

Histopathological spectrum of prostatic lesions and utility of p63 and Alpha-methylacyl-Co A racemase immunohistochemical markers in resolving suspicious cases

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Abstract

Introduction: The spectrum of diseases affecting the prostate gland in men can be inflammatory, benign, premalignant lesions and malignancy. Major diagnostic challenge of surgical prostate biopsy interpretation is either due to a small focus of cancer or presence of various benign mimickers of malignancy which is labeled as suspicious foci. Aim of the study was to evaluate complete histopathological spectrum of lesions encountered on transrectal ultra sonography (TRUS) guided prostate needle biopsy and transurethral resection of prostate (TURP) chips and to use immunohistochemistry (IHC) markers like Alpha-methylacyl-Co enzyme A racemase (AMACR) and p63 as an adjunct in resolving the suspicious cases.

Materials and Methods: We assessed total 60 cases of prostatic specimens received during December 2015 to November 2017. The received specimens were routinely processed and histopathological examination was carried out. IHC for AMACR and p63 was performed and results were analyzed using SPSS software.

Results: Majority of cases were benign prostatic hyperplasia (BPH) (73.3%). Incidence of prostate cancer was low (16.6%). After IHC, out of the six (10%) histomorphologically suspicious cases, three cases were positive for only AMACR; two cases were positive for only p63 and one case showed positivity for both. Immunohistochemistry with AMACR and p63 proved to be highly sensitive markers for detecting malignancy but AMACR marker showed less specificity.

Conclusion: Histomorphologically, benign lesions of prostate are more common than malignant ones. Combination of AMACR and p63 IHC enhances the diagnostic accuracy in suspicious cases by identifying premalignant lesions or malignancy and reduces misdiagnosis.

Keywords: Histopathology, prostate cancer, suspicious foci, immunohistochemistry, AMACR, p63.

Introduction

The common histopathological spectrum of diseases affecting prostate gland consists of inflammatory conditions, benign nodular hyperplasia, prostatic intraepithelial neoplasia and malignancy. Benign prostatic hyperplasia (BPH) is the most common condition in men over 50 years of age and shows remarkable racial and geographical variations in incidence and mortality.¹ Chronic non-specific prostatitis is the most frequent non-neoplastic finding commonly seen associated with BPH, where as non-specific granulomatous prostatitis is noticed occasionally.² Prostate cancer is the sixth leading cause of cancer in men.³ Screening of prostatic lesions constitutes prostate specific antigen (PSA) levels, digital rectal examination (DRE), and transrectal ultrasound (TRUS), but biopsy remains the gold standard diagnostic tool for final diagnosis. While the advent of PSA screening, led to earlier detection of prostate cancer, a major limitation of the serum PSA test is a lack of prostate cancer sensitivity and specificity and age-related cutoffs.⁴ The histological diagnosis of prostate cancer on a biopsy is based on architectural pattern, nuclear atypia and lack of basal cells. This can be a challenge when faced with a small focus of prostate cancer or in the presence of benign mimickers.⁵ Alpha-methyl acyl CoA racemase (AMACR), a peroxisomal and mitochondrial enzyme shows cytoplasmic positivity in prostate cancer.^{6,7} Since expression of AMACR is also seen in benign mimickers like high grade prostatic

intraepithelial neoplasia (HGPIN)⁸ and atypical adenomatous hyperplasia (AAH)⁹ combined use of p63, a basal cell marker, will enhance the diagnostic accuracy in premalignant lesions, benign mimickers and in cases suspicious for malignancy.

Materials and Methods

Selection of Cases in Histopathology Department

This was a prospective study conducted over a period of 2years (December 2015 to November 2017). A total of 60 prostate specimens, including 42 TURP chips specimens and 18 TRUS guided prostate biopsies were analyzed in department of Pathology. Specimen was all embedded and tissue was routinely processed.¹⁰ H and E stained slides were examined thoroughly by light microscopy and a provisional histopathological diagnosis was established by at least two pathologists. Cases were categorized into inflammatory lesions, benign lesions, prostatic intraepithelial neoplasia and malignancy.

IHC for p63 and AMACR Markers

The blocks from all suspicious and control cases were cut and mounted on poly L-Lysine coated glass slides. Endogenous peroxidase activity was blocked by freshly prepared 0.3% hydrogen peroxide in methanol for 20 min. Subsequently, heat induced epitope retrieval was performed. IHC was done by using anti AMACR antibody (Dako;

Monoclonal rabbit Anti Human AMACR-clone 13H4) and a monoclonal anti p63 antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA: Monoclonal mouse antihuman p63 antibody clone sc-8431). 3, 3'-diaminobenzidine (DAB) was used as chromogen and counterstained with hematoxylin or eosin. IHC signals were brown with eosin and dark brown or black with hematoxylin counterstains. Observed AMACR staining showed grades of staining intensity depending on the percentage of cells stained in accordance with Luo J and Zha S et al¹¹ study, which assigns grading as follows: "Grade 0:No cells were stained, Grade 1: <10% of cells showed staining, Grade 2:10-50% of cells were stained and Grade 3 if >50% showed staining". Positive AMACR staining is described as being easily visible on low power examination and interpreted as circumferential, granular, luminal (apical) to subluminal and diffusely cytoplasmic in nature. If the control slides were negative, the staining was repeated. Interpretation of p63 staining¹² was given as a score based on the percentage of tumor cells. Statistical analysis was performed using SPSS version 17.

