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IJPBS |Volume 3| Issue 1 |JAN-MAR |2013|162-178

Review Article
Biological Sciences

CLINICO-PATHOLOGICAL STUDY OF BENIGN & MALIGNANT LESIONS OF PROSTATE

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ABSTRACT

***Aims**: Benign prostatic hyperplasia and adenocarcinoma are common diseases that account for considerable morbidity and mortality of ageing population. In cancer related deaths in men, the prostatic cancer is the second most common to lung cancer. Purpose of this study is to analyze various clinicopathological features in benign and malignant prostatic lesions, to correlate of benign and malignant prostatic lesions with serum prostate specific antigen (PSA) and to analyze the utility of Alcian Blue (AB) and Elastin Von Gieson (EVG) stain in evaluation of prostatic adenocarcinoma. **Methods**: All the prostatic specimens received in the histopathology department of our institute, over the period of 2 years, from June 2010 to July 2012 were analyzed. **Results**: 83%(n=83) were BPH , 17% (n=17) were adenocarcinoma. 2 cases showed changes of prostatic intraepithelial neoplasia(PIN) which were associated with adenocarcinoma. Out of 22 specimens in which PSA was available, 10 cases were adenocarcinoma. PSA was raised in all 10 cases. In our study wispy blue material was seen in 17.6% cases, while A.B. stain demonstrated mucin in 35.2% of cases. **Conclusion**: Benign prostatic hyperplasia was the commonest lesion. PSA level of >10ng/ml has high positive predictive value. EVG stain clearly highlighted the neoplastic acini and was useful in upgrading Gleason score in one case. Alcian Blue stain confirms the acidic mucinous nature of luminal secretions which are diagnostic of neoplastic acini, as against the neutral mucin seen in the non neoplastic acini.*

KEY WORDS

Prostate, Hyperplasia, Adenocarcinoma, PSA, Gleason score.

INTRODUCTION

The prostate gland is the largest accessory reproductive organ in male. The prostate is an exocrine gland and forms a significant component of seminal fluid. Benign prostatic hyperplasia and adenocarcinoma are common diseases that account for considerable morbidity and mortality of ageing population. In cancer related deaths in men, the prostatic cancer is the second most common to lung cancer.[1] Prostate cancer is responsible for 3% of all deaths in men over age of 55 years.[2] Incidence of prostatic cancer increases rapidly with age than any other cancer. Thus, the numbers of prostate cancer cases are expected to increase, as average age of men is increasing.[3] The prostatic biopsies, total prostatectomy specimens and prostatic chips obtained by transurethral resection of prostate (TURP) forms a significant volume of surgical pathology material received in histopathology department of our institute, accounting for 1.97% of all surgical specimens.

Due to work done by various authors on prostate in last two decades, histological spectrum of benign prostatic hyperplasia has broadened and it has considerably expanded our knowledge

about pathology and biology of prostatic adenocarcinoma, special histological variants and most importantly about possible precursor lesions and prognostic factors. High-grade prostatic intraepithelial neoplasia (PIN) is considered as premalignant condition of prostatic adenocarcinoma. But some authors consider it as a separate entity. Establishing, or ruling out, the diagnosis of carcinoma of prostate has been a well known challenge for pathologists for many years and has become an even greater problem in recent times because of increased number of biopsy specimens and often limited amount of carcinoma, or questionable carcinoma, in such samples. There are many pitfalls associated with evaluation of prostatic adenocarcinoma, as there are many benign lesions, which mimic prostatic adenocarcinoma and requires considerable experience for correct diagnosis.Many investigators have studied various histomorphological features and tried to assess their usefulness in diagnosing or excluding prostatic adenocarcinoma.

As most of the patients of prostatic adenocarcinoma present at old age, it is necessary to weigh the benefits of aggressive treatment against possible morbidity, while treating the patients of prostatic adenocarcinoma. For this reason accurate staging and grading of prostatic carcinoma is mandatory. Many investigators have proposed various methods for grading of prostatic adenocarcinoma. But TNM staging and Gleason's grading system.is accepted worldwide.[4] Considering the magnitude of the problem and limited literature on prostatic lesions in india, the purpose of this study is to analyze various clinicopathological features in benign and malignant prostatic lesions, to correlate of benign and malignant prostatic lesions with serum prostate specific antigen (PSA) and to analyze the utility of Alcian blue (AB) and Elastin Von Gieson (EVG) stain in evaluation of prostatic adenocarcinoma.

MATERIALS AND METHODS

This is a prospective study of all the prostatic specimens received in the histopathology department of our institute, which is a tertiary public health care centre, during the period of 2 years, from June 2010 to July 2012.The prostatic material included prostatic biopsies, transurethral resection of prostate [TURP] chips and prostatectomy specimen. Our study included 100 prostatic specimens, which comprised of 22 prostatic biopsies, 77 TURP chips, and 1 prostatectomy specimens In cases of prostatic biopsies, all the tissue received was fixed and processed. In cases of TURP chips 3 to 4 cassettes were prepared in each case, which accommodated approximately 50% of total tissue, and weighed approximately 9 to 12gms. Specimens weighing <=12 grams were submitted entirely. In general, random chips were submitted; however, if some chips were firmer or had a yellow or orange-yellow appearance, they were preferentially submitted. If a carcinoma was detected in a TURP specimen that was not entirely submitted then all the remaining tissue was processed entirely irrespective of the amount.

