Prostatic Acid Phosphatase: Clinical Utility in Detection, Assessment, and Monitoring Carcinoma of the Prostate

ALEX A. PAPPAS, M.D.
and RICHARD H. GADSDEN, Sr., Ph.D.

Department of Laboratory Medicine,
Medical University of South Carolina,
Charleston, SC 29425

ABSTRACT

Prostatic carcinoma is a significant cause of male cancer death. The majority of cases present as incurable disease. The measurement of acid phosphatase has served to confirm clinically suspected disease and staging. The immunochemical methods have increased clinical sensitivity and specificity in detecting curable occult or confined disease, but not significantly so as to warrant mass screening. Prostatic acid phosphatase remains a test for confirming clinical staging of prostatic carcinoma and a response factor to therapy at present.

Introduction

Prostatic carcinoma is the third most common malignancy in males. It is the second most common cause of cancer death in males over the age of 55. In 1983 there will be an estimated 73,000 new cases and 23,000 prostatic cancer deaths.

Prostatic carcinoma is frequently called the pathologist's carcinoma in that it is often found as an occult malignancy at autopsy or in the course of a routine transurethral prostatectomy (TURP). This incidence of occult carcinoma is in direct proportion to the age of the patient at this demise and to the thoroughness for which the malignancy is searched at autopsy. The autopsy incidence increases from approximately 10 percent at age 50 to approximately 40 percent at age 80 or at a rate of one percent per year. The actual clinical incidence is much less; it is 0.2 percent at age 50, increasing to 0.8 percent at age 80. Thus, it appears there might be two different types of prostatic carcinoma: one of very low malignant potential which may never manifest itself clinically and one which early on fulfills the biologic and clinical criteria of malignancy.

Discussion

Prostatic carcinoma is most often an adenocarcinoma arising in the acinus of the gland, usually being multifocal or extensive in most cases. The carcinoma tends to be in the periphery of the gland in contrast to benign prostatic hyperplasia (BPH) which tends to localize to the periurethral center of the gland.
Prostatic carcinoma is a malignancy which is hormonally dependent upon the action of androgens, primarily dihydrotestosterone, but the hormones are not considered to play a primary role in the pathogenesis of the malignancy. Benign prostatic hyperplasia, although hormonally dependent, does not predispose towards malignancy.

Various clinical staging classifications are presently used which may or may not be comparable (table I). The American Urological Society (AUS) has defined four clinical stages which have been subsequently subdivided. Stage A is occult malignancy and stage B is localized within the prostatic capsule. Both stage A and stage B malignancies are potentially curable. Unfortunately, intracapsular malignancy presents clinically in less than 20 to 25 percent of cases. Most prostatic carcinomas present as locally invasive—Stage C—or as metastatic stage D disease. The overall survival is inversely correlated with the extent of the disease (table II). The clinical symptoms of advanced disease, stages C and D, may be urinary obstruction, bone pain, and/or a hard nodular prostate on rectal examination. These findings are present in over 50 percent of cases. The five to 10 year survival has been correlated with the clinical stages. The best survival is with intracapsular disease and the worst obviously with metastatic disease.

In initial staging, lymphatic metastases may have occurred and may not be recognized clinically. This would then reclassify initial intracapsular stage A or B or extracapsular C to a metastatic stage D category. The frequency of lymphatic metastases and initial staging appears to correlate even better with the overall survival (table III). The clinical stage of prostatic carcinoma dictates the therapy.

Beginning with the original reports by the Gutmans, serum acid phosphatase (ACP), in fact, the first described tumor marker, has been a valuable adjunct in the diagnosis and management of prostatic carcinoma. It became readily apparent with clinical experience that ACP determinations are neither entirely sensitive in detecting early prostatic carcinoma nor specific for prostatic carcinoma. There has been an evolution in the various methods for the analysis of ACP in regards to analytical specificity and sensitivity of the prostatic fraction of ACP culminating with the present immunoassays.

