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Histopathological Evaluation of Prostatic Lesions, PSA Correlation and Use of P63 in Prostatic Adenocarcinoma Mimickers

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ABSTRACT

Background

Prostatic lesions are common disorders causing morbidity and mortality among the elderly population. Benign prostatic hyperplasia (BPH) and prostatic adenocarcinoma are the common pathologies of prostate. Prostate specific antigen (PSA) and histopathological examination are important for diagnosis and management of prostatic adenocarcinoma. Prostatic adenocarcinoma mimickers may be difficult to diagnose for which p63 immunostaining is helpful in differentiating them from adenocarcinoma.

Methods

It was a hospital-based cross-sectional study conducted over one year period in the Department of Pathology, TUTH. Demography, procedure type, PSA levels, histopathological diagnosis and immunohistochemistry findings for suspected adenocarcinoma mimickers were collected and analyzed.

Results

A total of 123 cases of prostatic lesions were enrolled, out of which 74% were benign and 26% were malignant. The most common age group was 61-70 years for both types of lesion. The median PSA values for benign and malignant prostatic lesions were 3.21 and 33.55 ng/mL respectively and the difference was statistically significant. The commonest Gleason system score in prostatic adenocarcinoma cases was score 9 (43.8%) with predominant pattern being pattern 4. Similarly, the most common grade group was grade group 5 (46.9%). The commonest histopathological diagnosis was BPH (59.3%), followed by adenocarcinoma (26%). Immunohistochemistry, p63 was performed in 18 suspected prostatic adenocarcinoma mimicker cases, among which 5 cases were positive.

Conclusions

PSA is a sensitive tumor marker, helpful in diagnosis of prostatic cancer. However, histopathology remains the gold standard for the diagnosis of prostatic carcinoma. Immunohistochemistry, p63 plays an important role in differentiating prostatic adenocarcinoma mimickers from adenocarcinoma.

Keywords: gleason system scores; immunohistochemistry; prostate-specific antigen; prostatic carcinoma.

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INTRODUCTION

The prostate is a retroperitoneal fibromuscular organ that encircles the neck of the bladder. Enlargement of the prostate gland leads to problems related to urinary tract obstruction. Pathologies commonly affecting prostate are inflammation and tumors. BPH is the most common benign prostatic disease and begins from the transition zone while prostatic adenocarcinoma arises from the peripheral zone of the prostate gland. Prostatic lesions are responsible for significant morbidity and mortality among elderly men throughout the world.² According to Globocan 2022, prostate cancer was the second most commonly diagnosed cancer and the fifth leading cause of cancer death among worldwide.3 Diagnosis of prostatic adenocarcinoma includes correlation of clinical manifestations, digital rectal examination, ultrasonography, PSA level and prostatic biopsy for histopathology.4 Serum PSA levels can be used for diagnostic, therapeutic and prognostic purposes in prostatic adenocarcinoma. Histopathological findings provide important diagnostic information for prostatic diseases.⁵ Grading of prostate cancer is done by Gleason scoring system which depends on the degree of glandular architectural differentiation and growth pattern of tumor in relation to the stroma.⁶ However, the diagnosis of prostatic carcinoma on routine biopsies can be challenging if there is limited tissue sample, small foci of carcinoma or benign mimickers of prostatic carcinoma. Therefore, the application of immunohistochemistry is helpful and necessary to distinguish prostatic adenocarcinoma from benign mimickers. Combined cocktail immunohistochemistry markers, including AMACR, p63 and 34BE12 play a role in diagnostically challenging cases.⁵ The aim of this study is to evaluate the actual incidence of different prostatic lesions, to correlate histopathological diagnosis with serum PSA level and to use p63 immunohistochemistry in prostatic adenocarcinoma mimickers to distinguish from adenocarcinoma.