Results

Present study included a total number of 60 cases, 42 TURP chips specimens and 18 TRUS guided prostate needle biopsies. These cases were distributed in the age group of 42-82 years. All specimens were broadly classified into Prostatitis, Benign prostatic hyperplasia (BPH) (Fig. 1A), BPH with prostatic intraepithelial neoplasia (PIN), malignancy (Adenocarcinoma), Adenocarcinoma with PIN and Suspicious cases. BPH accounted for 73.3% (44) of the cases. Mean age for BPH was 65yrs while for carcinoma it was 69yrs. Majority of suspicious cases were in the age group of 60-69 yrs. (Graph 1).

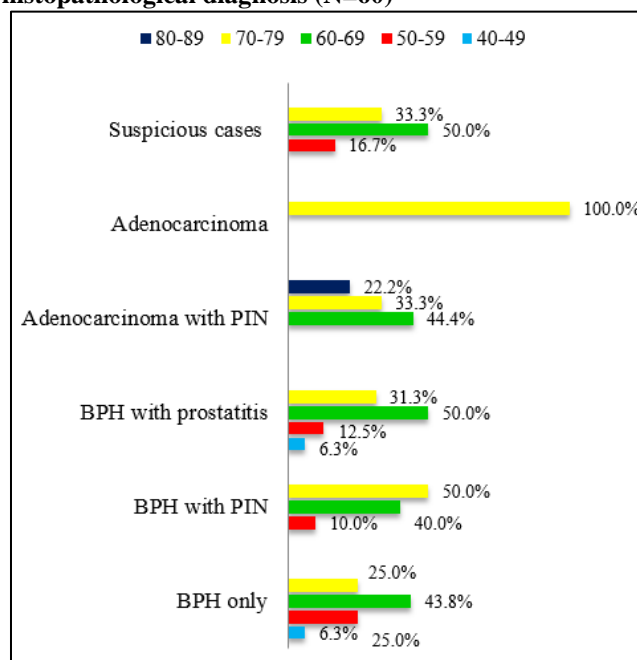
Chronic nonspecific prostatitis (CNSP) was the most common inflammatory lesion of prostate gland, all cases of which were seen associated with (15) 34% cases of BPH, while non-specific granulomatous prostatitis (NSGP) was rare and was seen only in one case with an incidence of 1.6% among total cases. Foci of PIN was identified in 19 cases, out of which LGPIN was seen in eight cases of BPH. HGPIN was seen in two cases of BPH as well as nine cases of adenocarcinoma. Thus, HGPIN showed more association with adenocarcinoma.

Remaining 41% cases of BPH showed association with miscellaneous features like cystic atrophy, basal cell hyperplasia, squamous metaplasia and transitional cell metaplasia. Prostate adenocarcinoma accounted for almost all cases of malignancy in the present study accounting for 16.6% (10) cases. Histopathological distribution of cases is plotted in Graph 1 and shown in Table 1. Gleason's score was 2-4, 5-7 and 8-10 in 14%, 29% and 57% cases respectively. Majority of patients diagnosed as conventional adenocarcinoma were scored 10. All cases of adenocarcinoma showed tumour quantification of >5%.

There were six cases with a suspicious area or atypical foci. Among these, three cases showed atypical small acinar proliferation (ASAP) which was suspicious for malignancy,

exhibiting small, crowded atypical glands with architectural and cytological atypia, but insufficient to be labeled as malignancy due to small area of focus (Fig. 3A, 4A). A small focus of prostatic adenocarcinoma was defined as a tumor focus of 1 mm or less in diameter that was present as a single focus with few malignant looking acini in the entire biopsy specimen. One suspicious case showed closely packed small glands resembling atypical adenomatous hyperplasia with camouflaged morphology, due to distorted architecture with uncertain nuclear features (Fig. 5A). Another case of BPH showed a suspicious focus, exhibiting a solid area of multilayered epithelium comprised of cells with vesicular nucleus, prominent nucleoli and clear cytoplasm (Fig. 6A). In the last case, there was discrepancy about a cribriform focus between adenocarcinoma and HGPIN. All these cases were subjected to IHC.

