Original Article

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Clinicopathological Study of Associated Lesions in Benign Prostatic Hyperplasia and Prostatic Adenocarcinoma in Surgical Biopsy Specimens

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) and prostatic adenocarcinoma are two principal conditions of prostate among elderly men. In spite of significant advances in early detection of prostatic carcinoma by transrectal ultrasound and serum prostatic specific antigen, major diagnostic problem exists in the diagnosis between adenocarcinoma and benign small acinar proliferations. This study aims to study the association of hyperplastic, metaplastic, inflammatory and premalignant lesions in prostate specimens over a period of 5 years and to analyze histological types and significance of associated lesions in BPH and different grades of prostatic adenocarcinoma.

Methods: Prostate specimens over a period of 5 years were analyzed for gross and microscopic findings. All prostatic adenocarcinoma cases are graded using Gleason grading system and analyzed for the presence of prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH) and other associated lesions.

Results: BPH constitute the commonest lesion (92.1%), followed by Adenocarcinoma (7.9%). All cases of focal acinar/cystic atrophy showed increase in trend towards increasing age. Among hyperplastic lesions, basal cell hyperplasia was found to be the most common epithelial lesion. Among premalignant lesions, PIN was found most commonly in association with prostatic adenocarcinoma. In concurrence with literature it was observed that high-grade PIN was the most common premalignant lesion associated with prostatic adenocarcinoma (51.2%) than AAH.

Conclusion: LGPIN, HGPIN and chronic prostatitis were found to be associated with adenocarcinomas (statistically significant with $P<0.05$), when they are compared with benign prostatic hyperplasia and not statistically significant ($P>0.05$) when comparison is done between low- and high-grade adenocarcinoma.

Keywords: *Prostatic Carcinoma, Benign Prostatic Hyperplasia, Adenocarcinoma, Basal Cell Hyperplasia, Atypical Adenomatous Hyperplasia*

Introduction

Benign prostatic hyperplasia (BPH) and prostatic adenocarcinoma are two principal conditions involving prostate among elderly men, accounting for more than 90% of all prostatic diseases. BPH remains one of the major causes of obstructive urologic symptoms. Transurethral resection of prostate remains the gold standard of treatment against which all other treatments of benign prostatic hyperplasia are measured. After the introduction of screening for prostatic specific antigen, transrectal ultrasound and MRI, trucut needle biopsy is used to detect prostatic carcinoma. In routine surgical pathology practice, making a morphological diagnosis of prostatic lesions, especially separating benign from malignant lesions is relatively straightforward. However, there are several glandular and stromal proliferations, which may be mistaken for malignancy especially in small tissue samples such as trucut needle biopsies.

For practicing pathologists and urologists there are currently two main issues in prostate pathology, one is the identification of prognostic factors that predict the outcome of individual patients with prostatic carcinoma. The other involves the early detection of prostatic carcinoma in the preinvasive phase. Hence, understanding the morphology of precursor or preinvasive lesions has become increasingly important. The relationship between prostatic carcinoma and premalignant lesions of the prostate is a subject of great interest analyzed in numerous publications. Despite many studies conducted over this area each year, there were still important questions remain about the cause and prevention of prostate cancer. Despite significant advances in the early detection of prostatic carcinoma by transrectal ultrasound, serum levels of prostate specific antigen, the major diagnostic problem with tumor pathology is making a diagnosis between adenocarcinoma and benign small acinar proliferations.

The present study was done to study the association of hyperplastic, metaplastic, inflammatory and premalignant lesions in transurethral resection of prostate, trucut biopsy and open prostatectomy specimens over a period of 5 years from January 2011 to December 2015 and to analyze the histological types and significance of associated lesions in benign prostatic hyperplasia and in different grades of prostatic adenocarcinoma.