METHODS

A hospital based cross sectional study was carried out at Department of Pathology, TUTH, over a period of 1 year. Ethical Clearance was obtained from Institutional Review Committee, TUTH [Ref. no. 310/(6-11) E²/076/077]. The data were entered in SPSS version 26 and analyzed. Continuous variables were expressed in frequency and percentage. Discrete variables were expressed in mean and median depending upon the type of distribution of data. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to check for normality of distribution. Mean values were taken for normal distribution and median values were taken for skewed distribution. Mood's median test was used to compare median values. Results were considered statistically significant at an alpha of 5% (p < 0.05). Correlation was evaluated non-parametric Spearman's correlation using coefficient.

RESULTS

A total of 123 cases of prostatic lesions were enrolled, out of which 91 cases (74%) were benign, and 32 cases (26%) were malignant. The most common age group was 61-70 years for both benign (40 cases, 44.0%) as well as for malignant lesions (14 cases, 43.7%). Minimum and maximum ages for prostatic lesions noted were 49 years and 96 years respectively. The median PSA level for malignant prostatic lesions was higher (33.55 ng/mL) than that for benign lesions (3.21 ng/mL) and the difference was statistically significant (p-value= <0.001). In histopathological examination, the most common pattern seen was discrete glands in 29 cases (90.6%) followed by fused glands in 16 cases (50%) and sheets pattern in 8 cases (21.8%) of arrangement. Perineural invasion was noted in 15 cases (46.9%) and lymphovascular invasion was noted in 2 cases (6.25%). The most common Gleason system scores in prostatic adenocarcinoma cases were score 9 including 7 cases (21.9%) of 5+4 and 7 cases (21.9%) of 4+5, followed by score 6 (6 cases, 18.7%) and score 7 (6 cases, 18.6%). The most predominant pattern was pattern 4 (25 cases, 46.3%), followed by pattern 3 (17 cases, 31.5%) and pattern 5 (12 cases, 22.2%). Similarly, The most common grade group was grade group 5 (15 cases, 46.9%), followed by grade group 1 (6 cases, 18.8%) and grade group 4 (5 cases, 15.6%). In comparison of PSA interval with

grade group for malignant lesions, majority cases had PSA level >20.1 ng/mL, among which grade group 5 was the commonest (12 cases, 60%) followed by grade group 1 (3 cases, 15%) and grade group 3 (3 cases, 15%). Weak positive correlation was seen between increasing grade group of prostate cancer and increasing PSA level (Correlation Coefficient= 0.289). p63 immunostain was performed in 18 suspected prostatic adenocarcinoma mimickers, out of which 5 cases (28%) were positive. After immunostaining in 18 cases, single case of prostatic carcinoma turned out to be AAH and 3 cases of AAH turned out to be prostatic carcinoma (Table 1). The commonest histopathlogical diagnosis was BPH (73 cases, 59.3%), followed by adenocarcinoma (32 cases, 26%). Other histopathological diagnoses were BPH with inflammation, AAH, basal cell hyperplasia and partial atrophy. The majority of BPH lesions had PSA range of 0-4 ng/mL (43 cases, 58.9%). Similarly, the majority of prostatic adenocarcinoma had PSA range of > 20.1 ng/mL (20 cases, 62.5%) (Table 2). None of the benign cases had PSA level >20 ng/mL and likewise, no malignant cases had PSA level < 4 ng/mL. The sensitivity and specificity of serum PSA for detection of prostatic adenocarcinoma at cutoff 4.0ng/mL were 100% and 56% respectively.

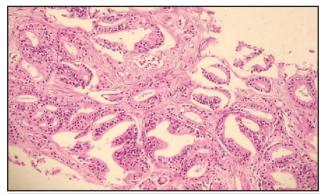


Figure 1. Prostatic adenocarcinoma, Gleason score 4+3 showing predominant pattern 4, cribriform glands (H&E, magnification X200).

