Sustained, Substantially Increased Concentration of Prostate-Specific Antigen in the Absence of Prostatic Malignant Disease: An Unusual Clinical Scenario

WILLIAM J. GLENSKI, B.A., Mayo Medical School; REZA S. MALEK, M.D., Department of Urology; JAMES F. MYRTLE, Ph.D., Boehringer Mannheim Corporation, Indianapolis, Indiana; JOSEPH E. OESTERLING, M.D., Department of Urology

A 60-year-old man had a persistent, marked increase in the serum concentration of prostate-specific antigen (more than 20 times the upper limit of the reference range) and no identifiable prostatic malignant involvement. To our knowledge, this is the first such case reported in the literature. Possible explanations for this increased value are described, and nonmalignant conditions that can increase serum concentrations of prostate-specific antigen are reviewed.

Prostate-specific antigen (PSA) is a serine protease that was isolated from prostatic tissue by Wang and associates in 1979. This unique glycoprotein is specific for and produced by all types of prostatic epithelial tissue—normal, benign hyperplastic, and malignant. Since the initial identification and characterization of this prostatic marker, numerous researchers have investigated the clinical properties of serum PSA values. An increased serum PSA concentration was found to have greater sensitivity for prostatic cancer than an increased value of serum prostatic acid phosphatase—the previous "standard" serum marker for prostatic malignant involvement. Thus, serum PSA has primarily replaced serum prostatic acid phosphatase in the diagnosis and management of prostatic cancer. Currently, serum PSA is widely accepted in clinical practice as the most useful tumor marker for prostatic malignant disease.

With increased clinical experience and basic science research, however, the usefulness of serum PSA has been further refined. In addition to adenocarcinoma of the prostate, many nonmalignant conditions such as benign prostatic hyperplasia, acute and chronic prostatitis, and prostatic infarction can increase the serum PSA concentration. Prostatic intraepithelial neoplasia, presumed to be a premalignant disorder, also has been associated with mildly increased serum PSA levels. Additionally, some instrumentation, such as cystoscopy and selected manipulations of the prostate (namely, prostatic massage and biopsy), can transiently increase the serum PSA value. The exact extent of these changes in the serum PSA concentration is still under investigation.

Herein we describe a patient with a sustained, substantially increased serum PSA concentration who had no evidence of prostatic malignant involvement. To our knowledge, this is the first such case reported in the medical literature.

REPORT OF CASE
A 60-year-old man was referred to the Mayo Clinic because of persistently increased serum PSA values. Three months before admission, during a routine annual examination, the patient's serum PSA level was 95 ng/ml (normal range, 0.0 to 4.0 ng/ml). (This and all subsequent serum PSA values were determined with the Tandem-R PSA assay, Hybritech Incorporated, San Diego, California.) This concentration was determined after a digital rectal examination showed normal findings; serum PSA was measured again 1 month later with no intervening rectal examination. The second serum concentration was 156 ng/ml (Table 1). The patient...
then underwent transrectal ultrasonography of the prostate and radionuclide bone scanning, both of which had normal results. Nevertheless, the patient underwent transrectal ultrasound-guided biopsy of the prostate, and the biopsy specimens exhibited only benign prostatic hyperplasia; no malignant involvement, prostatic intraepithelial neoplasia, acute or chronic prostatitis, or ischemic changes consistent with prostatic infarction could be identified.

At the time of referral to the Mayo Clinic, the serum PSA value determined before physical examination was 99 ng/ml. The only symptoms relating to the genitourinary tract were mild nocturia and a mild decrease in the force and caliber of the urinary stream. Results of physical examination were unremarkable; digital rectal examination revealed a smooth, soft, nontender, moderately enlarged prostate. Results of urinalysis and urine culture also were negative.

Because of the substantially increased serum PSA concentration, transrectal ultrasonography was repeated; no abnormalities were identified. Nevertheless, a transrectal ultrasound-guided biopsy of the prostate was conducted; six cores of tissue, three from each lobe, were removed and examined in their entirety. All contained tissue characteristic of only benign prostatic hyperplasia; again, no other pathologic conditions were identified.

On reassessment 3 months later, the patient had no notable change in history or results of physical examination. The serum PSA concentration determined before physical examination was again increased—98 ng/ml. Computed tomography of the abdomen and pelvis disclosed a prominent, asymptomatic right seminal vesicle and a moderately enlarged prostate. A saccular aneurysm of the distal abdominal aorta, 4.2 cm in maximal diameter with normal-caliber proximal iliac arteries, also was identified. Transrectal ultrasonography of the prostate showed a moderately enlarged (30- to 40-g) gland with a small (6-mm), nonspecific, hypoechoic area in the apex. Transrectal ultrasound-guided biopsy of the prostate, with use of the 7.5-MHz biplanar transducer, was performed again, and 12 cores of tissue were removed: 3 through the hypoechoic area, 3 from the left lobe, 3 from the right lobe, and 3 from the anterior transition zone of the prostate. Pathologic evaluation of all specimens demonstrated only benign prostatic hyperplasia; no prostatic malignant involvement, prostatitis, or prostatic infarct was evident. The stromal:epithelial ratio was 50:50. On subsequent follow-up, the patient’s serum PSA concentration remained increased but stable; no physical, radiographic, or histologic evidence of prostatic cancer was found.

