = CK-BB.

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Table 1. Serum CK and CK Isoenzyme Activities in This Patient

<table>
<thead>
<tr>
<th>Day</th>
<th>Total CK acty (&lt;50 U/L)</th>
<th>CK-MM acty (normal)</th>
<th>CK-MB acty (&lt;5 U/L)</th>
<th>CK-BB acty (normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0†</td>
<td>80</td>
<td>60</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>+1‡</td>
<td>108</td>
<td>105</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
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<td>75</td>
<td>73</td>
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<td>+3</td>
<td>32</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+4</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Day of surgery designated day 0.
† Upper limit of normal in parentheses.
‡ Specimen collected 1 h after completion of prostatectomy.
§ Specimen collected 18 h after completion of prostatectomy.

declined, to 1 U/L. By the third day after the operation, total CK activity was within normal limits and CK-BB activity was no longer detectable. CK-MB activity showed a slight increase, to 4 U/L, in the specimen collected 1 h after surgery but was still within normal limits in this and all other specimens assayed. When the agarose gel, after electrophoresis, was incubated with reagent lacking creatine phosphate, the gel showed no fluorescent bands.

Discussion

Although his total serum CK activity was low before the operation, this patient with marked benign prostatic hyperplasia had serum CK-BB activity detectable by agarose gel electrophoresis. The prostate gland has been shown to contain CK-BB (7). Also, the increase in serum CK associated with surgical manipulation of the prostate and the subsequent disappearance of serum CK-BB activity after removal of the markedly enlarged gland provide additional evidence that the prostate was the source of the CK-BB activity. In the study by Silverman et al. (7), nine of 15 patients with prostatic carcinoma and increased immunoreactive CK-BB also had increased CK-BB activity by agarose gel electrophoresis. Unfortunately, the serum CK-BB activity of their six patients with benign prostatic enlargement and increased immunoreactive CK-BB was not tested by electrophoresis. Although the incidence of occult prostatic carcinoma is very high in elderly men (12), our patient had increased serum CK-BB activity without any pathological or clinical evidence of prostatic carcinoma. Thus, this patient provides evidence that increased serum CK-BB activity in patients with prostatic disease does not necessarily indicate the presence of clinically significant prostatic carcinoma.

The case also has implications for the selection of CK isoenzyme methods to be used by clinical laboratories. Of the currently available methods, only electrophoresis consistently separates the isoenzymes (13). With column-chromatographic techniques, CK-MM and CK-BB may not be separated from CK-MB (14). Also, the immunological techniques in which anti-MM antibodies are used to inactivate the M subunit leave un-neutralized the B-subunit activity of both CK-MB and CK-BB (14). Further, immunoassay techniques in which anti-BB antibodies are used can detect B-subunit of both CK-MB and CK-BB (14). Consequently, in post-operative patients who have undergone prostatectomy, such as the one reported here, an erroneous diagnosis of myocardial injury could be made as a result of misinterpretation of CK-BB or CK-MM as CK-MB, if the method used does not consistently separate these isoenzymes.

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References