

Original Research Article**Histopathological Spectrum of Prostatic Lesions with Special Emphasis on Mimickers of Malignancy****Bharati Bhavikatti^a, Sunita S. Vernekar^b, Sujata Giriyan^c**^aAssistant Professor ^bAssociate Professor ^cProfessor, Department of Pathology, Karnataka Institute of Medical Sciences, Hubballi, Karnataka 580022, India.**Abstract**

With increase in the population of elderly male, the prostatic pathology has gained a separate domain of its own. Prostatic lesions on routine sometimes cause a diagnostic dilemma especially when malignant tissue is limited and is mixed with benign prostatic glands.

Aim: This study is aimed to evaluate a complete spectrum of various prostatic lesions with emphasis on the benign mimickers like, Basal Cell Hyperplasia (BCH), inflammatory atypia, atrophy and adenomatous hyperplasia.

Material and Methods: The present study was a hospital based 10 year retrospective study carried out in the department of Pathology, KIMS Hubli. The materials for the study included histopathology slides and blocks from 315 cases which constituted 0.72% of all the specimen samples received during the study period.

Results: The peak age at which the patients underwent prostatectomy was from the 6th to 8th decade. Benign Prostatic Hyperplasia (BPH) was the major histopathological diagnosis comprising of 90.1% cases, followed by adenocarcinoma in 6.7%, atrophy 1.9%, Prostatic Intraepithelial Neoplasia (PIN) 1.0% and 0.3% of metastatic deposits of transitional cell carcinoma.

The associated lesions with BPH were, inflammation in 17.1%, basal cell hyperplasia in 11.7% and atypical adenomatous hyperplasia in 0.4% case. There were 1.9% cases of atrophic prostate.

Conclusion: The study of prominent histopathological changes of senescence and the features of co-morbid prostate pathology are of great importance. A systematic approach is necessary to evaluate the lesions of prostate and to detect the mimickers of malignancy.

Keywords: Benign Prostatic Hyperplasia; Basal Cell Hyperplasia; Prostatic Intraepithelial Neoplasia.

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Introduction

The prostate gland is a functional conduit that allows urine to pass from the urinary bladder to the urethra, adds nutritional secretions to the sperm to form semen during ejaculation.

With the increasing longevity and ageing population the pathology of the prostate may claim a separate domain of its own. The histopathological changes due to disease processes and the simultaneous inevitable effects of ageing so intricately co-exist in the prostatic tissues that the study of prominent histopathological changes of

senescence and the features of co-morbid pathology become of great importance in diagnostic pathology.

Though Benign Prostatic hyperplasia constitutes the majority of prostatic lesions, this study was undertaken to know the co-associated mimickers of malignancy like Basal cell hyperplasia, inflammatory atypia, atrophy, and adenomatous hyperplasia.

The neoplastic lesions were also studied and graded according to Gleasons grading and scoring system which helps in predicting the prognosis.

Methodology

The present study was a hospital based 10 year retrospective study carried out in the department of Pathology, KIMS Hubli. The materials for the study included HPR slides and blocks from 315 cases which constituted 0.72% of all the specimen samples received during the study period. The Hematoxylin & Eosin stained slides of all these cases were retrieved. Fresh sections were taken from tissue blocks when required. Microscopic evaluation was done according to the updated protocol by John R. Shrigley et al¹. The various histopathological diagnosis were BPH, Atrophic Prostate, Prostatic Intraepithelial Malignancy (PIN), Adenocarcinoma and Metastatic deposits.

All the cases of adenocarcinoma were graded and scored according to the Gleason's grading and scoring system.

Results and Observation

The total number of 315 (0.72%) prostate specimens were studied of which, 114 (36.2%) prostates were obtained by Transurethral prostatectomy (TURP) procedure, 197

(62.5%) by suprapubic prostatectomy and 04 (1.3%) by transrectal biopsy. The age of patients ranged from 35 to 88 yrs, with a mean of 64 yrs ± 10 yrs.

