Brief Report

Elevated Prostate-Specific Antigen: A Case Report and Analysis

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Prostate cancer is a frequent concern of the clinician caring for older male patients. The certainty of arriving at the correct diagnosis is related to the presenting patient's risk for prostate cancer, the results of the digital rectal examination, and the value of the serum prostate-specific antigen (PSA). A case report of a patient with acute urinary retention and an elevated PSA is presented. Possible explanations for the elevated PSA are discussed. The clinician's intuitive thought process is compared with an analytic approach using calculated probabilities. Several factors that complicate the estimation of the likelihood of prostate cancer are discussed.

Key words. Prostate; prostatic hypertrophy; prostatic neoplasms; infarction; decision analysis. (*J Fam Pract 1993; 37:284-288*)

The practicing clinician is routinely involved with complex decisions. Decision analysis enables the physician to clarify this process. The discussion of the case below includes one clinician's thoughts and actions when he was presented with findings that suggested prostate cancer.

In the following discussion, the case presentation appears in boldface type, the physician's thinking in italics, and the literature analysis in regular type.

Mr F. was a 74-year-old white man in good health who had not seen a physician for 20 years. He presented with severe generalized abdominal pain, weakness, urinary urgency, and frequent urinary dribbling (his only urinary output for the past 3 to 4 days). He complained of thirst and an orthostatic near syncopal sensation. When the patient was asked about fluid intake, he said that he had been avoiding fluids because of the urinary frequency and urgency. All other physical examination findings were normal except for a large suprapubic mass. A digital rectal examination (DRE) of the prostate revealed a uniformly enlarged gland without induration or tenderness.

A Foley catheter was inserted, and approximately 2000 mL of cloudy urine was drained from the bladder, resulting in the resolution of the mass and abdominal pain. At the time of initial evaluation, the patient's BUN level was 23 mg/dL and his creatinine level was 2.6 mg/dL. The urinalysis indicated pyuria, and a urine culture grew *Klebsiella pneumoniae*.

Dehydration resulting from fluid restriction and benign prostatic hypertrophy with outlet obstruction best fit the patient's presenting symptoms. After the catheterization, it is clear that outlet obstruction is the cause of the pain. Secondary urine infection or obstruction uremia may explain the malaise. Furthermore, the sudden onset of obstruction would strongly favor a prostatic cause. Benign prostatic hypertrophy is highly likely, but prostatitis and prostate cancer are a concern because of obstructive symptoms and age. A negative rectal examination should rule out cancer in most men with these other prostate problems.

The renal insufficiency should resolve with bladder decompression. I would send this patient with bladder obstruction to a urologist because of the likelihood of bladder obstruction recurring at some point. The patient's meeting with the urologist at this time provides an opportunity to discuss therapeutic options for obstructive prostatic hypertrophy. Having

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this low threshold for referral to the urologist is dependent on the confidence I have that the urologist will follow a plan of action that I feel is appropriate.

The behavior of urologists with regard to the treatment of benign prostatic hypertrophy (BPH) has been subject to significant variation, and policies to arrive at a urologic consensus are pending.[1,2] Family physicians are aware of significant physician variation between urologists' practices because they observe the actions of consultants when presented with similar clinical situations. Awareness of this variation and then choosing a consultant who is acceptable to both the patient and the family physician is one of the most important components of the referral and consultation relationship.

