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Prostate Cancer: A Diagnostic Dilemma

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Prostate cancer is the most commonly diagnosed malignancy in American men, and its clinical incidence exceeds that of breast cancer in women. It is projected that 244,000 men will be diagnosed with this malignancy in 1995.[1] This represents a 230% increase since 1990.

This neoplasm is the second most common cause of male cancer deaths in the United States, and its mortality rate continues to rise (33% since 1990). Because the prevalence of this disease (30% to 40% of men > 50) is much higher than its clinical expression or incidence, there has been confusion and fear that large numbers of biologically insignificant cancers will be diagnosed.[2] Consequently, if widespread early detection or screening programs were established, a significant number of men would be treated unnecessarily. This confusion is partially based on what is believed to be the unpredictable natural history of this disease. It is generally believed that prostate cancer is a slow-growing malignancy with a doubling time measured in years, perhaps 2 to 5. In actuality, the natural history of this disease can be simply stated: over time, the cancer increases in volume, and as the volume increases, this neoplasm dedifferentiates, develops the ability to penetrate the fibromuscular rim (capsule) of the prostate, and eventually metastasizes.[3] The unknown factors are the time interval and the rate at which any given individual's tumor will grow and develop the properties necessary for invasion and metastasis.

Compounding the problem in detection of prostate cancer is the fact that both the prevalence and clinical expression of this disease increase with age. This irrefutable fact must be kept in mind when deciding who is an appropriate candidate for detection and treatment. Physicians must attempt to establish a balance between an individual's risk of succumbing to prostate cancer or to competing causes of death. After a diagnosis of prostate cancer is established, a urologist should be allowed to advise a patient that treatment is not necessary at a particular point in time. Anxiety, fear of the unknown, and the ravages of medical liability should not be the driving forces that determine the practice of medicine or dictate health care policy. It is usually better to know about something early and either remedy the problem or monitor the situation rather than to discover the problem when it is too late.

Another important issue regarding the diagnosis of prostate cancer is whether or not there is effective therapy that will improve mortality. There is no direct scientific proof that early detection of prostate cancer will decrease the mortality rate. Realizing the implications of lead time and length time biases, we know that men who have clinically organ-confined disease have a better cause-specific survival than men who are treated for locally-advanced or metastatic disease. Prospective randomized trials are now underway to address the impact of early detection on mortality. Until the results of these studies become available, it seems appropriate that if we want to maximize therapeutic benefit we must strive to diagnose this disease when it is organ-confined. This approach, I believe, is also supported by the fact that only 20% of men with locally-advanced prostate cancer can be cured, while the cause-specific survival for men undergoing

radical prostatectomy for organ-confined disease is 85%.[4]

The resolution power of the tools of the diagnostic triad--namely, digital rectal examination (DRE), prostate specific antigen (PSA), and transrectal ultrasonography (TRUS)--do not indicate that they will enhance the detection of insignificant disease. Historically, before the use of PSA and TRUS, only 25% of patients diagnosed with prostate cancer had clinically organ-confined disease. The DRE was the only method available to detect prostate cancer before the onset of symptomatic outlet obstruction or bony metastases. The subjectivity and lack of sensitivity associated with DRE have made it an unreliable tool for early detection.

TRUS has been shown to be better than DRE in detecting prostate cancer. Lee and associates detected twice as many cancers using TRUS compared to DRE.[5] However, a report from the M.D. Anderson Cancer Center indicated that TRUS was not sensitive enough to detect tumors with insignificant volumes.[6] TRUS has a low positive predictive value (approximately 30%), resulting in the recommendation for unnecessary biopsy with its associated direct and indirect costs.

PSA is a glycoprotein produced by the glandular epithelial cells of the prostate gland. Consequently, it is specific for prostate tissue, not prostate cancer. Approximately 30% of men who have cancer will have a normal serum PSA value ($\leq$ 4 ng/ mL), while approximately 20% of men with an elevated level will not have cancer.[7]

Several conditions other than cancer can result in an elevation of this marker, such as prostatitis, benign prostatic hyperplasia, prostatic infarction, and trauma. The serum PSA level is associated with both prostate gland size and age.[8] As a result, two indexes have been reported (PSA density and an age-specific reference range) for the purpose of interpreting levels and improving its positive predictive value. Two independent studies have shown that PSA is not sensitive enough to detect the insignificant cancers discovered at autopsy or at cystoprostatectomy. In a practical sense, the limitations in the resolution power of the available diagnostic tools are truly part of their strength and add to their use in the detection of this common and potentially deadly neoplasm.

