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Prostate Cancer Can Be Detected Even in Patients with Decreased PSA Less than 2.5 ng/ml after Treatment of Chronic Prostatitis

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Purpose: We evaluated men with documented chronic prostatitis and elevated serum prostate-specific antigen (PSA) to determine whether treatment with antibiotics and anti-inflammatory drugs can lower serum PSA and the cancer detection rate in patients with post-treatment PSA <4 ng/ml.

Materials and Methods: Eighty-six men who presented with serum PSA greater than 4 ng/ml and who were subsequently diagnosed with chronic prostatitis with greater than 10 white blood cells per high power field in expressed prostatic excretions were included in this prospective study. Patients meeting these criteria underwent treatment with a 4-week course of antibiotics and nonsteroidal anti-inflammatory agents. Follow-up PSA and transrectal ultrasonography-guided prostate biopsy were performed within 2 months of treatment for all patients.

Results: Mean patient age was 56.2 years (range, 37-72 years). Mean PSA (ng/ml) decreased by 33.8%, from 8.12 (range, 4.02-24.8) to 5.37 (range, 1.35-12.94), after treatment (p=0.001). Pathological studies revealed prostate cancer in 18 cases (20.9%), chronic inflammation in 64 (74.4%), and benign prostatic hypertrophy in 4 (4.7%). The prostate cancer detection rate according to the follow-up PSA level, below 2.5, from 2.5 to 4.0, and above 4.0, was 13.3% (2/15), 13.6% (3/22), and 26.5% (13/49), respectively.

Conclusions: When chronic prostatitis with elevated PSA is identified, antibiotic and anti-inflammatory treatment can lower these PSA levels. However, the possibility of prostate cancer remains in patients whose PSA level decreases to less than 4 ng/ml, even in those with a PSA level less than 2.5 ng/ml.

Key Words: *Biopsy; Prostate-specific antigen; Prostatitis*

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INTRODUCTION

Prostate-specific antigen (PSA) is the most commonly used marker for screening of prostate cancer, and men with elevated serum PSA of greater than 4 ng/ml are considered to be at higher risk for prostate cancer [1]. These patients are usually referred to undergo a prostate biopsy [2,3]. However, it is known that increased PSA is not necessarily due to prostate cancer, but can also be associated with conditions other than cancerous lesions, such as prostate inflammation [4,5]. The recommended cutoff value of PSA for needle biopsy of the prostate has recently been lowered to 2.5 ng/ml [2]. In support of the possible incidence of prostate cancer in men with a PSA level lower than 4 ng/ml, Gilbert et al reported a similar prostate cancer detection rate between patients with a PSA level of 2.5 to 4 ng/ml (27.48%) and patients with a PSA level between 4 and 10 ng/ml (30.8%) [3].

Until now, many studies have investigated the correlation of serum PSA and prostate inflammation to provide answers to the question of whether unnecessary biopsies could be avoided by treatment of chronic prostatitis and lowering of PSA [6,7]. These studies suggested that identification and treatment of prostatitis can decrease PSA and

thus decrease the number of men with an indication for prostate biopsy for cancer evaluation. However, the main drawback of the reported studies is that pathologic results are not available for patients with a post-treatment PSA level <4 ng/ml because they did not undergo a prostate biopsy. We evaluated men with documented chronic prostatitis and elevated serum PSA to determine whether treatment with antibiotics and anti-inflammatory drugs can lower serum PSA. In addition, we performed prostate biopsy after treatment in all cases and examined the cancer detection rate in patients whose PSA decreased to less than 4 ng/ml after treatment with antibiotics and anti-inflammatory agents to determine the real number of patients requiring prostate biopsy and the necessity of biopsy.

MATERIALS AND METHODS

Between January 2006 and December 2008, a total of 86 consecutive patients between the ages of 50 and 65 years who presented with serum PSA (ng/ml) above 4 with a normal digital rectal exam (DRE) result and who were subsequently diagnosed with chronic prostatitis were enrolled in this prospective, observational study. We identified chronic prostatitis as greater than 10 white blood cells per high power field in expressed prostatic excretions obtained from prostatic massage. All DREs were performed by the special medical doctor in urology. The presence of a palpable nodule, enduration, fluctuation, or fixed prostate was regarded as an abnormal DRE result. Patients with known prostate cancer or recent transurethral resection of the prostate, usage of prior 5-alpha reductase inhibitors, transurethral catheter insertion, or urinary retention in the past 6 weeks were excluded. The subjects provided informed consent for prostate biopsy and for participation in this study.

Patients meeting these criteria received treatment with a 4-week course of combination pharmacological therapy with antibiotics (ciprofloxacin, 500 mg/day) and a nonsteroidal anti-inflammatory agent (zaltoprofen 80 mg, three times a day). Follow-up PSA and transrectal ultrasonography-guided prostate biopsy were performed within 2 months after treatment for all patients. Transrectal ultrasound-guided 10-core prostate biopsies were obtained from patients by the same urologist with use of a 7.5 MHz probe (Viking 2400, BK Medical, Denmark). An automated biopsy gun and an 18-gauge needle were used. Prophylactic antibiotics were administered to all patients with ciprofloxacin 500 mg twice a day for 5 days starting the day before the biopsy. Pathologic specimens were evaluated by the pathologist with regard to the presence of carcinoma of the prostate.