Materials and Methods

This retrospective study was conducted in the Department of Pathology, Saveetha Medical College, Chennai after getting approval from the institutional ethical committee, wherein the prostate specimens referred from the urology department over a period of 5 years from January 2011 to December 2015 were analyzed for gross and microscopic findings. As a routine, all prostate specimens were fixed in 10% formalin. In most of the trucut biopsy specimens, we received only a bit of soft tissue measuring 0.5 to 1 cm and serial sections were taken from this. As a routine, 5 to 8 histological sections were taken from open prostatectomy specimens. All these histological sections were stained with Hematoxylin and Eosin stain and examined. In each benign prostatic hyperplasia and adenocarcinoma case diagnosed, evaluation was done on the following variables - associated inflammatory lesions, focal acinar atrophy, metaplastic lesions, hyperplastic lesions and premalignant lesions. All prostatic adenocarcinoma cases have been classified by Gleason grading system and analyzed for presence of PIN, AAH and other associated lesions. Histological spectrum of all associated epithelial and stromal lesions in benign prostatic hyperplasia and adenocarcinoma were analyzed statistically using SPSS statistical package version 23. The correlation between each of the associated lesions in different grades of adenocarcinoma and in benign prostatic hyperplasia was done and the statistical significance was then calculated.

Result

Out of a total of 520 cases analyzed in this study (447 cases of transurethral resection of prostate, 62 cases of trucut needle biopsies and 11 cases of open prostatectomy), BPH was found in 461 (88.6%) patients, prostatic adenocarcinoma in 41 (7.8%) patients and 18 (3.6%) trucut biopsy specimens were inadequate samples. The patients were in the age group ranging from 35 to 85 years with a peak of 61 to 70 years.

461 cases of BPH were analyzed for other associated hyperplastic, metaplastic and atrophic lesions. Out of these lesions, commonest was focal acinar atrophy constituting 35 cases (7.5%) followed by basal cell hyperplasia in 26 cases (5.6%) and transitional cell metaplasia in 23 cases (5.0%). Basal cell hyperplasia was classified into complete and incomplete forms with both the types showing almost equal incidence. (Table 1)

Of the associated putative premalignant lesions diagnosed in cases of BPH and prostatic adenocarcinoma, PIN constituted the major category. Among these, high grade PIN was the most prevalent premalignant lesion diagnosed in cases of adenocarcinoma. Low grade PIN was more prevalent than high grade PIN in benign prostatic hyperplasia (Figure 1).

Atypical adenomatous hyperplasia was diagnosed in 19 cases of benign prostatic hyperplasia. High-grade PIN changes were most commonly seen in trucut biopsy specimens in association with prostatic adenocarcinoma. Low-grade PIN changes and atypical adenomatous hyperplasia were predominantly seen in TURP specimens (Table 2).

The total number of prostatic adenocarcinoma cases diagnosed for a period of three years was 41 cases, of which 23 cases (56.1%) were low-grade adenocarcinoma and 18 cases (43.9%) were high-grade adenocarcinoma (Figures 2 to 5).

LG-PIN, HG-PIN and chronic prostatitis were the three lesions found to be associated with 35 cases of adenocarcinomas (statistically significant with $P<0.05$). Six cases of adenocarcinomas did not show any associated lesions. (Table 3)

The statistical significance of these associated lesions in different grades of adenocarcinomas were determined using the same method ($P>0.05$, Not statistically significant).

Table 1: Associated lesions in Benign prostatic hyperplasia.

