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Incidence of prostatic intraepithelial neoplasia in TURP specimens with special reference to p63 expression in various lesions of prostate

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***Abstract*---**Introduction: Prostate cancer is the second common malignancy in men. Prostatic intraepithelial neoplasia (PIN) is the precursor lesion of prostatic carcinoma. Histopathological examination is necessary to diagnose PIN lesions. Objective: The aim of the study is to determine the incidence of Prostatic intraepithelial neoplasia and to analyse the usefulness of basal cell marker p63 expression in various lesions of prostate. Methods: This is a two-year prospective study of 65 transurethral resection specimens of prostate, carried out in the Department of pathology, Dr B R Ambedkar Medical College, Bangalore. Immunohistochemical marker p63 is used and its expression in various lesions was analysed. Results: Out of 65 cases studied, 4 were inflammatory lesions, 52 were benign prostatic hyperplasia (BPH) and 9 were malignant lesions. Low grade PIN was identified in 8(12.3%) cases of BPH. High grade PIN was seen in

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9(13.8%) cases and tufting pattern was the commonest. HGPIN was predominantly associated with adenocarcinoma. p63 was expressed in all the benign glands in BPH and HGPIN. Malignant glands were negative for p63 expression. Conclusion: Basal cell marker p63 is really helpful in differentiating benign and HGPIN glands from malignant glands. In view of high degree of association of HGPIN with prostatic carcinoma, HGPIN patients need close follow-up with ancillary tests.

***Keywords*---**benign prostatic hyperplasia, high grade PIN, adenocarcinoma, basal cell marker.

Introduction

Prostate cancer is the second most common malignancy (after lung cancer) in men worldwide and the incidence is increasing with age[1]. Prostatic intraepithelial neoplasia (PIN) and Atypical adenomatous hyperplasia, were initially considered to be precursors of prostatic adenocarcinoma. However, PIN now remains as the only well-proven preneoplastic condition with clinical significance[2]. AAH is usually a microscopic finding, but occasionally it presents as a mass lesion. But Prostatic Intraepithelial Neoplasia can only be diagnosed by histopathological examination of prostatic tissue and impossible to detect by direct rectal examination, Prostate Specific Antigen assay or ultrasound. Prostatic intraepithelial neoplasia (PIN), first described in 1969 by McNeal, is a neoplastic proliferation of prostatic epithelial cells that is confined to pre-existing prostatic ducts or acini (glands). PIN was further termed as intraductal dysplasia by McNeal and Bostwick in 1986. Bostwick and Brawer in 1987 introduced the currently used term “prostatic intraepithelial neoplasia”, and endorsed by consensus at a 1989 conference.[3] It was originally graded from 1 to 3, but currently there are two grades of PIN (low grade and high grade). Grade 1 was defined as low-grade PIN, whereas grades 2 and 3 were considered together as high-grade PIN; currently, conventional use of the term 'PIN' refers to only high-grade PIN.[4] Protein p63, which shares homology with the suppressor gene of tumor p53, seems to play a critical role as a regulator of growth and development of cutaneous epithelium, uterine cervix, breast and the urogenital tract, and in particular, of prostate development.[5] Signoretti et al in their study, first confirmed that p63 represents a selective marker of basal cells within the prostatic epithelium by analyzing p63 expression in a series of normal prostates and in normal prostate basal cells. p63 expression may be used in the differential diagnosis between benign and malignant lesions of the prostate[6]. In view of increasing trend in the occurrence of both neoplastic and nonneoplastic lesions of the prostate in the elderly, the current study aims at evaluating the incidence of prostatic intraepithelial neoplasia in transurethral resection specimens of prostate by using p63 marker.

Aims and Objectives

1. To determine the incidence of Prostatic Intraepithelial Neoplasia in TURP specimens.

2. To study the expression of immunohistochemical marker p63 in various non neoplastic and neoplastic lesions of prostate.

