ORIGINAL ARTICLE

Correlation of Serum Prostate-specific Antigen Level in Various Prostate Pathology

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ABSTRACT

Introduction: Carcinoma of prostate is one of the common tumors of elderly men causing significant morbidity and mortality. Other prostatic pathology ranged from inflammatory lesions to benign prostatic hyperplasia (BPH). Screening programs with prostate-specific antigen (PSA) aimed at early detection of cancer is necessary. PSA is the most useful tumors marker in diagnosis and first-line test in screening. PSA, when combined with Gleason score, improves the prediction of pathological stage for prostate carcinoma.

Objective: The objective of this study was to investigate the relationship between serum PSA levels and histological finding in biopsy of men with prostatic disease.

Materials and Methods: A hospital-based descriptive cross-sectional study over a period of 1 year was carried out on biopsy specimen received at histopathology laboratory in the department of pathology. Histopathology slides were assessed and correlated with serum PSA level.

Results: Mean PSA value for BPH and prostatitis was 5.45 ± 7.109 and 5.77 ± 4.038, respectively. Prostatic adenocarcinoma was found in about 23.3% of total biopsy specimen. 16/20 cases (80%) of prostate adenocarcinoma have severe elevation of serum PSA level >20 ng/ml and majority of these cases were of high grade. Serum PSA in the range of 0–4 ng/ml was associated with benign lesions, and serum PSA more than 20 ng/ml was associated with malignant lesions (P <0.0001).

Conclusion: Serum PSA is elevated marginally in patients with BPH and active inflammation. Both benign and malignant pathologies can cause an increase in serum PSA levels, but the chances of finding malignancy increase with rising values of PSA.

Key words: Benign prostatic hyperplasia, prostate-specific antigen, prostatic adenocarcinoma

INTRODUCTION

Prostate cancer (PCa) is a significant growing health problem, most common malignant tumor in men in American population over the age of 65 years.[1] Patients do not experience many symptoms during early stage and are unlikely to seek medical help until the disease has progressed and extended beyond the confines of the gland, thus making it incurable.[2] Hence, screening programs aimed at early detection have been introduced.

Prostate-specific antigen (PSA) is an important tumor marker in the diagnosis of prostate carcinoma.[3] PSA is serine protease produced by ductal and acinar epithelial cells of normal prostatic epithelium, benign condition such as nodular hyperplasia, and inflammatory process such as prostatitis, prostate infarction, and malignant tissue of the prostate. Due to this pathological consequences, the cell integrity of epithelium is destroyed, leading to release of PSA into circulation and frequently causing rising and detectable level of serum PSA value.[4,5] According to the guidelines of the American Cancer Society, PSA along with digital rectal examination (DRE) has become recommended test since 1993 for annual checkup of men aged 50 years or above for PCa.[6,7] Serum PSA, a marker for prostatic carcinoma, has high sensitivity, specificity, and compliments histopathological diagnosis.[8,9]

At present, measurement of the PSA level has been used as the first-line screening tool for PCa. The upper limit of normal range for PSA values is generally 4.0 ng/ml, levels between 4 and 10 ng/mL are considered borderline and more than 10 ng/mL is considered high. After clinical assessment regarding history, age, and DRE, patient with PSA value > 4 ng/mL, correlation with histopathology finding is necessary.[10]

Studies have shown that value of serum PSA increases for 2.3 ng/ml in average for every gram of malignant prostate

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tissue, while every gram of hyperplasic/benign tissue increases the same parameter 10 times less compared to cancer tissue.[11,12] PSA is mainly produced by prostatic epithelial cells, but trace amount of PSA has also been detected in the periurethral glands, normal breast tissue, breast tumor, breast milk, adrenal neoplasm, and endometrium.[13,14] PSA is usually found in serum in low concentration and measurement of serum PSA during elevation has allowed it to become a useful marker for PCa.[15]

The cutoff value of 4.0 ng/mL represents the level, at which the highest sensitivity and highest specificity are present. As there is no value of PSA, at which the definitive diagnosis of PCa can be made; therefore, correlation PSA level with biopsy of the prostate is still required for the definitive diagnosis of PCa.[10]

Approximately 95–98% of PCa are adenocarcinomas developing in acini of prostate ducts. Other histologic types of PCa include adenoid cystic carcinoma, small cell carcinoma, signet ring carcinoma, and neuroendocrine tumor. Dysplasia of the epithelium lining prostate glands, which is prostatic intraepithelial neoplasia (PIN), is considered as a probable precursor of prostate carcinoma.[16,17] Other common prostate lesions are benign prostatic hyperplasia (BPH), chronic prostatitis, and basal cell hyperplasia.