Does the presence of urologic symptoms increase the risk of prostate cancer? Urologically symptomatic patients frequently have prostatic biopsies to rule out prostate cancer as a cause of the symptoms. Urologically asymptomatic patients may have screening tests but usually do not have prostatic biopsy. The failure to perform prostatic biopsy will cause the asymptomatic patients to appear as having a lower incidence of prostate cancer (increase in false-negative rate). Only one small (N = 73) study has reported on the incidence of prostate cancer for urologically asymptomatic men who were all subjected to prostatic biopsy (23%).[3] This is similar to urologically symptomatic patients undergoing biopsy (24%), and patients having transurethral resection of the prostate (27%).[4,5]

Mr F.'s DRE was found to be negative. The true-positive rate (sensitivity, or likelihood that a patient with cancer has prostatic induration) and true-negative rate (specificity, or likelihood that a patient without prostate cancer will not have prostatic induration) for the DRE in the general population is disputed. The sensitivity is reported to be from 69% to 86%.[4,6–8] When interpreting DREs, the subjectivity of the examiner's determination of normal will vary. If the examiner includes minimally suspect prostates in the group of abnormal DREs, then there will be a greater number of false positives (abnormal DRE with negative biopsy), and specificity will suffer. Specificity is 44% when 60% of the DREs are considered abnormal and all patients have had biopsies performed[8] (large numbers of false positives), to 96% when only 6% of DREs are considered abnormal and 13% have had prostate biopsies.[7]

The rate of detection of prostate cancer is dependent on the prevalence (number of men with prostate cancer divided by the population of men being considered) of prostate cancer and the methods used to detect the cancer. A point of confusion is that the detection of cancer is much lower than the prevalence of cancer. The rate of detection will increase with the number of patients who have microscopic examination of the prostate. The greater the number of biopsies, the more likely prostate cancer will be discovered.[7,9,10] When a group of urologically symptomatic men were all subjected to prostatic biopsies, 24% were found to have prostate cancer.[4] Although the results of a prostatic needle biopsy is the "gold" standard for confirming prostate cancer,[7] prostate biopsy carries a 1.5% risk of complication.[10]

The true prevalence of prostate cancer in patients like Mr F. (which includes all stages) should be the same as the rate of prostate cancer found in autopsy studies. Patients in their 70s have an incidence of 29% in several autopsy studies.[11] The likelihood of *detecting* prostate cancer in Mr F. will be much lower than 29% unless the prostate is removed and sectioned for histologic evaluation.

In this report there is no attempt to discuss the importance of finding prostate cancer. For a discussion of whether diagnosing prostate cancer will decrease mortality or morbidity, see Mettlin,[7] Mold,[12] and Johansson.[13] For the purposes of this report, it is assumed that all cancers found are important (including stage A). Some clinicians would argue that microscopic cancer (A1) is not important because they believe it will remain asymptomatic and fail to become disease. Most A1 prostate cancers found at the time of transurethral resection, biopsy, or other histologic examination may progress, but still remain clinically latent throughout the patient's life.[11] Some clinicians would reason that the true-positive rate is scientifically too high for those studies that include microscopic prostate cancer.

Most experienced clinicians intuitively formulate pre- and post-test probabilities of disease with each new piece of information, whether it is a symptom, sign, or test result. It is unusual, however, that the clinician will actually calculate a probability.[14] Personal experience has shown that not only is the clinician reluctant to explicitly state a probability, but these estimations do not accurately reflect the clinician's actions. Clinical confidence in the assessment and plan of action is a manifestation of a narrow range of probabilities when evaluating a clinical situation. As clinicians attain greater experience and knowledge about a particular test, their ability to utilize the test should improve.[15] Experience alone, without an accurate knowledge of outcome, does not ensure improvement in the accuracy of probabilities.[16] The wise clinician will come to rely heavily on a certain set of data for each disease process while ignoring data that the novice physician might carefully evaluate. This is described as the "art" of medicine.

Aware of the significant discrepancies in the sensi-

tivity and specificity of the DRE and the prevalence of cancer in Mr F.'s age group, Bayes' theorem is used to estimate the probability of prostate cancer after the negative DRE, which is reported to be 6% to 22%.[17]

Because of concern for prostate cancer as a cause of the outlet obstruction, a prostate-specific antigen (PSA) test was ordered. The PSA result was 232 ng/mL; an upper normal limit is 4 ng/mL.