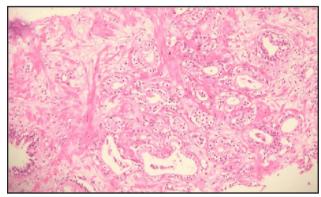


Figure 2. Partial atrophy showing small glands having pale to clear cytoplasm with small crinkly nuclei without prominent nucleoli (H&E, magnification X200).

Table 1. Re-evaluation of histopathological diagnosis after P63 immunostain.								
Provisional histopathological Diagnosis	Benign (After Immunostain)	Adenocarcinoma (After immunostain)						
Acinar adenocarcinoma (n=10)	1	9						
Atypical adenomatous hyperplasia (n=6)	3	3						
Basal cell hyperplasia (n=1)	1	0						
Partial atrophy (n=1)	1	0						
Total (n=18)	6	12						

Table 2. Distribution of histopathological diagnosis based on PSA										
PSA level (ng/dl)	AAH	ADC	всн	ВРН	BPH with prostatitis	Inflammation	PA	Total no. (%)		
0-4.0	0	0	0	43	2	5	0	50 (40.6%)		
4.1-10.0	0	2	1	24	3	1	0	31 (25.2%)		
10.1-20.0	3	10	0	6	0	1	1	21 (17.1%)		
>20.1	1	20	0	0	0	0	0	21 (17.1%)		
Total n(%)	4	32	1	73	5	7	1	123(100%)		

ADC: Adenocarcinoma, AAH: Atypical Adenomatous Hyperplasia, BCH: Basal Cell Hyperplasia, BPH: Benign Prostatic Hyperplasia, PA: Partial Atrophy.

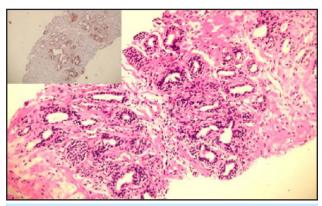


Figure 3. Adenosis showing lobules of glands with benign appearing nuclei (H&E, magnification X200). Basal cells showing p63 nuclear staining (inset).

DISCUSSION

Enlargement of prostate is an age-related process and the incidence increases with increasing age in male population beginning in their forties. One of the studies has shown that the rate of enlargement of prostate increases from 20% at 40 years of age to 70% by age of 60 and 90% by eighth decade of life.9 Diagnosis of prostatic lesions is made by clinical features, digital rectal examination, radiological findings, serum PSA value and histopathological findings.1 Among them, histopathology remains the gold standard for the final diagnosis. 10 In this study, 123 cases of prostatic lesions (91 benign and 32 malignant) were included during the period of one year in Department of Pathology, T.U. T.H. Age groups afflicted with prostatic pathologies in our study ranged from 49 years to 96 years. The age range was similar to the study done by Ramalingiah et. al¹¹ and Sinha et al.¹² In our study, 74% of the specimens were of benign lesions and 26% specimens were of malignant lesions. The findings were comparable to the studies done by Hirachand et al.,14 (79.7% and 20.3%) and Puttaswamy et al.,15 (80.6% and 19.4%). The commonest age group for benign prostatic hyperplasia as well as prostatic adenocarcinoma in our study was 61 to 70 years (43.9%). Similar findings were seen in studies done by Godbole et al., ¹³ Yousfani et al., 16 and Josephine A. 17 In study done by Chauhan et al.,18 the commonest age group for BPH was 60-69 years (54.9%) similar to our study. But their study