BPH was the major histopathological diagnosis comprising of 284 (90.1%) cases, followed by, adenocarcinoma in 21 (6.7%), atrophy 06 (1.9%), PIN 03 (1.0%) and 01 (0.3%) case of metastatic deposits of transitional cell carcinoma.

Benign Prostatic Hyperplasia (BPH) and Its Associated Lesions

There were 284 (90.1%) cases of BPH with age range from 35-85 yrs with a mean of 63 yrs ± 9 yrs.

Glandular and stromal proliferation was the predominant microscopic finding in 263 (92.7%) cases of BPH while 21 (7.3%) had only stromal proliferation. All the 280 (100%) had corpora amylacea, and 03 (1.1%) had squamous metaplasia.

The associated lesions with BPH were, inflammation in 48 (17.1%), basal cell hyperplasia in 33 (11.7%) and atypical adenomatous hyperplasia in 01 (0.4%) case.

i. BPH With Inflammation

There were 48 cases of BPH with inflammation of which, 38 (79.2%) showed features of chronic inflammation, 05 (10.4%) each showed acute inflammation and non-specific granulomatous inflammation. Two cases of chronic inflammation showed inflammatory atypia. In these two cases of inflammatory atypia the acini were arranged in nodular pattern. The lining epithelium was arranged in papillary pattern in one case and another had cribriform pattern. The nuclei were vesicular and had prominent eosinophilic nucleoli. Stroma had dense mixed inflammatory cells.

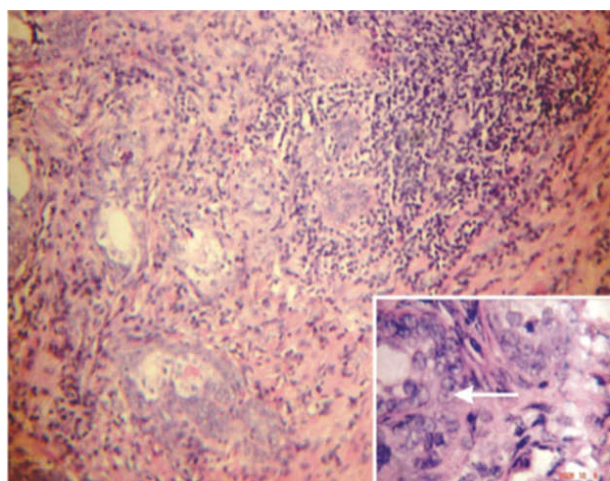


Fig. 1: Shows inflammatory atypia. The atypical glands are seen amidst dense chronic inflammatory infiltrate (H&E, 100X). Inset shows atypical epithelial cells with prominent nucleoli (H&E, 400X)

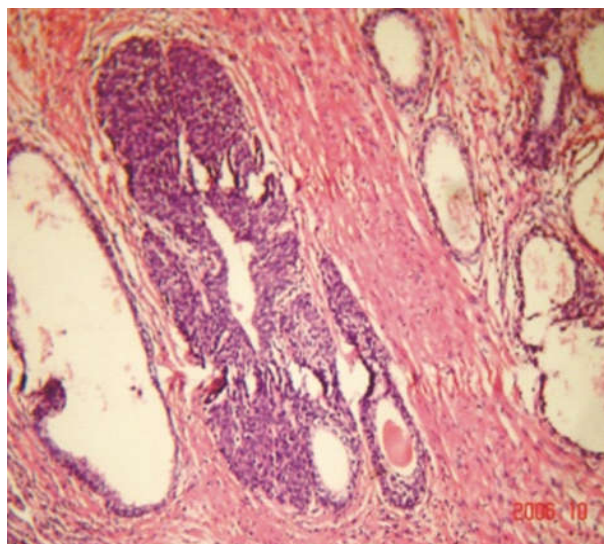


Fig. 2: Basal Cell Hyperplasia (H&E, 100X)

ii. BPH with Basal Cell Hyperplasia (BPH with BCH)

Thirty three (11.7%) cases of BPH were associated with Basal cell hyperplasia. The age range was 35-75 yrs, with a mean of 62yrs±9 yrs.