The PSA finding of 232 ng/mL is obviously sky high. Prostate cancer with widespread metastasis certainly needs to be ruled out, but with such a large tumor burden, wouldn't the prostate have obvious induration? My experience with a PSA value this high is limited. Am I unaware of other important, though benign, causes for an elevated PSA? If I had not previously sent Mr F. to the urologist, I would certainly do so now for further evaluation of prostate cancer.

Increasing confidence has been expressed in the literature on the correlation between the serum PSA value and the presence of prostatic cancer. In this case, the clinical impression was that the greater the abnormality of the test, the more likely the patient has disease. Or, specificity improves as the test result falls increasingly outside the normal distribution curve (therefore, false positives occur less frequently).

When the rectal examination is combined with the PSA, more rectal cancers are found than if either the rectal examination or the PSA is used alone. Brawer estimated that if all patients with a PSA >4 ng/mL were to undergo prostatic biopsy, the rate of detection would be 5%.[6] Cooner determined a positive predictive value (the probability that a positive test indicates the presence of disease) of DRE to be 35%.[10] The predictive value of the PSA alone was 36%. The predictive value of the PSA and DRE combined was 60%.

Interpretation of the literature concerning PSA testing and its ability to predict prostate cancer should be cautious for several reasons. Similar to the DRE, PSA values considered normal may be falsely negative unless these patients have had prostatic biopsies. The prevalence of prostate cancer in referred patients may be much higher than the prevalence of prostate cancer in patients seen by the family physician. Referred patients may not include the group of patients who already had negative tests, such as benign rectal examinations or PSA levels within the normal range (test referral bias). In addition, the more tests that are completed in a study that ultimately leads to a larger number of prostate biopsies, the more likely that prostate cancer will be detected and reported.

A number of researchers have shown that as the PSA value rises, the incidence of prostate cancer does increase (fewer false positives/increased specificity).[4,10,18] The debate is whether the results of the PSA can provide a benefit (find previously undiagnosed cancer) without causing harm (evaluation of patients without disease).[19]

Several authors have reported PSA sensitivities of 65% to 75% and specificities of approximately 60%.[4,5,18,20] All these studies are incomplete in their determinations because large numbers of men were assumed to be free of prostate cancer, although no biopsy specimen had been obtained. These patients may have had a high true-positive rate (sensitivity). If the patients had a high rate of prostate cancer, then the specificity calculated may be falsely elevated.[17] An important study of referred patients, all of whom had multiple biopsies, reported a sensitivity of 73% and a specificity of 62% (which is similar to the less rigorous studies).[8] In a group of asymptomatic patients with most (but not all) receiving prostatic biopsies, the sensitivity was 76% and specificity was 88%.[21]

Many recent articles have published the positive or negative predictive values for the serum PSA. The primary care physician must be cautious in applying predictive values to a population of men with a different prevalence of prostate cancer. Although Bayes' theorem is more cumbersome, this calculation will account for the differences in prevalence rates. Likelihood ratios will be cited and used with increasing frequency in the future. These ratios incorporate sensitivity, specificity, and Bayes' theorem into an easier-to-use predictive tool.[15]

Applying Bayes' theorem (or the positive likelihood ratio of 1.9) with a PSA sensitivity of 73% and specificity of 62%, and the previous calculated prevalence of 6% to 22%, the post–PSA-test probability of prostate cancer for Mr F. is 8% to 32%. This estimate is actually lower than the initial estimate of prostate cancer for Mr F.

However, these calculations are based on a normal PSA level ranging from 0 to 3.5 or 4.0 ng/mL. Mr F. had a PSA value of 232 ng/mL. For a PSA result greater than 10 ng/mL, the specificity (ability to rule in) is reported from 80% to 95%.[8,21] For a PSA value greater than 20 ng/mL, the specificity is 99% (although the sensitivity falls to 20%).[21] This information would raise the likelihood ratio to 20, and the probability of prostate cancer to at least 55% to 85%.