showed that commonest age group for prostatic adenocarcinoma was 70-79 (45%). In this study the median PSA values for benign and malignant lesions were 3.21ng/mL and 33.55ng/mL respectively. PSA level had significant association among benign and malignant lesions. In a study by Chauhan et al.18 reported that mean PSA value for benign prostatic hyperplasia was 5.05+ 3.15 ng/mL and that for prostatic carcinoma was 59.65+38.6 ng/mL. Another study by Hirachand et al.,14 demonstrated positive correlation of PSA level comparing in benign and malignant lesion. In contrast, study by Banerjee et al., 19 found no significant association of rising PSA level among benign and malignant lesions. In our study, the most common range of serum PSA value for benign lesions was <4 ng/mL (54.9%). Likewise, for malignant lesions, the most common range of PSA level was >20.0 ng/mL (62.5%). There were no malignant cases with PSA level < 4.0 ng/mL. Chauhan et al. 18 in their study also came up with correspondent findings. The most common Gleason system scores in prostatic adenocarcinoma cases was score 9 including 7 cases (21.9%) of 5+4 and 7 cases (21.9%) of 4+5 followed by score 6 (6 cases, 18.7%) and score 7 (6 cases, 18.6%) (Figure 1). Similar findings were reported by Deshmukh et al.,20 and Shah et al.,21 In another study done by Bhat et al.,22 found that Gleason score 8 and 9 were the most common with 28.5% cases of each. In contrary, studies of Puttaswamy et al.15 and Chauhan et al.,18, the most common Gleason score was score 7. The predominant pattern was pattern 4 (25 cases, 46.3%), followed by pattern 3 (17 cases, 31.5%) and pattern 5 (12 cases, 22.2%). Similar findings were observed in a study by Chauhan et al. 18, with pattern 4 being the most common predominant pattern (21 cases, 52.5%) followed by pattern 3 (14 cases, 35%). In another study by Deshmukh et al.²⁰, predominant patterns reported were pattern 3 (8 cases, 44.44%) and pattern 4 (7 cases, 38.9%). The most common grade group in our study was grade group 5 (46.9%), followed by grade group 1 (18.8%). The findings were congruent with the study by Shah et al.21 with grade group 5 being the commonest grade (45%) followed by grade group 4 (30%). Majority of cases of the grade group 5 (60%) in our study had serum PSA value >20.1 ng/mL. Similar findings were reported in studies done by Yousfani et al.,16 and Baneriee et al.19 Our study showed a weak positive correlation between increasing grade group of prostate cancer and increasing PSA level (Correlation Coefficient= 0.289). Immunohistochemical assays for the identification of basal cells represent a valuable tool for the differential diagnosis of benign versus malignant prostatic lesions, when morphology alone is not sufficient for the definitive diagnosis.²³ p63 has recently generated much interest due to its expression in the basal cells of the prostate and it is essential for prostate development.¹⁹ The study done by Grisanzio et al., 23 highlighted the role of p63 in the development of prostate gland and conclued its importance not only in the diagnosis of the prostate carcinoma but also in the understanding of the basic mechanisms that regulate prostate organogenesis. Signoretti et al.²⁴ demonstrated that immunohistochemical expression of p63 in prostatic acini was limited to basal cells with a nuclear pattern of immunoreactivity, while benign secretory cells and prostatic cancers were consistently negative. The p63 immunostain detects p63 protein in the nucleus of basal cells. It seems to be more sensitive in the basal cell detection than the immunostain using the 34βE12 antibody.²⁵ In cases of prostate cancer mimickers, positive basal cellspecific marker staining may definitively label a focus as benign.⁷ Samundeeswari et al.,² found sensitivity and specificity of p63 as 87.5% and 100% respectively. In this study, p63 immunostain was performed in 18 suspicious cases and out of them 5 cases (28%) were positive. After immunostaining a single case of suspected prostatic cancer turned out to be non neoplastic and three cases of benign lesions turned out to be neoplastic. There was a single case of partial atrophy with inconclusive p63 IHC, where the diagnosis was made based on histomorphological features. The diagnosis of basal cell hyperplasia remained unchanged even after the immunostaining (Figure 3). Partial atrophy is the commonest benign mimicker of prostatic carcinoma on needle biopsy 6 (Figure 2). In our study, atypical adenomatous