In case of prostatectomy specimens, multiple sections were made at the distance of 3 to 5mm. The slice in which tumor appears closest to the resection margin, is submitted entirely after dividing into adequate number of sections. All the tissues were fixed in 10% buffered formalin and paraffin processed. 3 to 5 micron sections were cut and stained with with routine Hematoxylin and Eosin (HE) stain. Alcian Blue (AB) and Elastin Von Geison (EVG) stains were done in cases of adenocarcinoma of prostate.

All the slides were thoroughly evaluated for histological features. All prostatic lesions were

categorized into benign and malignant. In cases of benign enlargement of prostate, number of bits predominantly comprised of stromal component was counted and accordingly cases of benign prostatic hyperplasia were categorized as: Stromal predominant: >60% of the bits comprising of predominantly stromal component with presence of stromal nodules. Epithelial predominant: >60% of the bits comprising of predominantly epithelial component. Mixed glandular stromal: >40% but <60% bits comprising of predominantly stromal component.

Inclusion criteria: Any prostatic tissue received in department of pathology for histopathological examination.

Exclusion criteria: Non prostatic tissue.

OBSERVATIONS AND RESULTS

Out of 100 specimens of prostatic lesions received for histopathological examination, 83%(n=83) were BPH , 17% (n=17) were adenoccarcinoma. 2 cases showed changes of PIN which were associated with adenocarcinoma. Out of 100 cases, maximum specimens received were TURP chips 77 %, followed by prostatic biopsy material 22 % and prostatectomy specimens were only 1%.Most of the patients(94%) in our study presented with obstructive urinary tract symptoms viz. acute and chronic urinary retention, hesitancy, weak stream, terminal dribbling while 45% had urgency, increased frequency, dysuria and nocturia. Only 03 patients came with history of fever and 01 patient had the complaint of bone pain.

Majority of the cases of both BPH and adenocarcinoma were in the age group of 61-70 years, accounting for 46.98% and 47.0% respectively. Approximately 6% cases of both BPH and carcinoma occurred in the fourth decade. Only 01 case of BPH was found in third decade, while there was no case of carcinoma below the age of 40years. [**Table 1**]

Majority of the cases of both BPH and adenocarcinoma were in the age group of 61-70 years, accounting for 46.98% and 47.0% respectively. Approximately 6% cases of both BPH and carcinoma occurred in the fourth decade. Only 01 case of BPH was found in third decade, while there was no case of carcinoma below the age of 40years. Around half of the cases (50.64 %) showed stromal predominance type of hyperplasia, followed by mixed pattern of hyperplasia (33.76%).Prostatic hyperplasia with epithelial predominance was seen in only 15.60% cases.Cystically dilated glands and Basal cell hyperplasia were the prominent features noted in our study. Basal cell hyperplasia was seen in 23 cases (27.71). Squamous metaplasia was seen in 08 cases (09.63%).Corpora amylacea was seen in 50 cases (60.24%).Infarcts were found in 4.81% cases [**Table2**]

Chronic inflammatory cells of varying degree were found in 87.9% (n=77) cases in our study. More than half of the cases (n=44) showed only mild chronic inflammation, while moderate to severe chronic inflammation was seen in 34% (n=29) cases. Acute inflammation was found in 4.81%(n=4) cases, while only 02 cases of granulomatous prostatitis were found, out of which one case was xanthogranulomatous prostatitis, and one case was post TURP granuloma. No case of tuberculous inflammation was found.

Only 03 cases of adenosis were found out of which 02 in TURP chips of BPH, while 01 was seen in adenocarcinoma. Adenosis was not detected in prostatic biopsies.Only 2 cases of PIN were noticed which were associated with adenocarcinoma. Both the cases of PIN showed tufted pattern were in high grade category.

Out of 22 biopsy specimens in which PSA was available, 10 cases were denocarcinoma. Out of

these 10 cases PSA was raised in all 10 cases. Out of 48 cases of TURP/ prostatectomy, 41 were BPH and 07 were carcinoma cases. Out of 07 carcinomas PSA was raised >10 ng/ml in 06 cases.Out of 41 BPH cases PSA was raised >10ng/ml in 06 cases and normal in 15 cases. [**Table 3**]

Out of 22 prostatic biopsies, 10 cases had shown carcinoma i.e. 45.4%.

In 12 cases i.e. 54.6%, biopsies did not show any evidence of malignancy. But in these cases benign etiology i.e; glandular proliferation associated with inflammation was noted and on follow up, TURP was done and these cases turned out to be BPH so they were considered as BPH as our final diagnosis and were included in our 83 cases of BPH out of 100 cases.

Out of 17 cases, 10 cases (58.82%). of carcinoma were diagnosed on prostatic needle biopsies. In 06 cases, carcinoma was diagnosed on TURP chips, 02 of which represented incidental carcinoma in our study. Incidence of incidental carcinoma in our study is 02 out of total 77 TURP chips i.e.; 2.5%.