S.No.	Lesion	No. of cases	Percent
	Associated epithelial lesions		
1.	Focal acinar/cystic atrophy	35	7.5%
2.	Squamous cell metaplasia	13	2.8%
3.	Transitional cell metaplasia	23	5.0%
4.	Mucinous metaplasia	1	0.2%

S.No.	Lesion	No. of cases	Percent
5.	Post atrophic hyperplasia	2	0.4%
6.	Basal cell hyperplasia	26	5.6%
	Complete	14	3.0%
	Incomplete	12	2.6%
7.	Clear cell cribriform hyperplasia	2	0.4%
Associated stromal lesions			
1.	Chronic Inflammation	132	28.6%
	Lymphocytic	125	27.1%
	Granulomatous	7	1.5%
2.	Stromal nodule/hyperplasia	32	7.0%
3.	Stromal calcification	1	0.2%
4.	Leiomyomatous nodule	3	0.6%
5.	Infarction	3	0.6%
6.	Abscess	4	0.8%

Table 2: Distribution of premalignant lesions in BPH and adenocarcinoma.

Lesion	AAH	Low grade PIN	High grade PIN
BPH	19 (4.1%)	59 (12.8%)	25 (5.4%)
Adenocarcinoma	0 (0%)	8 (19.5%)	20 (48.8%)

Table 3: Comparison of associated lesions in BPH and adenocarcinomas.

Associated Lesions	BPH	Adenocarcinoma	Total
Low-grade PIN	59	8	**67**
High-grade PIN	25	20	**45**
Chronic Prostatitis	92	7	**99**

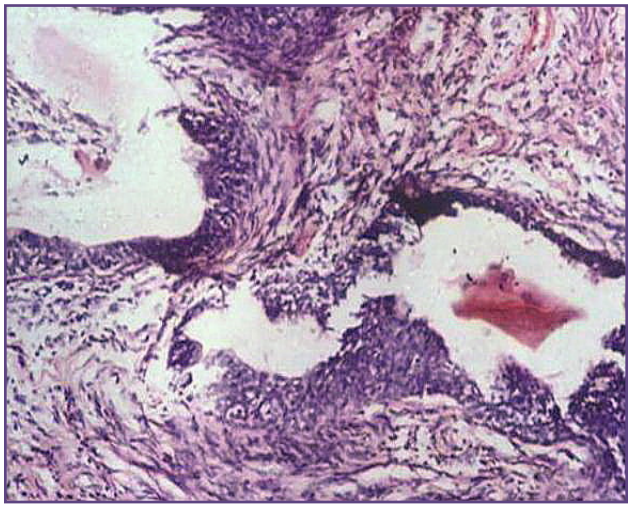

Fig. 1: High-grade Prostatic Intraepithelial Neoplasia – The glandular lining shows stratification, anisonucleosis and hyperchromasia. (H&E x100).

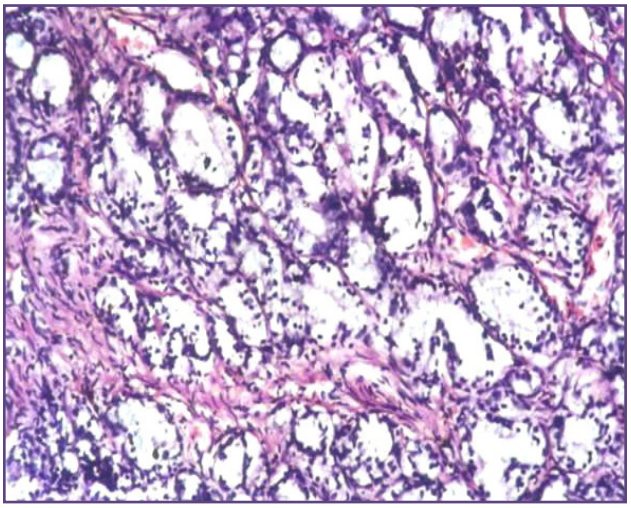

Fig. 2: Low-grade adenocarcinoma with areas showing Gleasons score 1 & 2. (H&E x100).