Materials and Methods

This was a prospective study which included 65 cases, conducted for a period of 2 years, at DR.B.R.Ambedkar Medical College, Bangalore. All the 65 cases were TURP specimens. The clinical history and the details of the patient were collected. All the specimens obtained were fixed in buffered neutral formalin for a period of 12- 24 hrs and then the entire specimen was submitted for processing. The weight of the specimen was noted and the findings were recorded. For light microscopy one slide from each block was routinely stained with H&E. p63 marker was done wherever necessary. Cellular localization of p63 is nucleus of basal cells of prostatic glands, urothelium. Positive control used is normal prostate glands

Results

A total number of 65 cases were studied. The cases were distributed in the age group of 45–85 years (Table1). The maximum number of patients were in the age group of 60-69 yrs. Out of 65 cases, 4 were nonspecific prostatitis, 52 were BPH, 8 were prostatic adenocarcinoma, 1 case was urothelial carcinoma (Table 2). Among premalignant lesions low grade PIN was identified in 8 (12.3%) cases out of 65 cases. All of these were associated with BPH. High grade PIN was seen in 9 (13.8%) cases. Out of these, 7 cases were associated with adenocarcinoma and 2 cases were seen in BPH. 87.5% of adenocarcinoma and 3.8% of BPH were associated with HGPIN (Table 3). Low grade PIN showed crowding and stratification of glandular secretory epithelium. The nuclei were variably increased in size with thin nuclear membrane and inconspicuous nucleoli. The basal cells were intact.

High grade PIN consisted of crowding and stratification of glandular secretory epithelium. The nuclei were enlarged with variation in size and shape and the nucleoli were prominent. The basal cells were intact but few cases showed discontinuity. There were four patterns identified in HGPIN usually with multiple patterns in each case. Tufting Pattern was seen in 6 (66.7%)out of 9 cases. Microscopy showed the neoplastic cells grow towards the lumen, forming wave- or mound-like structures. Flat Pattern comprised of 5 (55.6%) out of 9 cases. Microscopy consisted of the glands lined with one or two layers of atypical cells without significant architectural abnormality. Micropapillary pattern composed of glands lined by atypical secretory epithelial cells arranged in micropapillary structures, lacking fibrovascular cores and was identified in (3 33.3%) out of 9 cases of HGPIN. Cribriform Pattern showed glands with epithelium forming cribriform pattern, was identified in 1 (11.1%.) out of 9 cases. In this present study the commonest pattern identified was tufting type followed by flat type (Table 4).

Immunohistochemistry

p63 stain: In all the 52 (100%) cases of BPH the basal cell nuclei of the glands showed positivity for p63 immunostaining which was complete positivity. Basal cell nuclei of HGPIN glands showed positivity for p63 stain in all the 9(100%) cases. Out of the 9 cases, complete positivity was seen in 8 cases and 1 case showed partial positivity. p63 stain was negative in all the 8 (100%) cases of adenocarcinoma. Urothelial carcinoma showed score 5 p63 positivity (75--90% of cancer cell nuclei positive) (Table 5).

Discussion

The present study was carried out on 65 cases of TURP specimens. Basal cell marker p63 was used in benign prostatic hyperplasia, prostatic intraepithelial neoplasia and malignant cases. Out of 65 TURP specimens BPH was diagnosed in 52 (80%) of cases. In all the 52 (100%) cases of BPH the basal cell nuclei of the glands showed positivity for p63 immunostaining which was complete positivity. This is in concordance with studies done by Shah et al[7] and Kruslin et al[8] with the positivity rate of 95% and 100% respectively. Present study showed 12.3% (8 cases) of low grade PIN and 13.8% (9 cases) of high grade PIN in 65 TUPR specimens studied. Gaudin et al[9](3.2%) and Pacilli and Bostwick[10] (4.2%) observed slightly lower incidence of HGPIN in their studies. Skjorten et al[11] reported 33% of HGPIN in their study conducted in 1135 prostatic specimens. The higher incidence could be due to more number of cases studied.

The present study showed 8 cases of LGPIN associated with BPH and no LGPIN case was seen in adenocarcinoma. 15.4% of BPH cases showed LGPIN in this study. Rekhi et al[12] found LGPIN in 18.6% cases of BPH and 5.8% of cases of adenocarcinoma. HGPIN was observed in 3.8% of the cases of BPH and 87.5% of the cases of adenocarcinoma. This is similar to other studies by Rekhi et al[12] with incidence of HGPIN of 11.2% in BPH and 86.9% in adenocarcinomas. Desai and Borges[13] observed 85.24% of HGPIN in adenocarcinoma. In present study there were four microscopic patterns identified in HGPIN usually with multiple patterns in each case. The percentage of tufting, flat, micropapillary and cribriform patterns were 66.7%, 55.6%, 33.3% and 11.1% respectively. The commonest pattern identified was tufting type followed by flat type.