**DISCUSSION**

PSA is produced exclusively by the epithelial cells that line the acini and ducts of the prostate gland; any condition that disrupts the cell-to-cell architecture within these acini and ducts can allow the PSA to “leak” into the prostatic parenchyma. Then, PSA can enter the lymphatic and capillary system and increase the serum PSA concentration. Adenocarcinoma of the prostate gland can often cause such a prostatic change and concomitantly increase the serum PSA value. Although the serum PSA level is not increased in every case of prostatic malignant disease, numerous investigators have demonstrated a strong association between increasing serum PSA values and advancing tumor stage. The upper limit of the serum PSA concentration in a patient with prostatic adenocarcinoma is not established, but values into the thousands of nanograms per liter have been noted.

Many common nonmalignant prostatic diseases also can disrupt this cell-to-cell architecture and cause a sustained increase in the serum PSA concentration. In a study of 357 men with histologically confirmed benign prostatic hyperplasia, Ercole and colleagues found that 21% had increased serum PSA values (greater than 4 ng/ml), and 3% had serum PSA levels of more than 10 ng/ml. In a British study of 40 men with pathologically confirmed benign prostatic hyperplasia, 33% had a serum PSA concentration of more than 10 ng/ml (the highest was 80 ng/ml). Thus, these and other studies have shown that benign prostatic hyperplasia can cause a sustained mild increase—and occasionally a substantial increase—in serum PSA concentration.

Prostatitis, both acute and chronic, also has been shown to increase the serum PSA value. In a study of 30 men with chronic prostatitis, Robles and co-workers found that the serum PSA levels ranged from 0.2 to 11.8 ng/ml (mean ± SD, 2.88 ± 3.24 ng/ml). In 50 men with acute prostatitis, these same authors noted that the serum PSA concentrations ranged from 0.2 to 124 ng/ml (mean ± SD, 18.09 ± 33.01 ng/ml). Prostatic infarction, although certainly less common than prostatic cancer or benign prostatic hyperplasia, also has been shown to cause a sustained increase in serum PSA value.

Prostatic intraepithelial neoplasia is characterized by an increased proliferation and dysplasia of the epithelial cells

---

<table>
<thead>
<tr>
<th>Date (mo/yr)</th>
<th>Serum PSA concentration (ng/ml)</th>
<th>Serum PSA measured before DRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 1990</td>
<td>95</td>
<td>No</td>
</tr>
<tr>
<td>May 1990</td>
<td>156</td>
<td>Yes</td>
</tr>
<tr>
<td>July 1990</td>
<td>99</td>
<td>Yes</td>
</tr>
<tr>
<td>September 1990</td>
<td>98</td>
<td>Yes</td>
</tr>
<tr>
<td>January 1991</td>
<td>101</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*DRE = digital rectal examination; PSA = prostate-specific antigen.

---

Table 1. _Increased Serum Concentrations of Prostate-Specific Antigen in a Patient Without Prostatic Malignant Disease*

<table>
<thead>
<tr>
<th>Date (mo/yr)</th>
<th>Serum PSA concentration (ng/ml)</th>
<th>Serum PSA measured before DRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 1990</td>
<td>95</td>
<td>No</td>
</tr>
<tr>
<td>May 1990</td>
<td>156</td>
<td>Yes</td>
</tr>
<tr>
<td>July 1990</td>
<td>99</td>
<td>Yes</td>
</tr>
<tr>
<td>September 1990</td>
<td>98</td>
<td>Yes</td>
</tr>
<tr>
<td>January 1991</td>
<td>101</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*PSA = prostate-specific antigen.
that line the lumen of the ducts of the prostate gland. Many investigators consider this condition a premalignant change that has been closely linked to adenocarcinoma of the prostate gland. Prostatic intraepithelial neoplasia, either alone or in conjunction with benign prostatic hyperplasia, has been associated with a mildly increased serum PSA concentration. 

Brawer and associates meticulously analyzed the surgical specimens from 81 men who had undergone simple prostatectomy and compared the pathologic findings with the preoperative serum PSA concentration. Prostatic intraepithelial neoplasia was identified in 25 of the patients (31%), and the median PSA value for these men was 4.0 ng/ml (range, 0.3 to 22.3 ng/ml). In 52% of these patients, the serum PSA levels were 4.0 ng/ml or more. Benign prostatic hyperplasia was found in 26 patients, and the median preoperative serum PSA concentration in these men was 2.1 ng/ml (range, 0.3 to 47 ng/ml). Only one patient (4%) had a serum PSA value of 4.0 ng/ml or more. Thus, patients with prostatic intraepithelial neoplasia frequently have minimal to moderate increases in serum PSA concentrations. Few patients with simple benign prostatic hyperplasia in the absence of carcinoma, prostatic intraepithelial neoplasia, or acute inflammation had increased serum PSA levels.