In our study pattern 3 was most common primary pattern (64.7%), while pattern 4 was most common secondary pattern. Tertiary pattern was not identified. We did not have pattern 1 and 2 in our study.[**Table 4**]

52.94% of prostatic carcinomas were of Gleason score 7, which fall under moderately poor category. In score 7, 07 cases were 3+4, and only 02 cases were 4+3 tumors. [**Table5**]

In our study, 76.4 % cases showed infiltrating pattern. About half the cases (52.9) showed hyperchromasia, and 07 cases had prominent nucleolus. Amphophilic cytoplasm was seen in 29.4 % cases, while pale to clear cytoplasm was noted in (35.2%) cases. Wispy blue tinged mucinous secretions were noted in 17.6% carcinomas, perineural invasion was noted in 11.7% carcinomas. Mitoses were seen in 2 cases.[**Table 6**]

In our study wispy blue material was seen in 17.6% cases, while A.B. stain demonstrated mucin in more number of cases i.e. 35.2%. No case of mucinous adenocarcinoma was detected in our study[**Table7**]

TABLE 1: show correlation of Age and Type of Lesion

Age group (Years)	Benign Prostatic Hyperplasia (BPH)		Adenocarcinoma	
	No. Of Cases	%	No. Of Cases	%
31-40	01	1.22	0	0
41-50	06	7.22	01	5.7
51-60	23	27.72	03	17.7
61-70	39	46.98	08	47.0
71-80	11	13.25	03	17.3
81-90	03	3.61	02	11.7
91-100	0	0	0	0

TABLE 2: show secondary Changes in Benign Prostatic Hyperplasia (BPH)

Features	No Of Cases (%)
A) Epithelial features	
Basal cell hyperplasia	23 (27.71)
Squamous metaplasia	08 (09.63)
Cystically dilated glands	29 (34.43)
B) Intraluminal features	
Corpora amylacea	50 (60.24)
Crystalloids	00
Blue tinged mucin	00
C) Infarct	04 (4.81)

TABLE 03: Correlation of PSA

PSA (ng/ml)	Biopsy (n=22)		TURP/Prostatectomy (n=48)	
	Carcinoma(n=10)	No e/o Carcinoma (12)	Carcinoma (n=07).	BPH (n=41)
0 to 4	0	02	0	15
4 to 10	02	06	01	20
>10	08	04	06	06

TABLE-4: Gleason Pattern

	Primary	Secondary	Tertiary Pattern
Gleason Pattern	**Pattern (N=17)**	**Pattern (n=17)**	**(n=00)**
	No. Of Cases (%)	**No. Of Cases (%)**	**No. Of Cases (%)**
1	00 (0)	00(0)	0(0)
2	00 (0)	00(0)	0(0)
3	11 (64.7)	05 (29.41)	0(0)
4	06 (35.3)	09 (53)	0(0)
5	00	03 (17.65)	0(0)

TABLE- 5: Gleason Score

Gleason Score	No. Of Cases (n=17)	%	Differentiation
6	03	17.64	MODERATE
7*	09	52.94	MODERATELY POOR
8	03	17.64	POOR
9	02	11.76	
10	00	0	

*** In score 7, 07 cases were 3+4, and only 02 cases were 4+3 tumors.**

TABLE 6: Ancillary Features Seen In Carcinoma: On H&E Staining

Ancillary Features Seen InCarcinoma	% Of Cases
A) Infiltrating pattern	(76.4)
B) Nuclear features	
Nucleomegaly	13 (76.4)
Irregular nuclear membrane	07 (41.1)
Hyperchromasia	09 (52.9)
Prominent nucleoli	07 (41.1)
Marginated nucleoli	05 (29.4)
Mitotic figures	02 (11.7)
C) Cytoplasmic features	
Amphophilic cytoplasm	05 (29.4)
Clear cytoplasm	06 (35.2)
D) Intraluminal secretions	
Blue tinged mucin	03(17.6%)
Eosinophilic amorphous material	09 (52.9)
Eosinophilic crystalloids	02 (11.7)
Collagenous micronodules	00
E) Perineural invasion	02 (11.7)
F) Retraction clefting	01(8.9)
G) Associated PIN	02 (11.7)

TABLE 7: Mucinous Differentiation of Adenocarcinoma of Prostate

Type Of Mucinous Pool	H&E-Stain (n=03)		After AB – Stain (n=06)	
	No. Of Cases	%	No. Of Cases	%
Intraluminal Mucin	03	17.64	06	35.29
Extraluminal Mucin Pool	00	00	00	00

DISCUSSION

Benign prostatic hyperplasia is extremely common disorder in men over age 50.[5] The prevalence of this disease is believed to be highly significant in most communities. In cancer related deaths in men, the prostatic cancer is the second only to lung cancer.[1]

Prostate cancer is responsible for 3% of all deaths in men over age of 55 years.[2] In this prospective study, 100 prostatic specimens received over the period of two years in a tertiary public health care centre were analyzed. In our study BPH (83%) was the commonest lesion in specimens obtained at surgical pathology, followed by adenocarcinoma (17%). Out of 17 cases of adenocarcinoma two were associated with PIN. Our findings are in concordance with the study of Brawn et al.[6] in which out of 2842 prostatic specimens 14% cases were of adenocarcinoma where as BPH was diagnosed in 79% of cases. Our findings are similar to his study.