The acid phosphatases are a group of phosphohydrolases which hydrolyze phosphoric monoesters in an acidic medium. In prostatic epithelium, the major role of ACP is not known. In prostatic fluid, these ACPs are concerned with metabolic activity of spermatozoa by catalyzing the transfer of phosphates. In the normal prostatic epithelium, there is an orderly process of secretory product synthesis. In BPH and with carcinoma, there is a decrease in the amount of PAP secreted per cell but an increase in overall PAP production because of the overall increase in cellular mass.

Various isoenzymes of serum acid phosphatase have been identified. These isoenzymes have been conveniently classified as to being tartrate sensitive (the

### Table I

<table>
<thead>
<tr>
<th></th>
<th>Whitmore</th>
<th>Vacury *</th>
<th>AUS</th>
<th>AJC UICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I</td>
<td>A1</td>
<td>T0N0M0</td>
<td>T0N0M0</td>
</tr>
<tr>
<td>II</td>
<td>II</td>
<td>A2</td>
<td>N1M0</td>
<td>N1M0</td>
</tr>
<tr>
<td>III</td>
<td>III</td>
<td>B1</td>
<td>N2M0</td>
<td>N2M0</td>
</tr>
<tr>
<td>IV</td>
<td>IV</td>
<td>B2</td>
<td>N3M0</td>
<td>N3M0</td>
</tr>
</tbody>
</table>

*Veterans Administration Cooperative Group.
†American Urological System.
‡American Joint Commission/International Union Against Cancer.
§T = tumor; N = nodes; M = metastasis
TABLE II

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Physical Findings</th>
<th>Clinical Incidence Percent</th>
<th>Estimated Prevalence Percent</th>
<th>Adjusted Survival Percent*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Negative rectal focal tumor</td>
<td>10</td>
<td>15</td>
<td>100-95</td>
</tr>
<tr>
<td>A2</td>
<td>Negative rectal diffuse tumor</td>
<td>1</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>B1</td>
<td>Nodule &lt;1.5 cm or &lt;1 lobe (diffuse)</td>
<td>10-15</td>
<td>25</td>
<td>65-15</td>
</tr>
<tr>
<td>B2</td>
<td>Nodule &gt;1.5 cm or &gt;1 lobe (diffuse)</td>
<td>1</td>
<td>25</td>
<td>65-15</td>
</tr>
<tr>
<td>C1</td>
<td>No involvement of seminal vesicles &lt;70g</td>
<td>40</td>
<td>35</td>
<td>55-30</td>
</tr>
<tr>
<td>C2</td>
<td>Involvement of seminal vesicles &gt;70g</td>
<td>40</td>
<td>35</td>
<td>55-30</td>
</tr>
<tr>
<td>D1</td>
<td>Pelvic lymph node involvement or urethral obstruction</td>
<td>40</td>
<td>25</td>
<td>20-10</td>
</tr>
<tr>
<td>D2</td>
<td>Distant lymph node or bone involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Five to ten years.

prostatic fraction, PAP) or tartrate resistant (the non-prostatic fraction). The tartrate sensitive fraction, which is supposedly specific for the prostatic fraction of total acid phosphatase, is also found in leukocytes, platelets, and other tissues. Normally the prostatic fraction constitutes only 10 to 25 percent of the total serum acid phosphatase found in males, while the platelet fraction constitutes the majority of the remaining fraction.26,41

Elevations of PAP in patients with prostatic carcinoma are due to an actual increase in tumor mass, loss of ductal connections, tissue necrosis, and neovascularization with subsequent leakage of the enzyme into the circulation. Regional lymphatic spread and distant metastases may establish independent sites of enzyme secreting tumor. Parenthetically, nonelevations of PAP may be explained by poorly differentiated malignancies which have little activity, nondetection by the analytical method used, potential inactivation of the enzyme, tumor barrier, or concomitant hormonal, radiation or chemotherapy.12,14,16,33,40