There were 29 (87.9%) cases of classical pattern of basal cell hyperplasia and 04 (12.1%) cases of cribriform pattern of basal cell hyperplasia. The cases of basal cell hyperplasia in the present study were associated with chronic inflammation (7cases, 21.2%), non-specific granulomatous inflammation (03cases, 9.0%), transitional metaplasia (01case, 3.0%) and squamous metaplasia (01case, 3.0%).

iii. BPH with Atypical Adenomatous Hyperplasia (BPH with AAH)

A single case (0.4%) was diagnosed as BPH with atypical adenomatous hyperplasia in a 70 yr old man.

The lesion showed lobulated proliferation of small glands arranged in back to back fashion. The nuclear and cytoplasmic features were similar to the adjacent benign glands. (FIG 3)

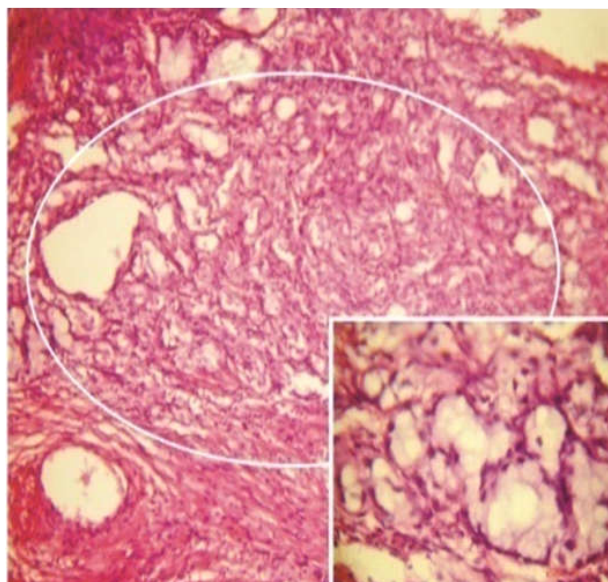


Fig. 3: Shows atypical adenomatous hyperplasia (H&E, 100X). Inset small benign glands closely arranged with minimal stroma in between (H&E, 400X)

Atrophic Prostate

Six (1.9%) cases of atrophic prostate were observed. Four cases (66.7%) in the age group 61-70 yrs and 01 (16.7%) each in the age groups 71-80 yrs and 81-90 yrs.

The atrophic glands showed dilated and small acini, lined by epithelial cells having bland nuclei and scant eosinophilic cytoplasm. The basal cell layer was intact.

Pre-Neoplastic and Neoplastic Lesions of Prostate

i. Prostatic Intraepithelial Neoplasia (PIN)

There were 6 cases of PIN, 3 were of Low grade PIN and 3 were high grade PIN.

Two cases of low grade PIN were in the age group 51-60 yrs and one in 61-70 yrs of which two were associated with BPH and basal cell hyperplasia and one case was associated with BPH only.

Further 2 cases of high grade- PIN were in association with adenocarcinoma in the age group 81-90 yrs and one case of high grade -PIN associated with metastatic deposits in age group 61-70 yrs.

The mean age of the patients with low-grade PIN was 57yrs and high-grade PIN was 75 yrs.

ii. Prostatic Adenocarcinoma

There were 21 (6.7%) cases of Prostatic adenocarcinoma. The age range was from 48-81 yrs mean 72yr±9 yrs. Two cases showed areas of high grade PIN adjacent to the adenocarcinoma (Figure 4).

The Primary and Secondary Grade was Calculated.

The Gleason score was assigned to all the cases of adenocarcinoma. Eighteen (85.7%) of the cases had a high score of 7-10 (Poorly differentiated), 2 (9.5%) had a score of 5-6 (Moderately differentiated) and one (4.8%) case had a score of 2-4 (well differentiated).