In about l/3rd of the cases, in which hard nodular prostate was palpated on digital rectal examination needle biopsy was performed. Transurethral resection of prostate (TURP) was done in patients having enlarged firm prostate with evidence of prostatic enlargement on sonography. Prostatectomy was done only in 01 patient. As compared to western literature, prostatectomy is done less frequently in India, and formed only 1% of total 100 prostatic specimens received in our institute. The possible explanation would be the fact that open prostatectomy is the treatment of choice for early prostate cancer, and in India, because of lack of public awareness and proper screening methods; prostate cancer is often diagnosed at a late stage.

TURP chips formed bulk of the specimens in our study, accounting for 77% of total specimens. (Table 2) This can be explained by the fact that TURP is the treatment of choice of BPH, as it is a simple procedure with fewer complications as compared to open prostatectomy. Also, BPH is much more common prostatic lesion than adenocarcinoma, and our study included 83 (83%) cases of BPH.

In study done by Brawn et al.[6], 2842 prostate specimens were included. Out of these, TURP chips formed 83.7% of total cases. Our findings were in accordance with his study.

Most of the patients came with obstructive urinary tract symptoms, while irritative lower urinary tract symptoms were the next common mode of presentation.[Table 3] Obstructive symptoms included hesitancy, weak stream, terminal dribbling and acute or chronic retention of urine. Irritative symptoms included urgency, increased frequency, dysuria and nocturia. 94% of patients presented with obstructive symptoms in our study.

In a study by Gaudin et al.[7] in 1998; the most common presentation was retention of urine that is obstructive symptom. In a study of 50 cases by Herawi et al.[8] in 2006; the major presenting signs and symptoms were urinary obstructive symptoms in more than 50% of patients. In another study by Wade et al.[9] in 2001; obstructive symptoms were the most

common presentation. In a study done by Khan et al.[10], in 2005, a total of 345 BPH patients were included in the study. Of these 270 (78.3%) patients presented with urinary retention. Our findings were in accordance to the above studies. In a study by Rijal et al,in 2011[11] the most common symptom associated with BPH with prostatitis was dysuria, however, there was a lot of overlap of the symptoms. In our study only 3 patients presented with fever. One of the patients came with bone pain. None of the patient came with the complaint of painful ejaculation.

Adenocarcinoma and BPH most commonly presented in the age group 61-70 years (7th decade). The mean age of presentation for BPH and adenocarcinoma was 63.8 years and 66.07years respectively. [Table 4] Youngest patient of BPH was 38 years, and the oldest was 86 years. In adenocarcinoma the youngest patient was 48 years, and the oldest was 83 years. According to study done by Brawn et al, the average age of presentation for BPH and adenocarcinoma were 69 and 67 years respectively.[12] In study done by Quian et al.[13], mean age for carcinoma was 64.4 years (44 to 77years). According to study done by Di Silverio et al.[14], mean age for BPH was 68.9years. In a study done by Kyungeun et al.[15] mean age was 64.4 yrs (42-78yrs) in 148 cases. Our findings are similar to the above studies.

There were 83 cases of BPH, which were diagnosed on 71 TURP chips and 12 on biopsy specimens (Table 5). According to study done by Vigilone et al.[16] with the exception of stromal nodules, glandular proliferation and inflammation, histological findings on biopsy are not specific for either clinical or pathological BPH. In a study done by Shakya et al.[17] all (106) specimens included in the series having BPH showed glandulostromal proliferation of which maximum cases showed predominantly stromal pattern. These findings were similar with our study. In our study, out of the 77 cases, 39 (50.64%) cases showed predominantly stromal hyperplasia with presence of stromal nodules, 26 (33.76%) cases showed mixed glandular-stromal pattern of hyperplasia, while only 12 (15.6%) cases showed predominantly epithelial hyperplasia. (**Table 5**) Most of the cases showing stromal predominant hyperplasia came with obstructive urinary symptoms such as acute or chronic retention of urine. In one study, Shapiro et al.[18] noted that stromal predominant nodules are more symptomatic than those of the other types. Our findings were in accordance with this study. TURP is usually done in the patients, which are clinically symptomatic. Thus it is obvious to find predominantly stromal hyperplasia in TURP specimens. BPH is classified in various different methods. The classification based on relative proportion of stromal and epithelial component is the simplest one, and was used in our study by applying the following criteria.[4,18]

1. **Stromal predominant:** >60% bits comprising of predominantly stromal component with presence of stromal nodules.
2. **Epithelial predominant:** >60% bits comprising of predominantly epithelial component.
3. **Mixed glandular-stromal:** >40% but <60% bits comprising of predominantly stromal component. In stromal nodules, capillary like blood vessels are surrounded by small, bland spindle cells with tapered nuclei and little cytoplasm along with marked edema with mild mononuclear infiltrate, giving them pale nodular appearance on scanner view.