Case Report 1

A 49-year-old white male presented in April, 1993, with irritative symptoms (decreased flow, urgency, dysuria, and hesitancy), and low back pain. A DRE was normal, but a PSA blood test result was elevated. The patient had a transrectal ultrasound, which was interpreted as showing no intrinsic abnormalities suspicious for carcinoma. Systematic as well as transition zone biopsies were performed. One core from a biopsy taken from the left side of the prostate revealed a tiny focus of well-differentiated adenocarcinoma that was too small for more precise grading. He was then evaluated with a CT and bone scan, both of which revealed no evidence of metastatic disease.

Figure 1: A TRUS examination in the (a) sagittal and (b) axial projections demonstrating a hypoechoic lesion (arrows) on the left side of the peripheral zone.

Figure 2: Whole-mount section of the prostate gland demonstrating (circle of black dots) a 5-mm focus of a well-differentiated prostate cancer.

The patient was then referred to M.D. Anderson for further evaluation. At presentation, he still had irritative symptoms, daytime frequency, nocturia 4 to 5 times a night, sensation of incomplete emptying, and double voiding. His DRE was interpreted as normal but a repeat TRUS revealed a 1.0 x 0.8 x 1.2 cm hypoechoic area in the left peripheral zone (Figure 1). A PSA was also obtained and was normal at 1.0 ng/mL. Repeat biopsies revealed a 1 mm focus of Gleason score 7 adenocarcinoma from the area of the hypoechoic lesion. All the other biopsy sites (systematic) revealed either atrophy and/or chronic inflammation. In September, the patient underwent an uneventful radical prostatectomy. Pathologically, a Gleason score 6 (Gleason score 24, well differentiated; score 5-7, moderately well differentiated; and score 8-10, poorly differentiated) cancer was found in the left anterolateral peripheral zone having the largest cross-sectional dimension of 5 mm (Figure 2). Postoperatively, the patient regained both his continence and potency.

Comment

This case illustrates two of the many dilemmas of prostate cancer detection. First is the problem of false-positive elevations and false-negative values relating to PSA. We as well as others have reported that approximately 20% of men who have elevated levels of the marker do not have clinically evident prostate cancer. PSA is specific for prostate tissue, not prostate cancer, and other entities can cause the PSA to be elevated, such as infection and benign prostatic hypertrophy. The corollary is that 30% of men who have prostate cancer will have a normal PSA value, as did this patient. An interesting, but as yet unresolved question, is: At what volume of cancer does the PSA begin to demonstrate a meaningful elevation of the serum level? If a patient with an elevated PSA is suspected of having prostatitis or if he has a large gland with an elevated PSA and negative biopsies, a course of antibiotics should be tried in an attempt to explain the PSA, which may result from either clinical or subclinical infection. We treat such patients with a 30-day trial of ciprofloxacin, 500 mg b.i.d., repeating the PSA on day 30.

Another key question is whether early detection using PSA, TRUS, and DRE will result in diagnosing insignificant cancer. The currently accepted tumor volume used to differentiate clinically significant from insignificant is 0.5 cc. Cancer below this threshold is amenable to observation. The limitations of DRE are well documented and historically have led to the diagnosis of clinically organ-confined disease in 20% to 30% of all newly diagnosed cases. We have reported on the limitations of TRUS in identifying cancers less than 5 mm in greatest cross-sectional dimension.[6] Brawn and associates have suggested that PSA values do not become abnormal until the tumor volume reaches 1 cc in most cases.[9] Therefore, the resolution thresholds of these diagnostic methods do not lend themselves well to diagnose small, insignificant cancers. As in this case, if for some reason an individual undergoes biopsy and is found to have cancer in only one site that is < 3 mm, a repeat biopsy from that area is recommended. If no additional cancer is identified and if the PSA is either ≤ 4 or below the predicted PSA based on gland volume, observation is a reasonable alternative. In our own series of patients undergoing radical prostatectomy, approximately 8% were determined to have insignificant disease based on tumor volume calculations from whole-mount processing of the extirpated prostate gland.