TABLE 1. Patients characteristics and comorbidity

Patients characteristics	Mean (%)
Age (yr)	56.2±12.3 (37-72)
Pre-treatment PSA (ng/ml)	8.12±3.2 (4.62-24.8)
Post-treatment PSA (ng/ml)	5.37±3.6 (1.35-12.94)
Relative changes (%)[a]	33.8
Post-treatment PSA (ng/ml) range	
PSA<2.5	15
2.5≤PSA<4.0	22
PSA≥4.0	49

PSA: prostate-specific antigen, [a]: p=0.001

RESULTS

The mean patient age was 56.2 years. The basal PSA level (ng/ml) was 8.12 (range, 4.62-24.8). After 4 weeks of antibiotics and nonsteroidal anti-inflammatory agents, mean PSA showed a significant decrease to 5.37 (range, 1.35-12.94) (p=0.001) (Table 1). The relative percentage change in PSA before and after treatment was estimated at 33.8%. PSA after 4 weeks of treatment was determined as below 2.5 in 15 cases, from 2.5 to 4.0 in 22 cases, and above 4.0 in 49 cases (Table 1). From the transrectal prostate biopsy after treatment, prostate cancer was detected in 18 cases (20.9%), followed by chronic inflammation in 64 cases (74.4%), and benign prostatic hypertrophy in 4 cases (4.7%) (Table 2). We found that PSA in 37 of 86 (43%) of the patients with elevated PSA above 4 ng/ml decreased to a normal range of below 4 ng/ml after 4 weeks of treatment. Among these cases, PSA was determined as below 2.5 in 15 cases (17.4%) after treatment. The estimated prostate cancer detection rate according to the follow-up PSA range, below 2.5, from 2.5 to 4.0, and above 4.0, was 13.3% (2/15), 13.6% (3/22), and 26.5% (13/49), respectively (Table 2).

DISCUSSION

In the present study, we demonstrated that the mean PSA was significantly decreased after 4 weeks of treatment with antibiotics and nonsteroidal anti-inflammatory agents, showing an estimated relative percentage change in PSA from before to after treatment of 33.8%. We found that PSA in 37 of 86 (43%) of the patients with elevated PSA de-

TABLE 2. The results of TRUS biopsy and prostate cancer detection rate in patients with various post-treatment PSA

Biopsy results	No. of events (%)
Prostate cancer	18 (20.9%)
BPH with prostatitis	64 (74.4%)
BPH alone	4 (4.7%)
PSA range (ng/ml)	Detected prostate cancer (%)
PSA<2.5 (15)	2 (13.3)
2.5≤PSA<4.0 (22)	3 (13.6)
PSA ≥4.0 (49)	13 (26.5)
Total	18 (20.9)

TRUS: transrectal ultrasonography, PSA: prostate-specific antigen, BPH: benign prostatic hyperplasia

creased to a normal range (below 4 ng/ml) after 4 weeks of treatment. Among those patients, PSA was determined to be below 2.5 in 15 cases (17.4%) after treatment. Furthermore, the prostate cancer detection rate according to the follow-up PSA level, below 2.5, from 2.5 to 4.0, and above 4.0, was 13.3%, 13.6%, and 26.5%, respectively. Overall, a relatively high rate of cancer of 13.5% (5/37) was detected in those with a decreased to normal value of PSA (below 4 ng/ml) after treatment. Our results suggest a strong link between prostate inflammation and neoplastic transformation, although others refute this connection [8-11]. Of the 5 patients, 1 patient (20%) had a Gleason score of 6 or less (PSA 2.5-4.0), 2 patients (40%) had a score of 7, and 2 patients (20%) had a score of 8 or above. The most important point of our study results is that clinically significant prostate cancer can be detected even in cases in which the PSA level is decreased to less than 2.5 ng/ml after treatment with antibiotics and nonsteroidal anti-inflammatory agents. These results suggest that a decreased PSA value after antibiotic treatment does not implicate the absence of prostate cancer and waive the necessity for biopsy.