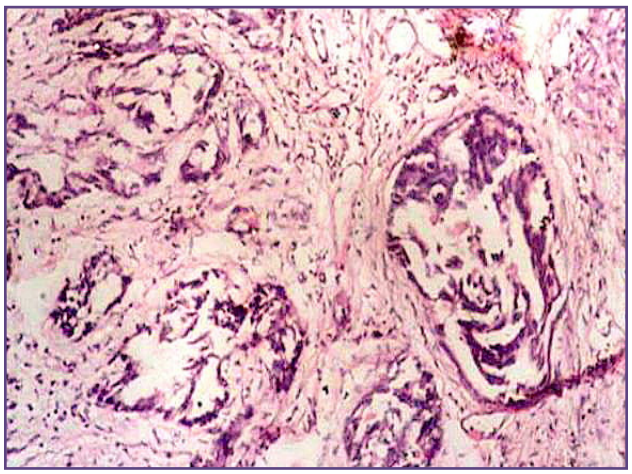

Fig. 3: Low-grade adenocarcinoma with area showing Gleasons score 3 with papillary pattern. (H&E x100).

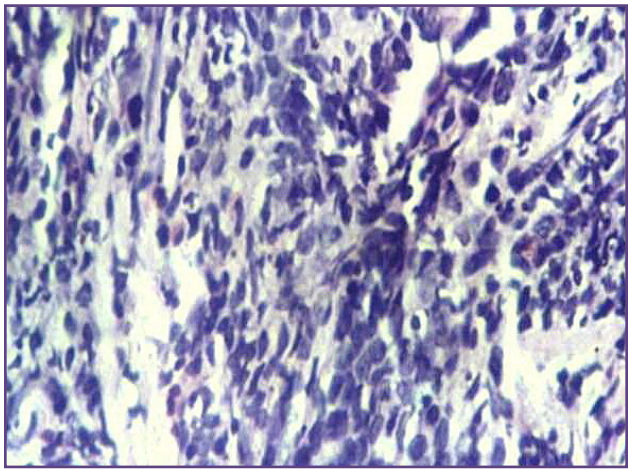

Fig. 4: High-grade adenocarcinoma with area showing Gleasons score 4 with fused glands and chain and cords of tumor cells. (H&E x400).

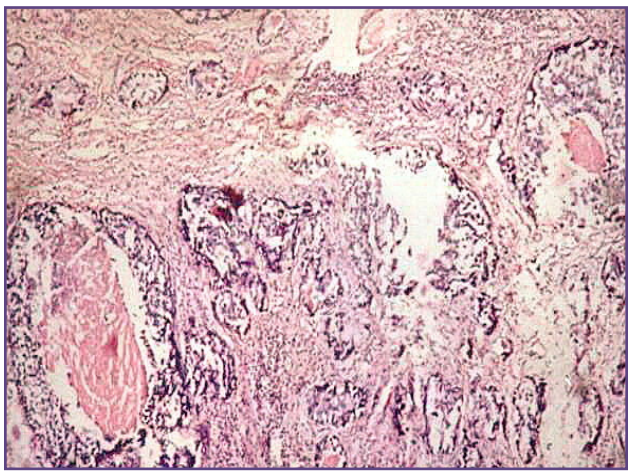

Fig. 5: High-grade adenocarcinoma with area showing Gleasons score 5 with areas of comedonecrosis. (H&E x40)

Discussion

Benign prostatic hyperplasia and prostatic carcinoma are the two common urologic conditions among elderly men with complaints of symptoms of urinary obstruction such as difficulty in micturition, hesitancy, frequency, and pain during micturition and feeling of incomplete voiding. Patients suspected of having prostatic carcinoma on digital rectal examination underwent trucut needle biopsy, few under the guidance of Transrectal ultra sound (TRUS).