Case Report 2

A 66-year-old white male presented to his family physician in September, 1991, with mild obstructive symptoms. A PSA was reported to be 6.1 ng/mL. He subsequently had two repeat PSA determinations, the last after a three-week course of antibiotics. These values were 6.4 and 6.2 ng/mL, respectively. An ultrasound of the prostate was unremarkable. The patient was then evaluated at M.D. Anderson, where the DRE was recorded as 1+, firm, symmetrical, with good lateral margin definition and with an overall impression of being benign. A TRUS revealed a gland volume of 24.3 cc but was otherwise normal. In October, 1991, systematic biopsies, including biopsies of the transition zone, were negative. The patient returned in May, 1992, and the DRE and TRUS remained normal but the PSA had risen to 10.3. Repeat systematic biopsies were again negative for tumor. Despite a negative TRUS and DRE, repeat biopsy was performed in September, 1992, when the PSA was 9.7. The biopsy from the left apex revealed a Gleason 8 adenocarcinoma involving 60% of a 1.2-cm core. In November, 1991, a radical retropubic prostatectomy was performed that demonstrated a Gleason 9 adenocarcinoma. There were five separate foci of disease. The dominant lesion was located in the left anterior and lateral peripheral zone. It measured 2.0 x 1.0 x 1.2 cm and it extended into the apical and base sections. On the right side there was focal extra-capsular extension at the bladder neck and focal perivesicular and seminal vesicle involvement (Figure 3). The surgical margins were free from disease.

Figure 3: Adenocarcinoma (arrow) in perivesicular tissue focally involving muscle coat of the seminal vesicle.

Comment

This case illustrates the potential significance of a PSA elevation in patients with normal DRE and TRUS studies. This finding is now used in the staging system and is classified as Tl, (PSA cancer). Multiple reports have documented that patients with Tl, prostate cancer fall between those with Tl and T2 cancers in the incidence of organ-confined disease, tumor volume, extraprostatic extension, and grade.[10] It has been concluded from these studies that, for the most part, these PSA-only cancers are not insignificant and do require therapy.

The second point illustrated by this case is that persistence and repeat biopsies are sometimes necessary. Given the size of this patient's prostate and the fact that infection as the etiology of his PSA elevation was considered and ruled out as a cause, the most likely etiology was the presence of cancer. Realizing the general rule of the slow-growing nature of this neoplasm, the cancer was present at the first biopsy. The misdiagnosis was a result of sampling error. In cases like this, the incidence of detecting the cancer is relatively high with the second biopsy (19%) and decreases significantly with additional biopsies (8%). However, as illustrated in this case, it is sometimes difficult to diagnose even large cancers with random systematic biopsies. Therefore, clinical judgment must be exercised when weighing the potential risks and gains in pursuing a diagnosis in men with PSAs between 4 to 10 when the incidence of cancer is approximately 20%. As the PSA rises above 10, so does the cancer incidence.

Case Report 3

Figure 4: A TRUS examination in the (a) axial and (b) sagittal projections demonstrating a hypoechoic lesion (arrow) in the apical regions of the left peripheral zone.

A 57-year-old white male presented to the prostate cancer detection clinic at this institution in October, 1989. He had a normal DRE, an abnormal TRUS showing a hypoechoic area in the left apex measuring 1.6 x 0.9 x 1.3 cm, a serum PSA of 11.2 ng/ mL, and a gland volume calculated to be 68.4 cc (Figure 4). Biopsies taken from the left apex as well as from the left and right sides of the prostate were negative for tumor. The patient underwent re-evaluation in August, 1990, at which time his DRE was normal, the TRUS was interpreted as showing a hypoechoic area in the left transition zone, and the PSA was 8.8. The abnormal area in the transition zone was biopsied and showed only chronic inflammation and glandular hyperplasia. In April, 1991, both the DRE and TRUS were normal and the PSA was 10.4. Systematic biopsies, as well as biopsies of the transition zone, were performed and all were negative for tumor. A repeat evaluation in August, 1991, including an unremarkable DRE and TRUS, revealed a hypoechoic area in the right peripheral zone. The serum PSA was 10.7 and repeat biopsies of the peripheral zone showed no pathologic alterations. One year later, in September, 1992, the PSA was still 10.7, the DRE was normal, and the TRUS was unchanged from prior studies. In April, 1993, the DRE and TRUS were again unchanged but the PSA had risen to 14. 1. Peripheral zone biopsies were again negative for cancer. The patient was given a 1-month course of ciprofloxacin, and a repeat PSA was 13.7. In October, 1993, the DRE was normal, the ultrasound showed hypoechoic lesions in the left transition zone and the right peripheral zone. Both lesions had been previously seen and biopsied. The PSA was 14.2 and systematic biopsies and transition zone biopsies were again performed and all were negative for cancer. However, a biopsy of the left peripheral zone revealed high-grade, prostatic intraepithelial neoplasia (PIN). In February, 1994, the ultrasound was unchanged, the PSA had fallen to 7.5, and repeat biopsies in the area of the prior PIN-positive biopsy were negative for any neoplasia. The patient's last visits to the clinic in August and December, 1994, were for PSAs alone. The values were 9.3 and 7.4 ng/mL, respectively, and his last ultrasound-determined prostate volume in February, 1994, was 71.2 cm.