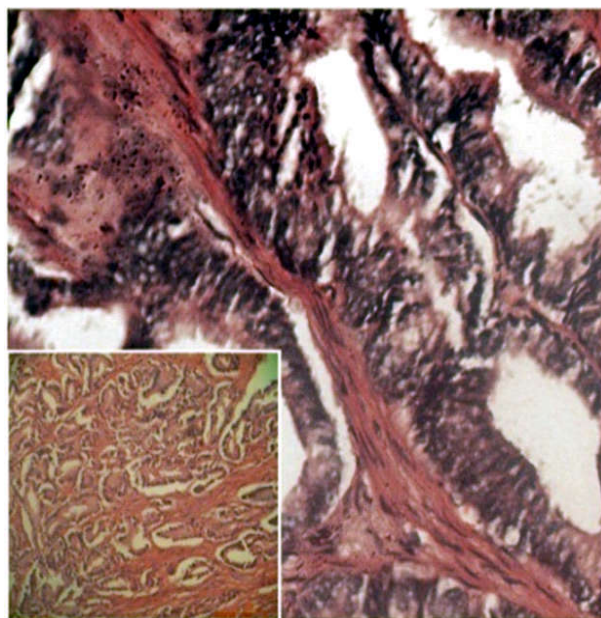


Fig. 4: Showing high grade PIN (H&E, 400X) in grade 3A Adenocarcinoma. Inset shows grade 3A adenocarcinoma of prostate (H&E, 100X).

Table 1: Comparison of the histopathological diagnosis in the present study with other studies.

Histopathological diagnosis	Mittal BV et al ² (n=185)		George E et al ⁵ (n=1163)		Present study (n=315)	
	No.	%	No.	%	No.	%
Atrophy	3	1.6	-	-	6	1.9
BPH	169	91.4	1029	88.5	284	90.1
PIN	-	-	7	0.6	3	1.0
Adenocarcinoma	13	7	127	10.9	21	6.7
Metastatic deposits	-	-	-	-	1	0.3
Total	185	100	1163	100	315	100

Table 2: Showing the comparison of associated lesions with BPH in the present study with other studies

Associated lesions with BPH	Mittal BV et al ² (n=172)		Shakya G et al ⁴ (n=106)		Present study (n=284)	
	No.	%	No.	%	No.	%
Inflammation	107	57.8	18	17	48	17.1
Based cell hyperplasia	10	5.4	-	-	33	11.7
AAH	4	2.2	-	-	1	0.4

Table 3: Showing lesions associated with PIN in the present study and other studies

Associated lesion	Low grade PIN (L-PIN)		Rekhi B et al ⁶ (n=40)	High grade (H-PIN)	
	Rekhi B et al ⁶ (n=35)	Present study (n=3)		Sakr WA et al ²⁵ (n=5)	Present Study (n=3)
BPH	33	3	20	-	-
Basal cell hyperplasia	-	-	-	-	-
Cribriform BCH	-	-	-	-	-
Adenocarcinoma	2	-	20	5	2
Metastatic adenocarcinoma	-	-	-	-	1

Table 4: Showing the Comparison of Gleason primary grade in present study with other studies

Gleason primary grade	Volmer RT et al ³⁰ (n=61)		Present study (n=21)	
	No. of cases	Percentage	No. of cases	Percentage
1	6	9.8	-	-
2	11	18.0	1	4.8
3	36	59.0	8	38.1
4	7	11.5	7	33.3
5	1	1.6	5	23.8

Table 5: Showing the comparison of Gleason score in the present study and other studies

Gleason score	Volmer RT et al ³⁰ (n=61)		Millis SE et al ²⁹ (n=15)		George E et al ⁵ (n=127)		Present study (n=21)	
	No.	%	No.	%	No.	%	No.	%
2-4	10	16.4	6	40.0	11	9.0	01	4.8
5-6	37	60.7	6	40.0	31	24.4	02	9.5
7-10	14	23.0	3	20.0	82	64.6	18	85.7

Discussion

The new development in the prostatic histopathology is the identification of premalignant conditions that can help in early diagnosis of prostate cancer. The differential diagnosis of prostatic carcinoma include several histologic mimicks like atrophy of prostate, inflammatory atypia, basal cell hyperplasia and atypical adenomatous hyperplasia which should be known to avoid misdiagnosis of cancer.