MATERIALS AND METHODS

This is a hospital-based cross-sectional study carried out in histopathology laboratory, department of pathology at tertiary care center, BPKIHS. The study was carried out over a period of 1 year from April 2017 to March 2018. Relevant clinical, radiological details and pre-operative PSA levels were collected. Serum PSA levels were estimated using chemiluminescent assay. Indications for biopsy were clinical history, elevated PSA, and abnormal DRE. Patients already diagnosed and treatment for carcinoma of the prostate and inadequate biopsy specimen were excluded from the study.

All submitted needle biopsy and transurethral resection of prostate bits were taken for processing. Hematoxylin and eosin-stained sections were studied under light microscopy for prostatic pathology and categorized as neoplastic and non-neoplastic. Diagnostic criteria followed for diagnosing BPH, prostatitis, PIN, and adenocarcinoma were adapted from guidelines laid down by the World Health Organization (WHO). For carcinoma of the prostate, considering the glandular differentiation, the growth pattern of tumor in relation to stroma, Gleason microscopic grading system as laid by the WHO was applied. Above histological findings were correlated with respect to serum PSA levels.

Statistical Analysis

Data obtained from the study were entered into Microsoft Excel 2007 and checked for consistency. They were further entered into SPSS version 11.5 for statistical analysis. Data distributions were represented in tables. For descriptive statistics, percentage, range for quantitative data, arithmetic mean, standard deviation, and standard error were applied. For inferential statistics, Chi-square test, linear-by-linear correlation, and Fisher's exact test were applied for the determination of significant differences between analyzed groups. Sensitivity, specificity, positive predictive value, and negative predictive value of PSA were calculated in relation to histopathological grade.

Chi-square test estimates the degree of association between the selected variables. Level of significance is set at $P < 0.05$. Ethical clearance was obtained from the institutional ethical review board BPKIHS to conduct the study.

RESULTS

Eighty-six specimens were received for histopathological examination. Carcinoma constituted 20 cases (23.3%), all diagnosed malignant cases were of adenocarcinoma. Benign prostate hyperplasia [Figure 1] comprises 54 cases (62.79%) and chronic prostatitis accounts 12 cases (13.9%). Seven cases of prostate adenocarcinoma (35%) have perineural invasion [Figure 2].

For chronic prostatitis, mean PSA level was 5.77 ± 4.038. Lowest level of PSA for prostatitis was 1.1.9 ng/ml and highest level up to 13.42 was recorded. Similarly, for BPH, mean PSA level was 5.45 ± 7.109. Lowest level of PSA for BPH was 0.05 ng/ml and highest level up to 45.56 ng/ml was recorded. The mean serum PSA value for prostate adenocarcinoma was 170.70 ± 137.91 ng/ml. Minimum PSA value was 2.81 ng/ml and maximum PSA value was 400.04 ng/ml found in the study [Table 1].

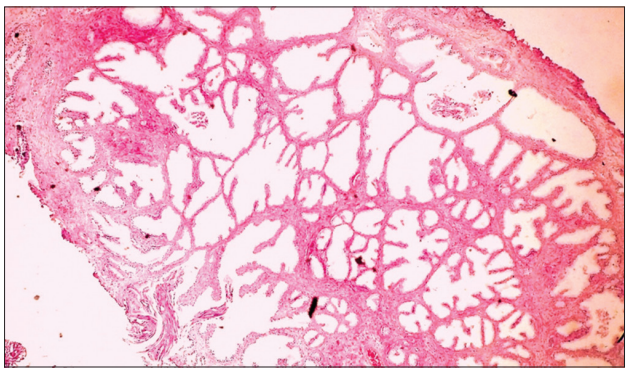

Figure 1: Photomicrograph showing glandular proliferation and fibromuscular stromal proliferation (×100 H and E stain). Benign prostatic hyperplasia

In the present study, 80.0% (16/20) of malignant cases have severely elevated serum PSA levels more than 20.0 ng/ml. Two malignant cases have serum PSA in the range of 0–4 ng/ml and remaining two cases were in the range of 4.1–10.0 ng/ml and 10.1–20 ng/ml, respectively. About 50% (27/54) of cases of BPH has serum PSA level in the range of 0–4 ng/ml; similarly, 20/54 cases (37.0%) have mild elevation of serum PSA level between 4.1 and 10.0 ng/ml, only 3.7% (2/54) of cases has PSA level >20 ng/ml. In prostatitis, majority of cases 10/12 (73.3%) have PSA level between 0–4 and 4.1–10.0 ng/ml. When serum PSA levels in benign and malignant cases were compared, serum PSA in the range of 0–4 ng/ml was associated with benign lesions, and serum PSA more than 20 ng/ml was associated with malignant lesions. Result was statistically significant, linear-by-linear association χ^2 =33.99, $P < 0.0001$ [Table 2].