Epithelial Lesions: Di Silverio F et al. studied 3942 patients with benign prostatic hyperplasia and observed that focal acinar/cystic atrophy was found significantly increased according to the patient age in decades. In concurrence with the above study this study also showed 7.5% cases with cystic/acinar atrophy showing an increased incidence towards the higher age group.[1] Mahul B Amin et al. stated that the most commonly encountered pattern simulating the microacinar architecture of carcinoma is atrophy. A less common glandular pattern that forms part of the spectrum of atrophy is postatrophic hyperplasia, a lesion that has attained a renewed attention in the recent past in the literature.[2]

The small acinar pattern is commonly a source of consultation material, and approximately 5% to 10% of the cases in our study have had a preliminary diagnosis of carcinoma or a serious consideration of it. So an awareness and firm understanding of the morphological spectrum of these epithelial lesions is of critical importance, especially in prostatic trucut needle biopsy specimens in which it shows some overlapping features with small acinar adenocarcinoma.

Post atrophic hyperplasia represents the process of hyperplasia and atrophy in transition and has less constant histology. The recognition of post atrophic hyperplasia in trucut needle biopsies is likely to be relatively straightforward, if the entire focus containing atrophic and hyperplastic glands is seen. Problems may arise when entire lesion is not represented.

Since basal cell hyperplasia (BCH) has a distinctive microscopic appearance, it may mimic adenocarcinoma of small acinar pattern. BCH is characterized by a nodular growth of nests, tubules and cords filled with proliferating, small, darkly staining basal cells. Most of the nests of basal cell hyperplasia show vertical palisading of basal cells towards the periphery. A study on prostatic lesions proved that BCH is relatively a common lesion in hyperplastic prostates examined.[3]

Squamous metaplasia of prostatic glands was made out in 13 (2.8%) cases and in three cases it was identified next to an area of infarct. Out of the 23 (5%) cases of transitional cell metaplasia most of the cases were found in the periurethral region/transitional zone, similar to the study done by Yantiss R.K. and Young, R.H.[4]

Clear cell cribriform hyperplasia (CCCH) is a rare entity made out only in two cases and it is important that it should not be mistaken for carcinoma or preneoplastic condition of the prostate with a papillary-cribriform pattern. The key to the diagnosis is the combination of bland cytology and architectural uniformity. In all these cases with small glandular proliferation basal cell layer is present. In problematic cases high molecular weight cytokeratin can be applied which will help accentuate the basal cells and confirm the benign diagnosis.

Frank et al in their study noted the alcian blue positivity in the luminal secretions of adenocarcinoma and they advocated this as a valuable aid to a make a diagnosis of well-differentiated carcinoma.[5] Later studies done by David J Grignon et al have shown alcian blue positivity in acid mucin secretions in the lumina of basal cell hyperplasia, post atrophic hyperplasia, atrophy, sclerosing adenosis and in transitional cell metaplasia. So the acid mucin positivity cannot be taken as a specific entity in making a diagnosis of carcinoma.[6]

Hence it is stated that once a small acinar proliferation is identified, it is recommended that a mention should be made of this finding in the microscopic features, particularly if carcinoma is considered in the clinical evaluation. Moreover, these are not distinct clinicopathological entities, but merely a pattern in the morphological spectrum, which mimic cancer. So, appreciation of key histological features is highly essential to make a reliable separation of small acinar carcinoma from there associated lesions, which will reduce the diagnosis of `atypia' and `suspicious of carcinoma' in transurethral resection of prostate and especially in trucut needle biopsy specimens.

Stromal Lesions: Di Silverio F et al study on 3942 patients with histopathological diagnosis of benign prostatic hyperplasia, the mean patient age was 68.85 ± 7.67 yrs. In particular, inflammatory changes were associated with BPH in a high percentage of the cases (43.1%=1700 cases). In our study about 132 cases having chronic inflammation were associated with BPH.[1]

Brian Difuccia et al demonstrated that the distribution of inflammation was more variable with multifocal and diffuse patterns being the most common and periglandular being less common.[7] Similar to the above study, evaluation of our cases showed 60 to 80% with multifocal involvement of the tissue sample and 20 to 40% showed diffuse infiltration by chronic inflammatory cells. One interesting case of tuberculous granulomatous prostatitis was also diagnosed in this study.