Bostwick et al[14] in their study found the percentage of tufting, flat, micropapillary and cribriform patterns 87%, 28%, 85% and 32% respectively. The commonest pattern was tufting type followed by micropapillary type. In the present study all the 9 (100%) cases of HGPIN showed positivity for p63 staining. Kruslin et al[15] showed in their study that 100% positivity for p63 staining in 28 cases of HGPIN. There were 8 (12.3%) cases of adenocarcinoma out of 65 TURP specimens identified. Present study showed p63 negativity in all the 8 cases of adenocarcinoma. The percentage of negativity was 100%. It is comparable with other studies done by Molinie et al[16] (100%), Signoretti et al[6] (97%), Shah et al[17] (100%) and Ud Din et al[18] (100%). There was 1 case of urothelial carcinoma found in this study which was in 9th decade of age. It showed positivity for p63 (Score 5 = 75--90% of cancer cell nuclei positive). Langner et al[19] performed p63 stain in 53 urothelial carcinoma and found positivity in 51 (96.2%) cases. Kunju et al[20] found p63 positivity in 92% of urothelial carcinoma cases.

Conclusion

High grade PIN is relatively uncommon and diagnosed predominantly in prostatic adenocarcinoma. Basal cell marker p63 is really helpful in differentiating benign and HGPIN glands from malignant glands. In view of high degree of association of HGPIN with prostatic carcinoma, it is suggested that these HGPIN patients need close follow-up with serum PSA and transrectal ultrasound. Rebiopsy might be helpful to rule out existence of carcinoma, especially in the peripheral zone.

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Tables

Table 1: Distribution of cases according to Age Group

Age	No of cases (n=65)	Percentage(%)
40-49 yrs	2	3.1
50-59 yrs	10	15.4
60-69 yrs	25	38.4
70-79 yrs	15	23.1
80-89 yrs	13	20.0

Table 2: Distribution of cases according to Histopathological Diagnosis

Diagnosis	No of cases (n=65)	Percentage(%)
Inflammatory lesions	4	6.2
Benign prostatic hyperplasia	52	80.0

Malignant lesions	9	13.8

Table 3: Distribution of Prostatic Intraepithelial Neoplasia in different cases

Type of case	PIN			Total
	LGPIN	HGPIN	Negative for PIN	
Adenocarcinoma	0	7	1	8
	0.0%	87.5%	12.5%	100.0%
BPH	8	2	42	52
	15.4%	3.8%	80.8%	100.0%
Inflammatory lesions	0	0	4	4
	0.0%	0.0%	100.0%	100.0%

Table 4: Different Microscopic patterns of HGPIN (N= 9)

Microscopic pattern	No of cases	Percentage
Flat	5	55.6%
Tufting	6	66.7%
Cribriform	1	11.1%
Micropapillary	3	33.3%

Table 5: Expression of p63 immunostaining in different cases.

Type of Case	IHC-p63 Stain		Total
	Positive	Negative	
HGPIN	9	0	9
	100.0%	0.0%	100.0%
Adenocarcinoma	0	8	8
	0.0%	100.0%	100.0%
BPH	52	0	52
	100.0%	0.0%	100.0%

Figures

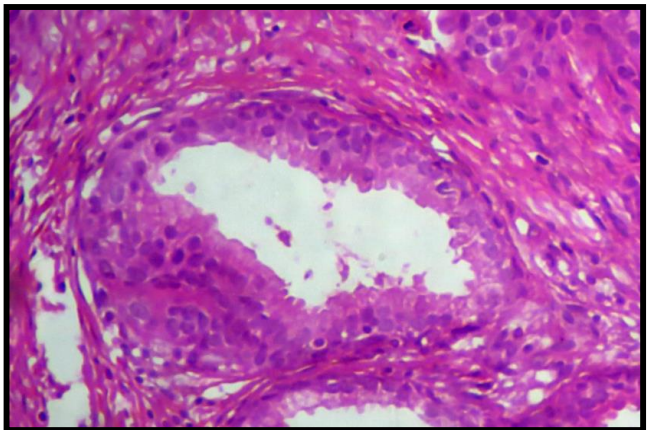

Fig 1: Photomicrograph of Lowgrade PIN (40x)