Nine cases (45%) of 20 prostate adenocarcinomas were in Group Grade 5; similarly, 6/20 cases (30%) were in Group Grade 4 [Figure 3]. Among these 15 cases in high grade, 13 cases have significant rise in serum PSA level >20 ng/ml. Remaining two cases in Group Grade 4 and 5, respectively, have PSA level between 4.1–10 ng/ml and 10.1–20 ng/ml. Only 1/20 case (5%) was encountered in Grade Group 1 with PSA level between 0 and 4 ng/ml, linear-by-linear association χ^2 =5.091, $P < 0.05$ [Table 3]. For detection of Prostate cancer, the sensitivity and specificity of PSA level was found to be 90.00% and 94.29% respectively [Table 4].

DISCUSSION

Epithelial cells lining the prostatic acini and ducts exclusively produce PSA. The clinically acceptable value of PSA is from 0 to 4.0 ng/mL, but even within the normal range of PSA, there is also the risk of cancer at a smaller rate of 2%. Value from 4.0 to 10.0 ng/mL could be seen in patients with BPH, prostatitis, PIN, and PCa.[5] Due to its high specificity for prostate tissue, PSA is the preferred serum marker

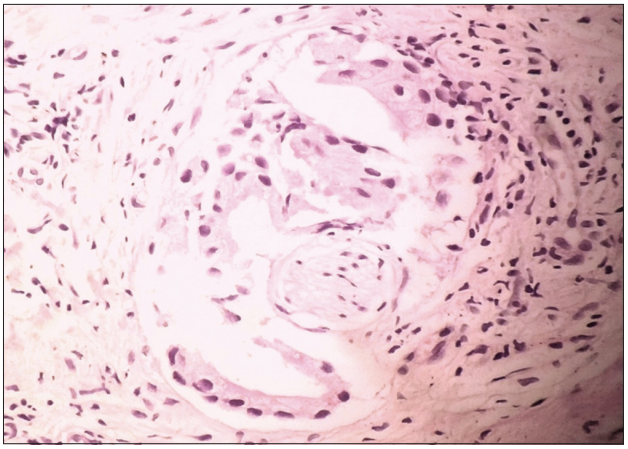

Figure 2: Photomicrograph showing perineural invasion by prostatic adenocarcinoma. (×100 H and E stain)

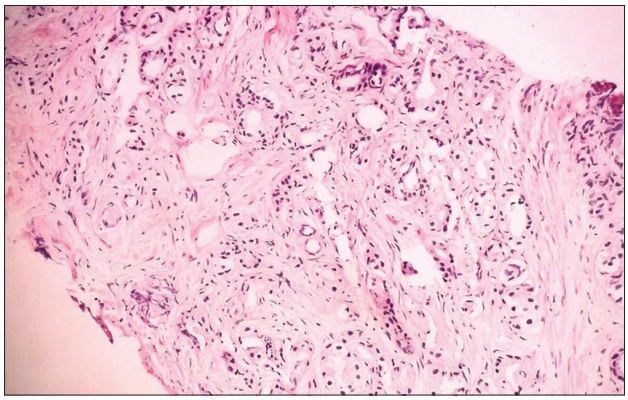

Figure 3: Photomicrograph showing fused poorly formed gland pattern 4, small poorly formed gland pattern 4. Gleason score 8 (4+4). Group Grade 4 (×100 H and E stain). Prostatic adenocarcinoma

Table 1: Mean prostate-specific antigen in ng/ml in various prostate pathologies

Histopathology prostate disease	*n*	Mean±standard deviation	Standard error	95% confidence interval for mean		Minimum	Maximum
				Lower bound	Upper bound		
Prostate adenocarcinoma	20	170.702±137.919	30.839	106.153	235.250	2.81	400.04
Prostatitis	12	5.7750±4.038	1.165	3.209	8.340	1.19	13.42
BPH	54	5.4548±7.109	0.9674	3.514	7.395	0.05	45.56
Total	86	43.9291±95.984	10.35	23.350	64.508	0.05	400.04

BPH: Benign prostatic hyperplasia

Table 2: Association of prostate pathology with prostate-specific antigen range

Histopathology category	Serum prostate-specific antigen level ng/ml (%)				Total
	0–4	4.1–10.0	10.1–20.0	>20.0	
BPH	27 (50.0)	20 (37.0)	5 (9.3)	2 (3.7)	54 (100.0)
Prostatitis	6 (50.0)	4 (33.3)	2 (16.7)	0 (.0)	12 (100.0)
Adenocarcinoma	2 (10.0)	1 (5.0)	1 (5.0)	16 (80.0)	20 (100.0)
Total	35 (40.7)	25 (29.1)	8 (9.3)	18 (20.9)	86 (100.0)