Predominant epithelial hyperplasia usually occurs within the transition zone. The glands are usually medium to large, sometimes cystic and may show architectural complexity and papillary infoldings The epithelium usually has a distinct

double layer of secretory and basal cells, but the basal cells are not always conspicuous. The cytoplasm is abundant and clear. Nuclei are uniform and nucleoli are inconspicuous. Mitosis is rare.[19]

Secondary changes associated with BPH were in the form of cystic dilation of glands, squamous metaplasia, basal cell hyperplasia, intraluminal secretions, inflammation, (Table 6) Similar changes were found in many studies.[17,20-23]

Adenosis and PIN are considered preneoplastic lesions of prostate although the evidence linking adenosis and adenocarcinoma is considerably weaker than the relating PIN and cancer.[5] Adenosis is usually seen in transition zone and PIN is usually seen in peripheral zone[5,24]

In our study, out of 100 specimens, adenosis was diagnosed in 3 cases out of which 2 were diagnosed in TURP specimens in association with BPH and one in prostatectomy specimen which was associated with carcinoma. Therefore the incidence of adenosis in carcinoma in our study was 1%. We did not encounter any case of adenosis in biopsy material. In two major studies done by Bostwick et al.[25] and Brawn et al.[6] adenosis has been identified in 1.5 and 6.1% of transurethral resectates respectively. It is uncommon in needle biopsy specimens. Our findings are in accordance with these studies.

Prostatic Intraepithelial Neoplasia (PIN): PIN is characterized by intraluminal proliferation of secretory epithelium that displays a spectrum of cytologic changes culminating in those that are indistinguishable from carcinoma. In our study, following prominent histological features helped us in diagnosing and grading PIN.[4] 1). Increased cellularity. 2] Pseudostratification 3] Intraluminal papillary formation 4] Bridging of lumen 5] Cribriform formation. PIN can be graded into a] Low grade PIN which is characterized by slight increase in cellularity, some variation in nuclear size, focal hyperchromasia and appearance of small nucleoli. b] High graded PIN is characterized by definitive increase in cellularity, nuclear pseudostratification , hyperchromasia and presence of large nucleoli. Various normal structures, benign, metaplastic, reactive and neoplastic conditions can be confused with PIN.

As PIN was considered preneoplastic lesion, various investigators studied incidence and tried to evaluate its preneoplastic role. In autopsy study, Sakr et al.[26]found that incidence of PIN precedes that of carcinoma by 10 years. The three major studies of PIN were done by McNeal and Bostwick.[27], Kovi et al.[28] and Troncoso et al.[29]

All these studies documented a greater incidence of PIN of some grade in carcinomatous glands than in benign glands. Also noted was a correlation between the quantity of PIN and multifocality of concurrent carcinoma. Like carcinoma, PIN was mainly identified in the peripheral zone.[5,25] Davidson et al.[30] found adenocarcinoma in 35% of subsequent biopsies from patients with previous diagnosis of PIN, as compared with 13% in control group without PIN. Incidence of PIN: Qian et al.[13] encountered PIN in upto 16.5% of contemporary needle biopsies. He also noted PIN in 86% of prostatectomy specimens with diagnosed adenocarcinoma. Pacelli et al.[31] found PIN in 2.4% of TURP chips. In our study, there were 2 cases of PIN which were found in carcinoma giving the incidence of 2%.

In our study the finding was similar with Picelliet al.[29] and Shakya et al.[17] In our study incidence of PIN in carcinoma was low, as compared with the literature. This can be attributed to the fact that cases of carcinoma in our study were predominantly needle biopsies providing limited material. The other main reason could be the single core biopsies done in our institute as against multiple core biopsies in other studies.

Bostwick et al.[32] studied various architectural patterns of PIN. Four common patterns of PIN were identified, usually with multiple patterns in each case: tufting (87%), micropapillary (85%), cribriform (32%), and flat (28%). In our study we found only tufted pattern. Both the cases of PIN were high grade.

Prostate specific antigen (PSA): PSA is the best marker for prostatic carcinoma. Serum PSA is usually advised to the patients who come with obstructive urinary symptoms and in whom hard nodule is palpable on digital rectal examination. Normal serum PSA is 0-4ng/ml. There are few theoretical limitations to the use of this serum marker. A normal PSA level does not exclude diagnosis of carcinoma. About 33% of cancers were detected in men who had PSA levels within normal limits. Moreover false positive results are also common; since PSA levels are often elevated in men with common benign conditions such as BPH or acute prostatitis [2, 30]

In our study, serum PSA was available in 70 cases. Out of these cases, 22 cases were biopsy specimens, 47 cases were TURP specimens, while 1 case was prostatectomy specimen. Out of these 22 biopsy specimens with available PSA levels, 10 were carcinoma, while 12 cases were negative for malignancy. PSA was raised in all 10 (100%) cases. 10 biopsies in clinically suspected cases with high PSA were negative for malignancy. Reasons may be that in our institute usually single core biopsies are done, so the chances of missing focus of malignancy are high. Out of 48 TURP/prostatectomy specimens with available PSA levels, 7 cases were carcinoma while 41 were BPH. Out of these 7 cases, PSA was raised in all 7 cases.