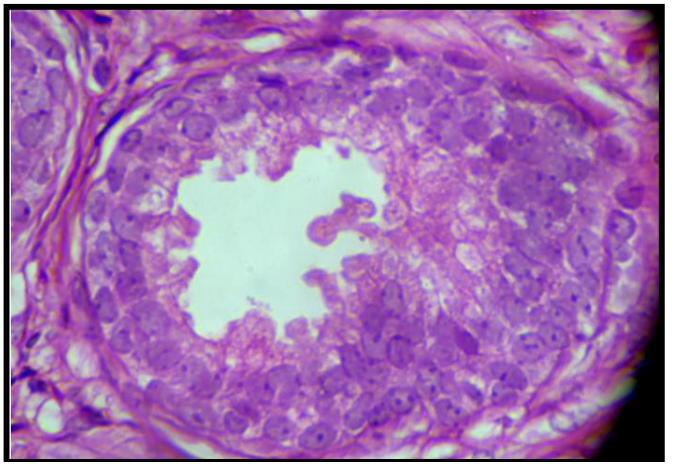

Fig 2: Photomicrograph of High grade PIN – Tufting pattern. (40x)

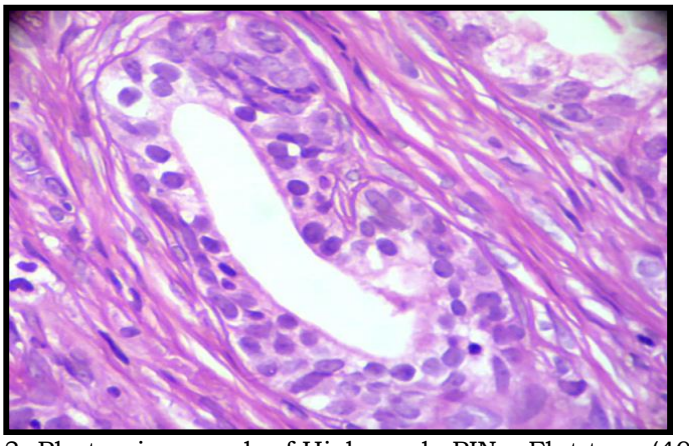

Fig 3: Photomicrograph of High grade PIN – Flat type (40x)

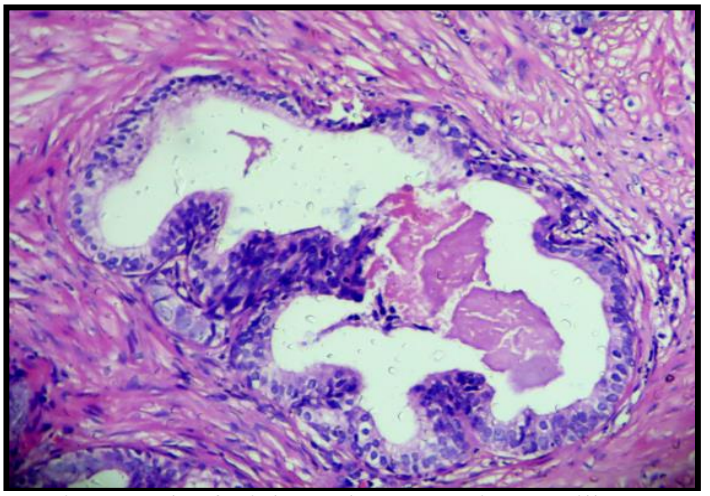

Fig 4: Photomicrograph of High grade PIN – Micropapillary pattern (40x)

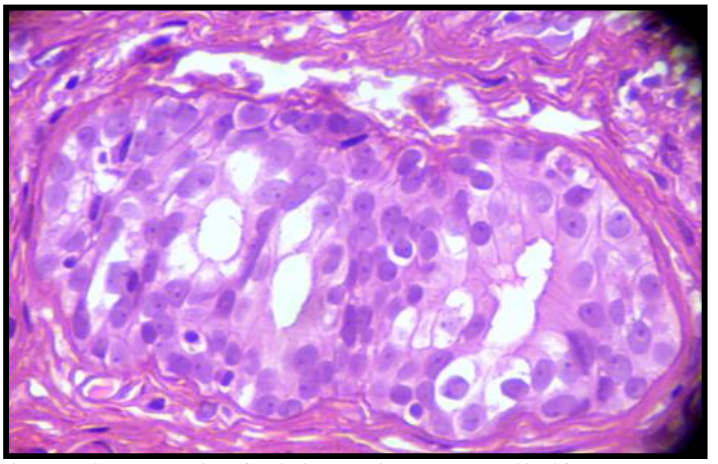

Fig 5: Photomicrograph of High grade PIN – Cribriform pattern (40x)