Premalignant Lesions: PIN and AAH are considered as putative premalignant lesions of adenocarcinoma. PIN is defined as architecturally benign ducts and acini lined by abnormal secretory cells with changes similar to those in cancer. AAH denotes the presence of suspicious glands with insufficient cytological or architectural atypia for a definitive cancer diagnosis. McNeal & Bostwick study of 100 specimens of prostatic adenocarcinoma and 100 benign prostates obtained at autopsy, identified PIN in 82 prostates with carcinoma and 43 prostates without carcinoma.[7]

Troncoso et al studied sections from 100 prostate glands obtained from patients undergoing cystoprostatectomy for bladder carcinoma. PIN was identified in 89 cases out of 100 prostates, most of them multifocal and high grade.[8] Similar to this, this study also showed LGPIN in 59 cases (12.8%) of BPH and in 8 cases (19.5%) of adenocarcinoma. HGPIN was identified in 25 cases (5.4%) of BPH and 20 cases (48.8%) of adenocarcinoma. This fact has been emphasized by Junqi Qian, M.D. et al study of 195 radical prostatectomy specimens with clinically localized cancer. They identified PIN in 86% of prostates and it showed increased incidence of PIN with prostatic adenocarcinomas.[9, 10]

Kien T. Mai et al, in his study of 533 and 449 prostate specimens studied before and after the introduction of PSA screening respectively suggested that AAH may be related to a subset of carcinoma that arises in transitional zone in association with benign prostatic hyperplasia.[11] In this study all the 19 cases (4.1%) of AAH were found in benign prostatic hyperplasia showing the representation from transitional zone.

There are many histological mimics for PIN such as atypical BCH, cribriform hyperplasia and metaplastic changes associated with radiation and infarction. AAH can be confused with simple lobular atrophy, post atrophic hyperplasia, sclerosing atrophy, basal cell hyperplasia and veru montanum mucosal gland hyperplasia. High grade PIN was identified in 20 (48.8%) cases of adenocarcinoma and 25 cases (5.4%) of BPH.

Prostatic Adenocarcinoma: Prostatic adenocarcinoma is often a multicentric malignant process consisting of two rather distinct types of PCa with different origins – Non-transitional zone prostatic carcinoma and Transitional zone prostatic carcinoma. Non-transitional zone prostatic carcinoma is a tumor that is accessible to digital rectal examination and trans rectal ultrasound and is associated with high-grade carcinoma, PIN and a high incidence of tumoral invasion into the prostatic capsule, perineural spaces and seminal vesicles. In contrast, transitional zone prostatic carcinoma is characterized by a low-grade acinar pattern of carcinoma that is rarely associated with capsular invasion and seminal vesicle involvement. It is most likely to arise from prostatic epithelium often in association with atypical adenomatous hyperplasia (AAH). Furthermore, AAH is more commonly identified in the transitional zone where as PIN is more prevalent in peripheral zone.

In this study, Gleason's grading system was applied over 41 cases of prostatic adenocarcinoma, out of which Low grade adenocarcinomas constituted 56.1% of cases (23 cases) and High grade adenocarcinomas constituted 43.9% of cases (18 cases).

Conclusion

From this study it has been shown that the frequency of PIN in prostates with cancer is significantly increased when compared with benign prostates. In concurrence with the literature it was observed that high-grade PIN was the most common premalignant lesion associated with prostatic adenocarcinoma (51.2%) rather than atypical adenomatous hyperplasia. HGPIN provides the highest risk ratio of all known predictive factors and the identification of PIN in biopsies predicts the presence of carcinoma in subsequent biopsies. LGPIN, HGPIN and chronic prostatitis were found to be associated with adenocarcinomas and that the association of these lesions were statistically significant ($P<0.05$), when they are compared with benign prostatic hyperplasia and not statistically significant ($P>0.05$) when comparison is done between low grade adenocarcinoma and High grade adenocarcinoma.

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