With the potential of increased sensitivity and specificity using radioimmunoassay (RIA), the probability of detecting (screening) intracapsular prostatic carcinoma became a potential reality.12 However, this initial enthusiasm has waned considerably.10 In comparing the clinical sensitivity (positive test (p)/presence of disease (d)) of PAP in detecting non-invasive prostatic carcinoma, there is a wide range of sensitivities ranging from 12 to 33 percent in occult stage A disease and eight to 79 percent in intra-capsular stage B disease (table IV). There appears to be a general increase in sensitivity as the extent (stage) of disease increases. Stages C and D disease, however, are quite often evident clinically by either rectal exam or by a suspicious history. Measurements of PAP in stages C and D disease are usually only confirmatory of the disease and are usually indicative of the probable extent of the disease. The overall sensitivity of PAP determination by radioimmunoassay for all stages is approximately 50 percent. The various nonisotopic immunoassays appear to have comparable clinical sensitiv-
TABLE IV
Clinical Sensitivity in Detecting Prostatic Carcinoma by Clinical Stage
Percentage Positive (%) - Positive Test/Presence of Disease (P/D)

<table>
<thead>
<tr>
<th>Quinones</th>
<th>Mahan</th>
<th>Bruce*</th>
<th>Griffiths</th>
<th>Griffiths</th>
<th>Foti **</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>8-(1/12)</td>
<td>26-(9/16)</td>
<td>29-(11/38)</td>
<td>32-(13/41)</td>
<td>40-(10/25)</td>
<td>79-(26/33)</td>
</tr>
<tr>
<td>D</td>
<td>52-(14/27)</td>
<td>63-(20/32)</td>
<td>88-(36/41)</td>
<td>76-(19/25)</td>
<td>92-(23/25)</td>
<td>78-(174/222)</td>
</tr>
</tbody>
</table>

It is now evident that the use of PAP in screening the asymptomatic patient is not warranted because of the relatively low sensitivity in detecting stage A, or even stage B disease, when coupled with the relatively low prevalence of prostatic carcinoma. Even the screening of higher risk groups — older men and negroes — does not increase the predictive value of a positive test. It has been suggested that baseline levels may be drawn on an individual patient and subsequently followed periodically. Although the decision level may not be reached, any upward change from the baseline value may be significant for the individual patient.

In BPH, elevations of PAP are observed in the various immunoassays: RIA, 10 percent; enzyme linked immunosorbent assay (ELISA), 30 percent; and EIA, six percent. Possible etiologies for the observed PAP elevations in this benign process are: prostatic manipulation, cytolysis of acinar cells, cellular hyperplasia with a concomitant overall increase in enzyme secretion or indeed an occult malignancy which has not been clinically detected.

It is interesting that elevations of PAP...
CARCINOMA OF THE PROSTATE

Prostatic Acid Phosphatase (PAP)-Elevations in Benign Prostatic Hypertrophy (BPH)

Percent Elevations-(Number Positive Tests/Total Number Patients)

<table>
<thead>
<tr>
<th>RIA</th>
<th>ELISA</th>
<th>EIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poti12</td>
<td>6-(2/36)</td>
<td>Cooper9</td>
</tr>
<tr>
<td>Quinones32</td>
<td>9-(2/22)</td>
<td>Davies11</td>
</tr>
<tr>
<td>Griffiths16</td>
<td>9-(19/213)</td>
<td>Davies11</td>
</tr>
<tr>
<td>Griffiths17</td>
<td>20-(17/84)</td>
<td>Davies11</td>
</tr>
</tbody>
</table>

Cumulative 10-(46/423) 31-(39/140) 6-(4/68)

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<th>TABLE VII</th>
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Summary

The newer immunochemical methods are more analytically sensitive and specific. The sensitivity in detecting clinically occult and curable disease has increased, but not significantly enough to warrant using PAP as a screening procedure. The rectal exam remains still the most effective screening procedure. The increased analytical sensitivity has resulted in observed elevations of PAP in the presence of clinically evident BPH. An elevated PAP with a negative rectal exam and prostatic biopsy places the physician in a dilemma as to resolving whether or not occult malignancy indeed exists. This question of “false positive” PAP is yet to be resolved clinically. The presence of PAP elevation is non-pros-
tactic malignancies is of interest and generally indicates a secretory type of malignancy which is elaborating a protein similar in antigenic qualities as PAP. Prostatic acid phosphatase remains a response factor in monitoring the progression or regression of clinical disease and confirmation of initial clinical disease.

References