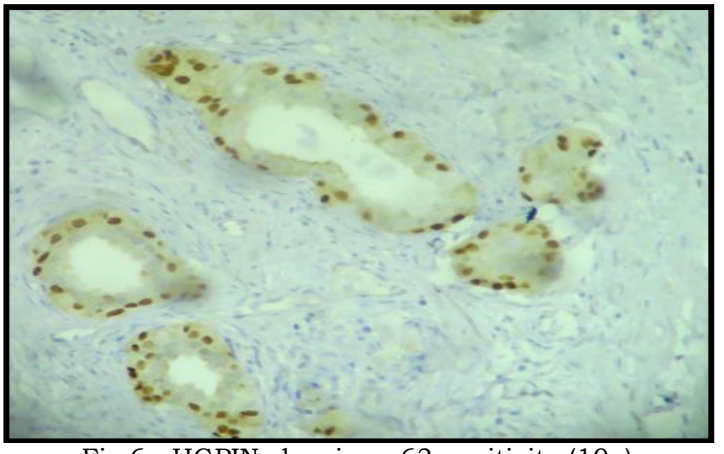

Fig 6: HGPIN showing p63 positivity (10x)

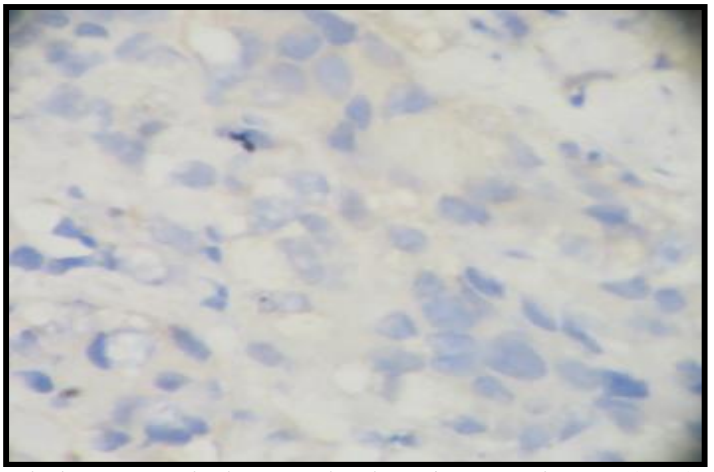

Fig 7: p63 stain is negative in Adenocarcinoma (40x)

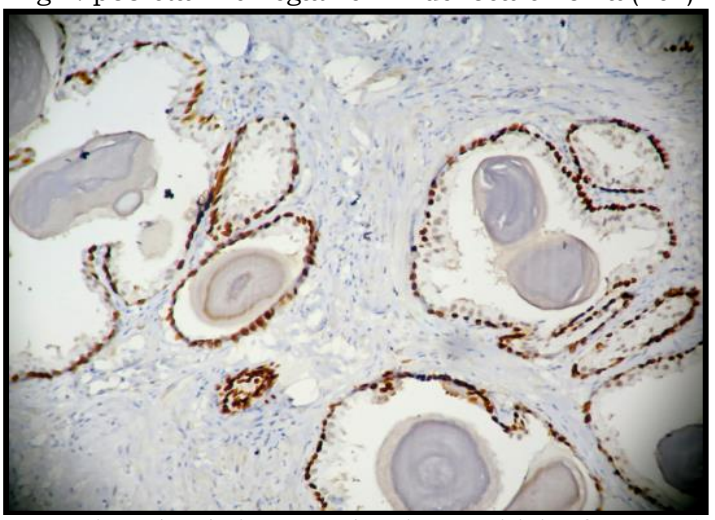

Fig 8: Benign glands in BPH showing positivity for p63. (40x)