Our patient had no evidence of malignant involvement, premalignant changes, prostatitis, or prostatic infarction. Although he did have a moderate amount of benign prostatic hyperplasia, the gland was not so enlarged as to cause such a substantially increased serum PSA value. Thus, other possibilities for this increase must be explored.

One etiologic explanation is that the patient could have occult adenocarcinoma of the prostate—primary, metastatic, or both. The frequency of unsuspected adenocarcinoma of the prostate can be considerable. In cystoprostatectomy specimens from patients with cancer of the bladder and no clinical evidence of prostatic malignant disease, the incidence of adenocarcinoma ranged from 38 to 61%. Similarly, in a study of fine-needle aspiration of the prostate in 64 patients, 17 (27%) who previously had negative results of core-needle biopsy had adenocarcinoma on the basis of results of a subsequent fine-needle aspiration (Markham CW: Personal communication). Most of these patients also had an increased serum PSA concentration. In our patient, however, 18 cores of tissue were obtained from both the peripheral and the transition zones of the prostate during a 3-month period. Unless the malignant tumor is located most anteriorly and extremely high in the transition zone, the presence of adenocarcinoma is unlikely. The fact that the serum PSA values are not increasing is consistent with the absence of malignant involvement.

A second explanation for this sustained, appreciably increased serum PSA concentration without an identifiable malignant lesion could be prostatic infarction. Typically, it manifests with hematuria; on biopsy, squamous metaplasia of the tubuloacinar structures may be noted. These obvious findings, however, were not evident in our patient.

A third potential explanation is that in some patients who undergo catheterization procedures for heart disease, a “borderline prostatic ischemia” can apparently develop, possibly attributable to the dislodging of atheromatous plaques (Markham CW: Personal communication). This condition has been correlated to a prostatic abnormality with a subtle, fallen-apart appearance. Like prostatic infarction, this condition could disrupt the cell-to-cell architecture as a result of ischemia; this outcome would allow PSA to escape the acini and ducts of the prostate gland and enter the serum. Conceivably, in a patient who has an abdominal aortic aneurysm, as our patient did, dislodged atherosclerotic emboli could occlude the vessels that supply the prostate gland. Such an event could result in the typical prostatic infarction. If, however, such a patient had sufficient collateral circulation to overcome most but not all of this obstruction, “borderline prostatic ischemia” (as described by Markham) could occur.

A fourth possible explanation is that other tissues, either benign or malignant, within our patient were producing PSA that contributed to the increased serum value. In an autopsy study of the urachal remnants of 25 persons (15 women and 10 men), Golz and Schubert found that 4 (16%) had immunostaining results that were positive for PSA. Similarly, in a study of unusual urinary bladder mucosa, Deldetsima and associates reported six cases of prostatic-type epithelium. In all six cases, the bladder mucosa contained PSA, as evidenced by immunohistochemical staining. Thus, perhaps tissue that is not located specifically in the prostate gland can produce and express PSA.

A fifth etiologic explanation might derive from the fact that serum PSA is a serine protease and, as such, it exhibits important sequence homology (35 to 67%) to several other serine proteases, including kallikrein, trypsin, chymotrypsin, tonin, epidermal growth factor-binding protein, and the α and γ subunits of 7S nerve growth factor. Therefore, if one of these proteins were present in high concentrations in the serum, theoretically it could cross-react with the antibodies in the PSA assay and be measured; however, the two-site design of the Tandem-R PSA assay, which uses two specific monoclonal antibodies, makes this result technically unlikely. No cross-reactivity to these or other antigens has been reported to date. In addition, numerous immunologic studies were performed, both at the Mayo Clinic and at Hybritech Incorporated, to verify that the reaction was due to PSA in the serum and not to some other heterophil or non-specific cross-reacting agent. These studies support the conclusion that the glycoprotein being measured is indeed PSA.
Finally, perhaps the cell-to-cell architecture within our patient's prostate gland is not as "tight" as in the "average" prostate gland. Such a lack of cohesiveness between the epithelial cells that line the acini and prostatic ducts could result in more PSA being allowed to "leak" out of the prostate and subsequently being detected in the serum as an increased PSA value, even though the prostate gland itself was completely free of cancer.

CONCLUSION

Although many investigators consider PSA the best available tumor marker for adenocarcinoma of the prostate gland, some limitations to our understanding of its clinical application remain. In addition to overt prostatic malignant involvement, several other conditions (such as benign prostatic hyperplasia, prostatic intraepithelial neoplasia, prostatitis, and prostatic infarction) can increase the serum PSA value. Some less common and more subtle disorders, such as the proposed "borderline prostatic ischemia," may also increase the serum PSA concentration. Further research, at both the clinical and the basic science levels, is necessary to understand more completely the clinical characteristics of serum PSA. As our knowledge of this serum marker increases, practicing physicians will be able to use it in the most effective manner possible when managing patients with suspected prostatic disease.

REFERENCES