In the present study, majority 197 cases (62.5%) underwent suprapubic prostatectomy procedure followed

by TURP in 114 cases (36.2%). Only 4 (1.3%) underwent biopsy.

Suprapubic prostatectomy and TURP procedures are feasible and cost effective in our set up compared to biopsy. Hence they are more frequently carried out procedures. Other Studies [2-6], which were undertaken in the similar set up also have shown that suprapubic prostatectomy and TURP as commonly carried out procedures.

Prostatism is the common malady in the geriatric age group. In the present study 85% of the cases who

underwent prostatectomy were from the 6th to 8th decade which is similar to the study done by George E et al [5].

The various histopathological diagnosis of prostatic lesions were compared with other studies as shown in the Table 1.

Benign Prostatic Hyperplasia (BPH) and Its Associated Lesions:

In the present study majority, 70% of the cases of BPH were from the 6th to 7th decade, similar observations were made by George E et al⁵.

However studies by Shakya G et al [4] showed that majority of the cases were from 7th to 8th decade.

Berry SJ et al [7] observed that first pathological sign of BPH is seen in the 4th decade with the prevalence rate of 8%. By the seventh decade, the prevalence of BPH increases to about > 70%. Of the men between 51-60 yrs, 50% have pathological signs of BPH.

The stromal and epithelial components vary in their sensitivity to androgen; hence different BPH lesions exhibit differences in their stromal to epithelial cell ratios [7].

In the present study 92.5% cases of BPH had glandular and stromal proliferation, while 7.5% had predominant stromal proliferation. Similar to observation made by Shakya G et al [4].

The associated lesions with BPH were studied and compared as shown in Table 2.

i. BPH with Inflammation

In the present study 17% of cases of BPH were associated inflammation, with predominantly chronic inflammation (79.2%) followed by 10.4% cases each of acute inflammation and non-specific granulomatous inflammation. Similar observations were made by Shakya G. et al [4].

In the present study 10.4% cases of non-specific granulomatous inflammation were diagnosed as the only type of granulomatous inflammation. Mohan H et al [8] studied granulomatous lesions in 20 cases out of the total 1353 cases of prostate, majority (60%) were non-specific granulomatous inflammation.

Non-specific granulomatous inflammation is the most common type of granulomatous prostatitis [8].

Inflammatory atypia were diagnosed in 2 cases of BPH with chronic inflammation in the present study. Rekhi B et al [6] observed 1.6% cases of inflammatory atypia in their study of 200 cases.

Inflammatory atypia should be distinguished from carcinoma, as atypia may mimic carcinoma. Carcinoma can only be diagnosed when the atypical glands are away

from inflammation or when the pattern of small crowded glands is so characteristic of adenocarcinoma that their appearance cannot be attributed to inflammation [9].

ii. BPH with Basal Cell Hyperplasia (BPH with BCH)

Basal cell hyperplasia is a benign process, which occurs in the 7th and 8th decade of life and should not be mistaken for carcinoma [10].

Basal cell hyperplasia is preferentially observed in transitional zone [11]. BCH is most often seen as secondary change in BPH and may sometimes be mistaken for malignancy.

In the present study 79% cases of BPH with BCH were detected in suprapubic prostatectomy and 21% in TURP specimens. Both the type of specimens represents the transitional zone of prostate.

Cleary KR et al [10] in their study, detected 92.3% cases of BCH in TURP specimens and 8% in perineal prostatectomy.

It is an uncommon finding in prostatic needle biopsies, but study by Hosler GA et al [12] reported BCH in needle biopsies and discussed the diagnostic difficulty in their 13 year retrospective study material.

In the present study, all the cases of basal cell hyperplasia were associated with BPH, 21% of them were also associated with chronic inflammation, 9.0% with nonspecific granulomatous inflammation and 6% with metaplastic changes.

However, Cleary KR et al [10] observed that all the 13 cases they studied were associated only with BPH and 2 cases, in addition to BPH were associated with adenocarcinoma and one with transitional cell carcinoma bladder.