Out of 41 BPH cases, 26 cases had high PSA. The reasons for this false positivity can be attributed to acute prostatitis, severe chronic inflammation, increasing age. In our study positive predictive value and negative predictive value of PSA were calculated as follows:

True positive (TP): Serum PSA >4ng/ml or the respective range with histological evidence of carcinoma.

True negative (TN): Serum PSA within normal range (0-4ng/ml) and no histological evidence of carcinoma.

False positive (FP): serum PSA >4ng/ml or the respective range but no histological evidence of carcinoma.

False negative (FN): Serum PSA within normal range (0-4ng/ml) with histological evidence of carcinoma.

Positive predictive value=TP/TP+FP x 100 Negative predictive value= TN/TN+FN x 100The positive predictive value for PSA level >10ng/ml was 58.33% in our study. The positive predictive value for PSA levels 4-10ng/ml was 10.3% in our study. According to studies done by Brawer et al. positive predictive value for serum PSA >10ng/ml was 60-70%, while it was 20-30% for serum PSA 4-l0ng/ml.[33]

Our findings were in accordance with Brawer et al.[33] certain variations are may be due to difference in sample size in studies. We did not calcuated the negative predictive value because out of 100 cases in all the 17 cases diagnosed as carcinoma, the PSA value was not in the normal range. It was raised in all cases.

Total number of biopsies out of 100 cases were 22. The indication of prostatic biopsy almost always is to rule out prostate carcinoma. In our study adenocarcinoma was detected in 10 cases (45.4%) in prostatic biopsies, which is considerably expected.

12 biopsies (54.6%) were negative for adenocarcinoma. Reasons could be single core biopsies done in our institute. So the chances of missing focus of malignancy were high.

But in these cases benign etiology i.e; glandular proliferation associated with inflammation was

noted and on follow up, TURP was done and these cases turned out to be BPH so they were considered as BPH as our final diagnosis and were included in our 83 cases of BPH out of 100 cases. In a study done by Cheville et al.[34] out of 1000 consecutive needle biopsies, almost 5% were reported as 'Suspicious of carcinoma'. Most common factors responsible include dense inflammation obscuring morphology of glands and relatively scanty amount of tissue with few atypical glands. In our study no case was reported as 'Suspicious of carcinoma' may be due to difference in sample size.

Establishing, or ruling out, the diagnosis of carcinoma of prostate has been a well known challenge for pathologists for many years and has become an even greater problem in recent times because of increased number of biopsy specimens and often limited amount of carcinoma, or questionable carcinoma, in such samples. In our study we have tried to analyze various histomorphological features such as various types of intraluminal secretions, morphological features of nucleoli, and tried to assess their usefulness in diagnosing or excluding prostatic adenocarcinoma. In our study there were 17 cases of adenocarcinoma, which accounts for (17 out of 100) 17% of total cases. Out of these 17 cases, 10 (58.82%) cases were detected on needle biopsies, 6 (35.29%) cases were detected on TURP chips and 1 (5.88%) cases were detected on prostatectomy.

When prostatic tissue removed for clinically benign hyperplasia of the prostate and histological examinations reveals carcinoma, it is called incidental prostatic carcinoma.

According to study by Mai et al[35], there was a decrease in incidence of incidental carcinoma over the period of last 10 years. Specifically, there was a significant decrease in T1b carcinoma over time, while the incidence of Tla carcinomas remained unchanged with the introduction of PSA screening. Furthermore, incidental carcinomas from the period 1997-1999 were associated with a higher proportion of cases of low-grade carcinoma. In our study, 06 out of 77 TURP chips showed presence of carcinoma out of which 2 cases (2.5%), represents incidental prostate cancer.

Gleason grading:

In our study we used Gleason grading system [36] which is most popular worldwide. Important features of various patterns can be summarized as follows:

Pattern-1 Closely packed, single, separate, round, uniform glands with well defined margins.

Pattern-2 Similar to pattern 1, but the glands are less uniform and less well defined margins.

Pattern -3 The size of glands is variable. Both small and large glands and a papillary or cribriform pattern appear. Margins are poorly defined.

Pattern-4 small fused glands; the glands may have papillary, Cribriform or solid pattern.

Pattern-5 Few discernible glands; a comedo pattern is usually present. Tumor cells infiltrate the stroma as single cells or as ill defined cords. The presence of necrosis in any pattern automatically upgrades it to pattern 5.

The Gleason score: It is the sum of the primary (most predominant) Gleason grade and the secondary (second most predominant) Gleason grade. Where no secondary Gleason grade exists, the primary Gleason grade is doubled to arrive at a Gleason score.

Tertiary pattern is least common, which show 3 different Gleason patterns[36]. According to recent literature[37,38] tertiary pattern should be reported in diagnosis only if it is Gleason pattern 4 or 5. It should be reported even if it is less than 5%, because presence of even small amount of high grade tumor affects the prognosis. The primary and secondary grades should be reported in parenthesis after the Gleason score,

i.e. Gleason score 7(3+4) or 7(4+3). When multiple needle biopsy specimens are submitted and they have differing Gleason scores, an overall (composite) Gleason score for the case should be clearly reported in a note.[36,-38]

Differentiation score: [39]

a) Well-differentiated 2-4
b) Moderately differentiated 5-6
c) Moderately differentiated / poorly differentiated 7
d) Poorly differentiated.8-10

In pattern 7, 3+4 tumor has been found to have better prognosis than 4+3 tumor. This grading system has been used in classifying carcinoma in this study.