The clinician is skeptical. There are two pieces of data that do not fit into his deductive process. The PSA value is just too far out of the normal range, and the DRE is negative, while the PSA is extremely elevated. This is inconsistent with his physiologic model.

Because of the elevated PSA, a transrectal ultrasound and six prostatic biopsies were completed. All of the findings were normal. The patient failed several voiding trials; therefore, transurethral resection of the prostate (TURP) was completed. A PSA test done the day before surgery was 18 ng/mL, which is still elevated but much lower than the initial PSA value. The tissue samplings from the TURP revealed multiple small areas of healing infarctions, with several calculi and small pockets of liquid. There was no evidence of cancer. The pathologist related through personal communication to the author that calculi and pockets of fluid are typical for BPH, and infarction is a frequent finding in severe prostatic hypertrophy. Four months later, the patient's PSA level was 3.9 ng/mL.

So the PSA test was a "false positive" resulting from prostate infarction or infection rather than prostate cancer.

Benign prostatic hyperplasia is the most frequent cause of an elevated PSA.[11,22] This may be a contributing factor in this case, but would not explain the dramatic chronological decrease in the PSA levels. Manipulation of the prostate does result in elevations, but digital prostate examination of patients with a PSA level of <10 ng/mL does not result in statistically significant changes.[23] Patients with a PSA >20 ng/mL, however, can exhibit dramatic elevations after prostate palpation. Prostatitis is another reason for a false-positive PSA elevation, although the diagnosis often remains occult until prostatic resection.[22]

Several authors have previously noted an association between acute urinary retention, prostatic infarction, and abnormal elevations of prostatic acid phosphatase (PAP). The anatomy of arterial flow at the bladder neck is vulnerable to trauma, which, if it occurs, results in periurethral prostatic infarction. Seventy-four percent of patients with BPH and acute urinary retention have an elevated PAP level.[24] Eighty-five percent of patients with acute retention have evidence of prostatic infarction on pathological examination.[24,25] Sixty percent of patients with acute urinary retention had abnormal elevations of PAP before catheter decompression; all returned to normal within 48 hours after decompression.[26]

Benign prostatic hypertrophy with infarction and acute prostatitis are the only causes, other than prostate cancer, for PSA levels greater than 22 ng/mL.[27] Acute urinary retention is a frequent cause of raised PSA levels, but the etiology of this elevation was not addressed.[28]

The most likely biological model is that either acute urinary retention or catheter trauma causes prostatic infarction with possible secondary prostatitis, or prostatic infarction or prostatitis is the precipitating event, which leads to elevations of PAP and PSA with consequential edema and outlet obstruction.

Well, Mr F. would have had urologic evaluation anyway because of the obstructive symptoms, but the prostatic ultrasound and biopsies could have been avoided by waiting and monitoring his falling PSA levels.

The harm and expense of the prostate ultrasound and biopsy were relatively small, so the threshold for deciding to refer the patient would have been reached on the basis of the PSA alone. At what point should the patient be sent to the urologist for further evaluation? At what likelihood for prostate cancer does the patient pass the threshold where testing would be beneficial? Referral of patients with a relatively low probability of having prostate cancer entails a large cost and potential harm to nondiseased patients, but may be appropriate if the clinician feels that the disease represents a severe risk of morbidity in a particular patient that can be reduced with treatment. If the probability level used for referring men is too high, then significant numbers of men with disease will be missed. If prostate cancer is believed to represent a severe risk for patient morbidity, then this threshold should be set very low. The physician must also believe that therapy is available that will decrease the morbidity of prostate cancer. Because of the difficulties encountered when estimating the probability and the lack of consensus on when to refer patients, many clinicians rely on a gestalt, or pattern-recognition, method. An example would be: "All patients with an elevated PSA will receive further evaluation by a urologist." As the literature becomes more complete about the accuracy of the PSA and the best therapy for prostate cancer, the use of an algorithm or a deductive approach to diagnosing prostate cancer would be of great use.

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