Increased PSA can be associated with conditions other than cancerous lesions, such as benign prostatic hyperplasia, prostate inflammation, and interventions such as prostate massage, prostate biopsy, and transurethral resections. An elevated PSA level is reported to be related to prostatitis [4,6,7,12], and prostate inflammation is known to be a main reason for compromise of the specificity of PSA [13]. Many studies have shown that treatment of chronic prostatitis can decrease the PSA level, which suggests that the use of antimicrobial or nonsteroidal anti-inflammatory agents may reduce the number of men who require prostate biopsy [6,7]. These reports have raised the question of how to manage men with elevated PSA and chronic prostatitis. Potts investigated 122 medical records of patients with elevated PSA and found 41% to have inflammatory signs in expressed prostatic secretions or post-prostatic massage urine [6]. The author reported that the PSA value decreased to the normal value in 43% of patients with laboratory signs of prostatitis after antibiotic treatment. However, prostate biopsy was conducted only in patients with persistently elevated PSA after antibiotic treatment, not in those with normalized PSA. Bozeman et al performed a retrospective evaluation of the medical records of 95 patients with an elevated PSA level and inflammation in expressed prostatic secretions who received treatment with antibiotics and anti-inflammatory drugs for a period of 4 weeks [7]. They reported that the PSA value decreased by 36% from the baseline after treatment with antibiotics and nonsteroidal anti-inflammatory agents in men with chronic prostatitis and that 44 (46.3%) of the patients had post-treatment PSA values of lower than 4 ng/ml, hence avoiding biopsy, whereas the remaining 51 (53.7%) underwent biopsy, revealing the presence of cancer in 13 (25.5%). They conclusively suggested that their positive biopsy rate improved from 13.7% to 25.5% with initial treatment of chronic prostatitis. The major limitations of the two studies described above are that biopsy was not performed in all cases but was undertaken only in patients who had had post-treatment PSA levels that remained persistently elevated above the normal value. Lowering the PSA level may not completely preclude the performance of a prostate biopsy to rule out the presence of prostate cancer.

The recommended cutoff value of PSA for needle biopsy of the prostate was recently lowered to 2.5 ng/ml [2]. In support of the possible incidence of prostate cancer with a PSA level lower than 4 ng/ml, Gilbert et al reported a similar prostate cancer detection rate between patients with a PSA level of 2.5 to 4 ng/ml (27.48%) and patients with a PSA level between 4 and 10 ng/ml (30.8%) [3]. Also recently, Lee et al reported that the prostate cancer detection rate was 9.6% in men with a PSA level lower than 4 ng/ml, which is lower than the 12.4% previously reported by Lee at al in Koreans [14,15]. Those authors suggested that a prostate cancer screening test is required with a PSA level of 2.5 to 2.9 ng/ml if the patients have conditions such as older age, smaller prostate, and higher PSAD. Most of these studies lacked histopathological sampling of the prostate in patients with normalized PSA levels after treatment [7]. Baltaci et al reported that although antibiotic therapy will decrease total serum PSA, it will not decrease the risk of prostate cancer, even though the PSA level decreases to less than 4 g/ml [16]. After performance of prostate biopsy in all patients, they found prostate cancer in 23 of 100 men (23%) presenting with a PSA value in the range of 4-10 ng/ml. Most importantly, they determined that 17 of 100 men had a PSA value of less than 4 ng/ml after antibiotic treatment and that prostate cancer was detected as many as 5 of these 17 (29.4%) men. Thompson et al have already reported that as many as 26.9% of men with a PSA level between 2.5 and 4 ng/ml have biopsy-detectable prostate cancer [17]. Stopiglia et al conducted the first prospective, double-blind, randomized study comparing the behavior of PSA after treatment with antibiotics vs placebo in patients with type IV prostatitis and elevated PSA [18]. They included patients presenting with a PSA as low as 2.5 ng/ml in the prostate biopsy procedure and unexpectedly found a relatively high rate of cancer in those with a PSA even lower than 2.5 ng/ml during follow-up with placebo (30%) or antibiotics (55.5%). They conclusively stated that in patients with normalized levels of PSA (below 2.5 ng/ml), the absence of prostate cancer is not indicated, and should not be valued in the decision to perform prostate biopsy or not.

This report calls attention to the not infrequent presence of prostate cancer, even in patients with normal PSA, after antibiotic treatment in patients with elevated PSA and chronic prostatitis. This clinical event should be considered in counseling on the necessity of prostate biopsy independent of the post-treatment PSA level in patients with elevated PSA and chronic prostatitis, even with a PSA decrease to <2.5 ng/ml.

This study had some limitations. The number of patients included in the study was very small. In addition, our study did not have a placebo control group. Thus, considering the

low number of cases of chronic prostatitis with elevated PSA in the clinical setting, a multicenter, double-blind, placebo-controlled trial would be ideal for further determination of the exact relationship between elevated PSA and prostate inflammation. Many important variables in this analysis, such as the severity of benign prostatic hyperplasia and prostate volume, were not considered. Despite these limitations, we believe that our study provides some valuable clues for guidance in the decision on whether to perform prostate biopsy in these patients.

CONCLUSIONS

The results of this study demonstrate that chronic prostatitis can cause elevation of serum PSA levels. When chronic prostatitis with elevated PSA is identified, treatment with antibiotics and anti-inflammatory agents can lower these PSA levels. However, the possibility of clinically significant prostate cancer remains in patients with a decreased PSA level of less than 4 ng/ml, even in those whose PSA decreases to less than 2.5 ng/ml. Therefore, active screening tests for prostate cancer should be conducted in patients within the normal range of PSA after treatment of chronic prostatitis.

Conflicts of Interest

The authors have nothing to disclose.

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