BPH: Benign prostatic hyperplasia

Table 3: Distribution of Gleason grade group based on prostate-specific antigen level

Prostate-specific antigen level ng/ml	Histopathology Gleason grade group				Total *n* (%)
	Grade Group 1	Grade Group 2	Grade Group 4	Grade Group 5	
0–4	1	1	0	0	2 (10)
4.1–10.0	0	0	1	0	1 (5)
10.1–20.0	0	0	0	1	1 (5)
>20.0	0	3	5	8	16 (80)
Total *n* (%)	1 (5)	4 (20)	6 (30)	9 (45)	20 (100)

Table 4: Sensitivity and specificity of prostate-specific antigen (diagnostic test) for the detection of prostate adenocarcinoma

Statistic	Value (%)	95% confidence intervals
Sensitivity	90.00	68.30–98.77
Specificity	94.29	80.84–99.30
Positive predictive value	90.00	69.92–97.21
Negative predictive value	94.29	81.55–98.40
Accuracy	92.73	82.41–97.98

for PCa.[18] PSA levels variation in prostatic hyperplasia can be explained by the association of various degrees of inflammatory changes detected in biopsy samples.

The results of our study reveal PSA levels in BPH without inflammation and patients with chronic inflammation ranged from normal level to 45.0 ng/mL. Serum PSA levels in inflammatory lesions are elevated due to stimulation of epithelial cells surrounding the affected area through release of unknown substances in association with inflammation.[19] Hasui *et al.*[20] suggested that explanations for abnormal elevation of serum PSA levels are possibly due to death of epithelial cell and leakage of PSA stored in the epithelial cells into the stromal tissue and blood circulation.[20]

Our study showed mean PSA level in BPH and prostatitis to be 5.45 ± 7.10 and 5.77 ± 4.038, i.e., in the range of 4–10 ng/ml. The results were comparable with the study done by Wadgaonkar *et al.*[21] and Jasani *et al.*,[22] in which they found mean PSA value of BPH 8.90 ± 12.77 and 4.86 ± 3.03, respectively, and in prostatitis mean PSA level 9.12 ± 14.45 and 4.36 ± 3.59, respectively. In our study, most of the patients (80%) with prostatic carcinoma had serum PSA levels more than 20.0 ng/mL. Several investigations have suggested raising level of PSA more than 20.0ng/ml and positive bone scintigraphy. Spread of PCa occurs by direct local invasion, bloodstream, and lymph. Hematogenous spread occurs chiefly to the bones.[23]

Bone metastasis has a characteristic osteoblastic lesion. Common bony metastasis sites include lumbar spine, proximal femur, pelvis, thoracic spine, sacrum, and ribs. These PCa spreads are as a result of spread through Batson's vertebral venous system. Lymphatic spread occurs initially to the obturator nodes followed by perivesical, hypogastric, iliac, presacral, and para-aortic nodes. Lymph node spread occurs frequently and generally precedes spread to bones.[23]

Perineural invasion was seen in seven cases of adenocarcinoma (35%) of our study. In a study by Gurumurthy *et al.*, 52.9% of the cases showed perineural invasion.[24] Perineural invasion is a recognized mechanism by which cancer cells spread beyond the prostatic tissue using the rich innervations of the posterior aspect of the prostate.

The diagnosis of bony metastasis secondary to PCa significantly alters patient treatment. According to the study done by Abdellatif *et al.* and Chybowski *et al.*, the incidence of skeletal metastasis in bone scans in patients with PSA <20 ng/ml is low. Thus, evaluating bone scans in patients with PSA <20 ng/ml can be avoided resulting in saving of large economic burden. On the other hand, few studies done in Japanese population, the incidence of positive bone scintigraphy in patient group with low PSA levels was much higher than that in other studies performed in Western countries. This raises the question that nature PCa is different in Asian population as compared with Caucasians, and PSA might not be a good indicator for predicting bone scans results in some ethnic group.[25]

CONCLUSION

Serum PSA is elevated marginally in patients with BPH and active inflammation. Both benign and malignant pathologies can cause an increase in serum PSA levels, but the chances of finding malignancy increase with rising values of PSA ($P < 0.0001$). Assessing PSA level more than 4.0 ng/ml along with histological correlation is most useful and accurate diagnostic method for prostate malignancy. For the detection of PCa, the sensitivity and specificity of PSA level was found to be 90.00% and 94.29%, respectively.

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