The rarest pattern is pattern 1 and consists of tightly packed collection of small to medium sized acini, with relatively little variation in size and shape. Pattern 2 carcinoma shows greater separation of acini with limited infiltration of adjacent prostatic tissue.[5] Distinction between Gleason grade 1 and 2 is often difficult but of no practical significance. Most of these tumors arise in the transition zone and are typically encountered in the transurethral resectates or in the prostatectomy specimens.

Gleason pattern 2 and 1 were not encountered in our study, which could be explained as follows.In our study carcinoma was detected predominantly in needle biopsy specimens. According to Young et al.[5] and Epstein et al.[40] Pattern 2 and 1 are almost never diagnosed on needle biopsy. This is because the caliber of needle core does not generally enable all the edges of nodule to be seen. In addition low-grade cancers are predominantly located anteriorly in the prostate within transition zone and tend to be small. There is poor reproducibility in its diagnosis even among urologic pathologic experts. Recently in studies by Rajal B. Shah[41], current perspectives on the Gleason Grading were discussed. The carcinomas, which constitute Gleason grade 3, show greater degree of gland separation, greater variation in the size and shape. An intermingling of neoplastic acini with the nonneoplastic ones is an important feature of Gleason grade 3. Infiltration is usually readily evident in grade 3 carcinoma in transurethral resectates and prostatectomy specimens. In some of our problematic or suspicious cases of adenocarcinoma, EVG stain highlighted the single layer of malignant cells and the clefting of neoplastic acini. The neoplastic acini have appreciable cytoplasm on high power evaluation with single layer cells, a feature much more in keeping with grade 3 adenocarcinoma. In Gleason scheme, grade 3C consists of generally rounded, smooth, circumscribed masses of glands with a cribriform or papillary architecture. There could be focal grade 4 carcinoma due to fusion of cribriform glands. If necrosis is present, grade becomes 5A.

Gleason grade 4 **carcinoma** is characterized by growth as fused glands or chains of acini with little or no stroma within the aggregate. It is very important that Gleason grade 4 tumors should be recognized, since they are associated with a significant deterioration in prognosis compared to tumors that are Gleason grade 3 or lower. Strict criteria should be applied in recognizing the gland fusion that is definitional for Gleason grade 4 neoplasms. Most of these tumors are composed of cells with relatively scant eosinophilic or amphophilic cytoplasm, but some have abundant clear cytoplasm. The latter pattern has been referred to as hypernephroid , which is Gleason grade 4B. It has been linked to renal cell carcinoma, but the resemblance is only superficial. A cribriform pattern is common in grade 4 neoplasms and should not lead to confusion with the cribriform pattern that represents grade 3 neoplasms.

Solid growth without specific features represents Gleason grade 5B. Sheets, cords and irregular aggregates of tumor cells may show focal lumens or cytoplasmic vacuoles. These formations are haphazardly arranged than in Gleason grade 4 carcinoma, and individual infiltrating tumor cells sometimes arranged in thin cords are also common. At times it is difficult to appreciate the tumor as adenocarcinoma except for focal luminal differentiation or the accompanying lower grade patterns that may be present.

Some grade 5 carcinomas grow in large trabeculae, which may be difficult to distinguish from transitional cell carcinoma or as solid nests, which rarely have rosette-!ike structures. In Gleason grade 5 tumors, the nuclear morphology is highly variable. Small, dark and irregular nuclei with relatively inconspicuous nucleoli may be seen but in most

cases, atypical nuclei with enlarged nucleoli are conspicuous. In general the nuclear pleomorphism of prostatic carcinoma is less striking than in most other carinomas[36-38,41]

Gleason grade 3 was the most common in 11 cases (64.7%) primary pattern in our study. The most common secondary pattern was Gleason grade 4 in 9 cases (53%), while tertiary pattern was not identified. In our study, most common Gleason score was 7 in 9 (52.94%) cases. Out of these 9 cases, 7 (77.77%) cases had Gleason score 3+4. Only 2 (22.22) cases showed 4+3 pattern. Moderately differentiated tumors (Gleason score6) were 17.64 %, while 29.4% tumors were poorly differentiated (Gleason score8-10). In a study done by Babaian RJ[42] et al. the overall Gleason scores in 244 cases were 4 (one case 0.4%), 5 (63 cases 25.81%), 6 (114 cases 46.72%), 7 (151 cases 61.88%), 8 (9 cases 3.68%), and 9 (26 cases 10.65%). In a study conducted in 2002 by Egevad L. et al.[43] out of 305 cancers, 22% had a Gleason score of 4–5, 29% of 6, 18% of 7 and 32% of 8–10. The overall Gleason score in the study done by Falzarano et al[44] was 6 in 21 (34%), 7 in 34 (55%) and 9 in 4 (6%) cases. In our study the Gleason score was 6 in 17.64% cases, 7 in 52.94% of cases, 8 in 17.64 % of cases and 9 in 11.76 % of cases. Our findings are almost similar with the studies of Babaian et al.[42] and Falzarano et al.[44].