Morphology ranges from focal basal hyperplasia (BCH) in the setting of nodular hyperplasia to florid BCH. In the study of 23 cases of unusual BCH done by McKenney JK et al [13], the florid BCH is divided into adenoid cystic like hyperplasia, adenoid cystic carcinoma and basaloid carcinoma.

In the study of 25 cases of unusual morphologic patterns of BCH by Rioux-Leclercq NC et al [14] BCH with globules, BCH with calcification, BCH with squamous features, BCH with cribriform patterns were described. They described Cribriform BCH in 1.6% cases and concluded that cribriform basal cell hyperplasia occupies 10-100% of Basal cell hyperplasia focus. In the present study cribriform basal cell hyperplasia was seen in 12% cases.

It's crucial to distinguish cribriform BCH from cribriform PIN and cribriform adenocarcinoma. There are several features that allow their distinction. The glandular

arrangement and nuclear features are the important features [15].

iii. BPH with Atypical Adenomatous Hyperplasia (BPH with AAH)

AAH is a benign glandular lesion with histological features of crowded small glands that may be confused with carcinoma. A long-term follow up studies have to be carried out to assess the risk of cancer [9].

In the present study, one (0.4%) case was diagnosed as AAH with associated BPH. Mittal BV et al [2] observed 2.2% cases of AAH, which were also associated with BPH. However, in a study of 200 cases by Rekhi B et al [6], AAH was observed in 19% of the cases among which 20.3% were associated with BPH and 11.7% were associated with adenocarcinoma.

Srigley et al [16] observed foci of AAH in 19.6% cases of BPH and 60% in carcinoma cases where as Qian J et al [17] noted 31 % association of AAH with prostatic carcinoma. The latter data reported in the literature is based upon autopsy studies and also whole mounted specimens.

AAH has been presumed to be a precursor of well differentiated transitional zone carcinoma.

Atrophic Prostate

Acinar atrophy in the prostate is commonly confused with adenocarcinoma [18]. In the present study atrophic prostate was observed in 1.9% cases in the 7th to 9th decade.

However, Mittal BV et al [2] observed 1.6% of atrophic prostate cases in their study.

The atrophic glands shows dilated and small acini, lined by epithelial cells having bland nuclei and scant eosinophilic cytoplasm. The basal cell layer is intact [18].

Prostatic Intraepithelial Neoplasia (Pin)

The term Prostatic Intraepithelial Neoplasia (PIN) endorsed in 1989 is defined as cytological alteration in architecturally normal glands [19]. The cytological alteration ranges from low grade i.e PIN 1 to high grade i.e PIN 2.

PIN is more commonly found in the peripheral zone of the Prostate.

Prostatic Intraepithelial neoplasia warrants further study as an important phase in the evolution of adenocarcinoma in the prostate [20]. Hence, careful search of Prostatic Intraepithelial neoplasia was made in the present study.

In the present study 6 cases of PIN were encountered of which 3 cases were of Low grade PIN (L-PIN) in the 6th to 7th

decade and 3 cases of high grade PIN (H-PIN) in 7th to 9th decade.

A wide variation in the incidence and prevalence of PIN in nodular hyperplasia has been reported in the world literature ranging from 12.8% to 43% in literature [21-24].

Low grade PIN was the most commonly observed grade in cases of nodular hyperplasia, whereas cases of adenocarcinoma showed high grade PIN as the most commonly observed grade.

In the present study 3/284 cases of nodular hyperplasia (1%) showed low grade PIN whereas 3/21 cases adenocarcinoma (14.3%) showed high grade PIN

Rekhi B et al [6] also observed that 33 cases of L-PIN associated with nodular hyperplasia and 2 cases associated with adenocarcinoma.

In the studies by Rekhi B et al [6] and Sakr WA et al [25], it is observed that the HPIN was associated with adenocarcinoma. However, Rekhi B et al [6] observed that HPIN was also associated with nodular hyperplasia as shown in Table III.