hyperplasia the was commonest prostatic adenocarcinoma mimicker. Garg et al.,10 reported basal cell hyperplasia in 3.9% cases, AAH in 1.7% cases and atrophy in 0.6% cases. Similarly, in a study by Mahapatra et al.,8 incorporating 50 cases of prostatic adenocarcinoma demonstrated basal cell hyperplasia was reported in 26%, AAH in 2% and prostatic atrophy in 4% cases. The commonest histopathological diagnosis in our study was BPH (59.3%), followed by adenocarcinoma (26%), BPH with inflammation (9.7%), AAH (3.3%), basal cell hyperplasia (0.8%) and partial atrophy (0.8%). In addition, a single case of high grade prostatic intraepithelial neoplasm (HGPIN) was also observed in a radical prostatectomy specimen in which prostatic adenocarcinoma was diagnosed. Thus, separate entity of HGPIN was not made. Studies done by Chauhan et al. 18 and Akhter et al., 26 also showed BPH to be the commonest histopathological diagnosis, followed by prostatic adenocarcinoma. In another study done by Anushree et al..27 BPH was the most common diagnosis, followed by BPH with prostatitis, PIN and adenocarcinoma. In our study, among BPH lesion the most common range of PSA was 0-4 ng/mL (58.9%), followed by 4.1-10.0 ng/mL (32.8%) and 10.1-20.0 ng/mL (8.2%). Similarly, maximum number of prostatic adenocarcinoma had PSA range of >20.1 ng/mL (62.5%), followed by 10.1-20.0 ng/mL (31.3%) and 4.1-10.0 ng/mL (6.3%). There were no BPH cases with PSA >20.1 ng/mL or prostatic adenocarcinoma with PSA < 4.0 ng/mL were observed. All the cases of atypical adenomatous hyperplasia (100%) had PSA value in the range of 10.1-20 ng/mL. Single case each of basal cell hyperplasia and partial atrophy were detected and they had PSA value in range of 4.1-10 and 10.1-20ng/mL respectively. Similar findings were seen in the study done by Mainali N. et al., which showed that the commonest range of PSA among BPH cases was <4.0 ng/mL (62.5%), followed by 4.1-10.0 ng/mL (33.3%). They also found that the commonest range of PSA among prostatic adenocarcinoma was >20.1ng/mL (60%) followed by 4.1-10.0 gm/mL (20.0%) and 10.1-20.0 ng/mL (13.3%). They also found a single case of prostatic adenocarcinoma with PSA level <4.0 ng/mL which differ from our study. Similar findings were shown in study done by Chauhan et al.¹⁸ except that they showed 5.55% cases of BPH having PSA value >20.1 ng/mL which differ from our study. Another study done by Mahapatra et al.8 found that 86.3% cases of mimickers of carcinoma had PSA value <4.0 ng/mL and 13.7% cases had PSA value 4.0-10.0 ng/ mL. The sensitivity and specificity of serum PSA at cutoff 4.0ng/mL in our study were 100% and 56% respectively. In a study by Hoffman et al.29, PSA sensitivity and specificity at cutoff 4 ng/mL were 86% and 33% respectively. On the contrary, study done by Nogueira et al.,30 reported sensitivity and specificity 20.5% and 93.8% respectively which was different from our study.

CONCLUSIONS

Prostatic diseases are common among elderly males, the most common age group affected being 61 to 70 years in this study. Benign prostatic hyperplasia was the most common prostatic lesion found, followed by prostatic adenocarcinoma. Both benign and malignant pathologies can cause an increase in PSA level with

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significantly higher level of PSA in malignant cases. This study has also elucidated that the majority of the adenocarcinoma cases encountered were of high grade, which could possibly be due to late detection of the disease. Hence, we suggest that a routine screening for prostatic malignancy in elderly males may be helpful for early detection of the disease and also for better management as well as improved prognosis in the patients. PSA assessment can be used for screening purpose due to its high sensitivity at cutoff of 4ng/mL. Patients with PSA > 4ng/mL should be kept on close follow up and if needed, should also be considered for early biopsy. Similarly, based on our observation, p63 can be beneficially used in diagnostically challenging cases in order to distinguish prostatic adenocarcinoma from its mimickers.

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