Reproducibility of Gleason score can be defined as the percentage of grades that remained unchanged on second grading and are a measure of intraobserver variability.According to study done by Harada et al.[45] reproducibility of the same examiner for the same slides on two different examinations was 38%. Gleason's own reproducibility was 80%.[46] Cintra and Billis [47] had regraded 139 radical and transurethral resection prostatectomy specimens on 2 occasions and compared different grading systems. These authors found an intraobserver reproducibility of 63%.Ozdamar et al.[44] had regarded 96 prostatic carcinomas and found an intraobserver reproducibility of 78%. In our study reproducibility of Gleason score by the same examiner on two different occasions was 94.11%. There was upgradation of Gleason score in 1 (5.57%) case. The upgradation was from pattern 3 to pattern 4. This was attributed to appreciation of Gleason patterns and associated ancillary features with the aid of special stain EVG.

The frequency of various ancillary features that help in establishing diagnosis of adenocarcinoma of prostate in needle biopsy specimens as seen in studies done by Epstein et al.[40], Thorson et al.[48] and Varma et al.[49] old are tabulated below

FEATURES	STUDIES			
	Epstein et al	Thorson et al	Varma et al	Our Study
A) Infiltrating pattern	-	88%	-	76.4%
B) Nuclear features				
Nucleomegaly	77%	96%	-	76.4%
Hyperchromasia	-	30%	-	52.9% 52.952.9
Prominent nucleoli	76%	64%	78%	41.1%
Mitotic figures	11%	2%	-	11.7%
C) Cytoplasmic features				
Amphophilic cytoplasm	39%	36%	-	29.4%
D) Intraluminal secretions				
Blue tinged mucin	34%	-	52%	17.6%
Eosinophilic amorphous Material	53%	78%	86.7%	52.9%
Crystalloids	25%	22%	40.6%	11.7%
Collagenous micronodules	-	2%	2%	0
E) Perineural invasion	3%	2%	22%	11.7%
F) Retraction clefting	-	-	38.6%	8.9%
G) Associated PIN	13%	40%		11.7%

In our study we have done a special stain EVG in all cases of carcinoma to evaluate its utility in diagnosis of carcinoma. In EVG stain, collagen is stained red; nuclei are stained blue/black, while rests of the tissues are stained yellow/green. We found that certain features were highlighted on EVG which is discussed in cases given below:

Case-1 - In one case, few atypical acini were seen with abundant pale cytoplasm, irregular nuclei, and smudging artifact. Few of them showed few fibroblasts close to acini, which were mistaken for basal cells. Sometimes it is difficult to discern them on light microscopy. The EVG stain easily highlighted single layered glands with surrounding retraction clefting.

Case-2- In another case of carcinoma diagnosed on needle biopsy, one focus showed 2-3 acini with abundant pale cytoplasm were seen adjacent to large benign gland, which appeared suspicious for carcinoma. However, lack of prominent nucleoli and other nuclear abnormality precluded the diagnosis of carcinoma. The EVG stain highlighted the two layers of acini and similar nuclear features as that of adjacent benign gland.

Case-3 -In one of our cases Gleason pattern 3 tumor was identified. As no other grade was identified, Gleason grade given was 6. On EVG stain of the same slide, another bit showed few tumor cells with pale cytoplasm and dark nucleus infiltrating the stroma in cord like pattern i.e. pattern 5 tumor. When H&E stained slides were reviewed, featureless growth of poorly differentiated malignant cells (pattern 5) was noticed. On review Gleason score given was 3+5=8.The EVG stain in our study upgraded

Gleason score in this case and helped to easily identify retraction clefting (one of the ancillary features in diagnosis of carcinoma.)

CONCLUSION

Thus our study concluded that benign prostatic hyperplasia was the commonest lesion and most common pattern of inflammation associated with BPH was chronic inflammation. The commonest age group of presentation for both carcinoma and BPH was seventh decade and obstructive urinary symptoms were the most common mode of presentation. Incidence of PIN associated with carcinoma was less in our study. Both the cases with high grade PIN were associated with carcinoma. Strong correlation of PSA levels with adenocarcinoma was seen in our study. The range of 4-10ng/ml has a low positive predictive value. PSA level of >10ng/ml has high positive predictive value. The percentage of positivity of biopsy material was satisfactory. We concluded that in diagnosing prostatic adenocarcinoma, evaluating a constellation of architectural, cytoplasmic and nuclear features along with ancillary features is essential. Gleason grade 3 was the commonest pattern seen. Majority of cases were of Gleason score 7 i.e. of moderately poor differentiation.EVG stain clearly highlighted the neoplastic acini and was useful in upgrading Gleason score in one case. Alcian Blue stain confirms the acidic mucinous nature of luminal secretions which are diagnostic of neoplastic acini, as against the neutral mucin seen in the non neoplastic acini.

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