Comment

This case exemplifies some of the many problems in detecting prostate cancer. Despite the advantages of the diagnostic triad in detecting cancer, these tools can be misleading. As in this case, the hypoechoic lesion visualized represented a false positive. TRUS is associated with a sensitivity of 77.2% and a specificity of 89.4%, as reported from a multi-institutional study sponsored by the American Cancer Society. This group also reported a very low positive predictive value of 15.2% for TRUS compared to 28% for the DRE. The positive predictive value for TRUS is directly related to

the size of the cancer. Because it has a lower specificity and a higher sensitivity compared to the DRE, TRUS is associated with a higher recommendation rate for biopsy. In a study of 2,425 men in an early detection program, a recommendation for biopsy was made in 13.6% of the men based on TRUS compared to 6.3% for the DRE. The overall cancer detection rate was 2.4%.

How best to use PSA in the detection of this neoplasm is still evolving. As seen in this patient, there was also a presumed false-positive elevation of the serum PSA. Using any of the present threshold criteria, this patient's PSA was elevated, ie, absolute cut-off of 4 ng/mL, PSA density or age-specific reference range. Interestingly, this particular patient illustrates another significant problem, the variability in assay determination even when it is performed in the same laboratory and with the same assay. This variability compounds the interpretation of PSA because the decision to observe or to biopsy is also made by considering changes over time in the serum level. Why this individual's PSA has gone from above 10 to its most current level of 7.4 is not known.

This case also demonstrates the problem when high-grade PIN is observed on a biopsy. Approximately 90% of cancers are associated with this histology finding. In addition, PIN is considered a premalignant lesion. For these reasons, a repeat biopsy is recommended, as well as continued observation.

Summary

Prostate cancer is a disease of paradox.

The number of clinically diagnosed prostate malignancies is considerably lower than the number of pathologically detectable cancers found in autopsy or cystoprostatectomy specimens, the latter removed for bladder cancer. It has been estimated that only 1 of 323 men dies of the disease. Clearly, not all men with prostate cancer need to be diagnosed, not all men with cancer need to be treated, and not all men with this malignancy will die from it. Yet, prostate cancer is the second most common cause of male cancer death in the United States, and furthermore, it is associated with a rising cancer-specified death rate.

An analysis from this institution of the positive predictive value of DRE, TRUS, and PSA alone and in various combinations revealed that the combination of DRE and PSA was equivalent to all three tests combined.[11] If TRUS had not been performed as part of the initial early detection examination, only 4 of 170 cancers (2.4%) would have been missed. As a result, if the TRUS was omitted from the initial evaluation, not only would there be significant economic savings in cost per cancer diagnosed, but perhaps more importantly 105 unnecessary biopsies would have been avoided with their associated potential for patient morbidity. Based on this information, we now recommend the combination of DRE and PSA as the first-line detection evaluation for prostate cancer. TRUS is best reserved for examination and biopsy of patients who have either an abnormal DRE and/or PSA. Because age and prostate volume should be taken into consideration when interpreting PSA levels, the absolute cut-off value of 4 ng/mL is being re-evaluated. Algorithms for early detection with guidelines establishing the age to initiate evaluations, intervals of evaluation, the age early detection can be terminated, as well as indication for biopsy, are undergoing study and reevaluation. We now practice the "art" of early detection.