The four architectural patterns of high grade –PIN, viz, cribriform, tufting, flat and micro-papillary were looked for, in the present study. These patterns, merged with each other from gland to gland, although fields with only one single pattern were not observed. In the 3 cases of high grade PIN studied, the flat and tufting pattern was the commonly observed pattern in all the cases while cribriform pattern was seen in only one case. However observations made by Rekhi B et al [6] showed that cribriform was the most common pattern, followed by tufting.

Adenocarcinoma of Prostate

Prostatic adenocarcinoma is rare before 40 yrs of age, but the incidence rises quickly thereafter, studies of thoroughly evaluated prostates from men without clinical evidence of cancer have shown a very high level of latent cancer, increasing from 10% at 50 years of age to 80% by 80 years of age [9].

The increase in the prevalence of prostate cancer parallels that of BPH, but begins 15-20 yrs later [26].

Adenocarcinoma was diagnosed in 12 cases of TURP, 5 suprapubic prostatectomies and 4 biopsies in the present study.

In the present study the number of cases have increased from 14.3% to 57.1% from the 6th to 8th decade. One case each was in the 5th decade and 9th decade. Similar studies by George E et al [5] have shown that cases have increased from 27% to 51.2% from 6th to 7th decade. However Harbitz and Haugen [27] noted that 50% of their 70 cases of carcinoma of prostate were above the age of 80 years.

In 2 cases each, vascular invasion and perineural invasion was observed. In perineural invasion the malignant glands circumferentially involved the nerve.

Perineural invasion is one of the few features diagnostic of Prostatic carcinoma [28].

Grading and Scoring of Prostatic Adenocarcinoma.

i. Tumor Grade

There is considerable evidence that the histologic grade of prostatic carcinoma correlates with both local invasiveness and metastatic potential [29].

Gleason grading system was applied to all the 21 cases of adenocarcinoma in the present study and compared with Volmer et al [30] as shown in table 4.

In both the studies primary Gleason grade-3 carcinoma was seen in the majority of the cases.

ii. Tumor Score

In the present study 86% of the cases were poorly differentiated (score 7-10) and compared with other studies as shown in the Table 5.

Gleason score (GS) is a powerful predictor of disease progression in men with prostate cancer. The majority of the clinically localized prostate cancers, however, are moderately or moderately to poorly, differentiated tumors with indeterminate prognosis [31].

Metastatic Deposits

In the present study one (0.32%) case of metastatic deposits of transitional cell carcinoma was diagnosed in a 65 yr old man, who came with intermittent urinary obstruction.

Microscopic sections from the TURP specimen showed nests of cells having hyperchromatic nucleus and moderate amount of eosinophilic cytoplasm. Extensive vascular invasion was seen. The stroma had mucinous areas. Areas of high grade-PIN and BPH were also seen. Cystoscopic biopsy of the patient from the bladder revealed grade-3 transitional cell carcinoma.

Prostatic involvement by urothelial carcinoma varies from 12% to 55%. The patterns of involvement of the prostate by urothelial carcinoma include, intraductal, infiltrating, and involvement of the Prostatic urethra [32].

Primary transitional cell carcinoma of the prostate without the involvement of the bladder is very rare [21].

Conclusion

With the increasing longevity and ageing population, the pathology of prostate has claimed a separate domain of its own. This study was undertaken to understand the

spectrum of histopathological lesions of prostate. Emphasis was laid on the benign mimickers of malignancy like Basal cell hyperplasia, inflammatory atypia, atrophy, and adenomatous hyperplasia which are commonly associated with BPH.

The spectrum of lesions in prostate is vast. It ranges from benign to premalignant to malignant. The intermediate lesions which mimic malignancy need to be thoroughly studied. A systematic approach and the awareness of the microscopic features like the glandular arrangement, nuclear features and stromal reaction of these mimickers of malignancy will help us distinguish the non neoplastic lesions from neoplastic lesions.

Further, the premalignant lesions have to be also noted as high grad-PIN is associated with adenocarcinoma or metastasis. Gleason score (GS) is a powerful predictor of disease progression in men with prostate cancer which needs to be thoroughly done.

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