Graph 1: Age wise distribution of cases according to histopathological diagnosis (N=60)



Immunohistochemistry was done using p63 and AMACR markers. (Table 2) In all cases of BPH, the basal cell nuclei of the glands showed complete positivity for only p63 immunostaining (Fig. 1B). In two cases of BPH, the benign glands showed circumferential luminal positivity for AMACR (Fig. 1C). In HGPIN, glands were positive for both p63 and AMACR (Fig. 2A, B, and C). Adenocarcinoma showed strong cytoplasmic granular positivity for AMACR only. The sensitivity and specificity of markers were calculated taking 44 benign and 10 malignant cases as controls and inflammatory lesions were excluded as seen in Table 3. IHC with p63 was highly sensitive and specific with an accuracy of 100% for excluding malignancy. AMACR was found to be equally sensitive to p63 but less specific (95.3%) in differentiating HGPIN or AAH from adenocarcinoma. The positive and negative predictive value of AMACR was 83.3% and 100%

respectively with an accuracy of 96.2% (Table 3). Of the six suspicious cases, three cases were positive for only AMACR marker, i.e suggestive of malignancy; two cases were positive for p63 only which excludes a malignancy;

one case showed positivity for both suggesting a premalignant lesion ie HGPIN.

Table 1: Distribution of cases according to histopathological diagnosis (N=60)

HP diagnosis	Frequency	Percentage
BPH with prostatitis (CNSP+NSGP)	16	26.6%
BPH with PIN changes	10	16.6%
BPH	18	30%
Adenocarcinoma	10	16.6%
Suspicious for malignancy	06	10.0%
Total	60	100.0%

†HP =Histopathology, #BPH=Benign Prostatic Hyperplasia ##CNSP = Chronic Non Specific Prostatitis, NSGP=Non Specific Granulomatous Prostatitis, ‡PIN=Prostatic Intraepithelial Neoplasia

Table 2: Expression of p63 and AMACR immunostaining in different cases (N=60)

Type of case	IHC-p63		IHC-AMACR		Total
	Positive	Neg.	Positive	Negative	
BPH without PIN	34	0	2	32	34
	100.0%	0.0%	5%	95%	100.0%
LGPIN (with 8 BPH)	8	0	0	8	8
	100.0%	0.0%	0.0%	100.0%	100.0%
HGPIN (With 2BPH & 9 Adenocarcinoma)	11	0	11	0	11
	100.0%	0.0%	100.0%	0.0%	100.0%
Adenocarcinoma	0	10	10	0	10
	0%	100%	100.0%	0.0%	100.0%
Suspicious for malignancy	3	3	4	2	6
	50%	50%	66.6%	33.3%	100.0%

Table 3: IHC expression of p63 and AMACR in benign and in the malignant controls

Category	Malignant on H&E	Benign on H& E
Malignant on p63 stain	10(TP)*	0(FP)
Benign on p63 stain	0(FN)*	44(TN)
Malignant on P504S stain	10(TP)*	2 (FP)
Benign on P504S stain	0(FN)*	42(TN)

(*TP=True Positive,FP=False Positive,TN=True Negative, FN=False Negative †Sensitivity = (TP/TP+FN)X100, ‡Specificity= (TN/TN+FP)X100, #Positive predictive value(PPV)=TP/TP+FP, ##Negative predictive value (NPV)= TN/TN+FN)

†Sensitivity of p63 =100%, ‡Specificity of p63=100%, = 100%), #PPV=100%, ##NPV=100%. †Sensitivity of AMACR =100%, ‡Specificity of AMACR=95.4%, #PPV=83.3%, ##NPV=100%

Table 4: Change of diagnosis in suspicious cases after IHC

S. No	Provisional diagnosis on Histopathological examination	Final diagnosis after IHC of p63 and AMACR
1.	BPH with ASAP suspicious for malignancy	Prostate adenocarcinoma (Tumor quantification<5%) with HGPIN
2.	BPH with ASAP suspicious for malignancy	BPH with foci of Atrophic glands
3.	BPH with foci of atypical adenomatous hyperplasia	Prostate adenocarcinoma, GS-07 (Tumor quantification>5%)
4.	BPH with foci of ASAP suspicious for malignancy	Prostate adenocarcinoma (Tumor quantification <5%) with HGPIN
5.	BPH with a suspicious focus	Basal cell hyperplasia
6.	Cribriform type of prostate adenocarcinoma	BPH with Cribriform HGPIN

Change of Diagnosis after IHC

These were the final diagnosis considered after evaluating all the data work up including the IHC evaluation. (Table 4) There was a change in diagnosis in three cases of BPH with a focus suspicious for malignancy

which was rendered as adenocarcinoma after IHC. One case with a focus of cribriform adenocarcinoma turned out to be HGPIN, which showed positivity for both AMACR and p63 markers. Another case of BPH with a suspicious focus was confirmed as basal cell hyperplasia after IHC.

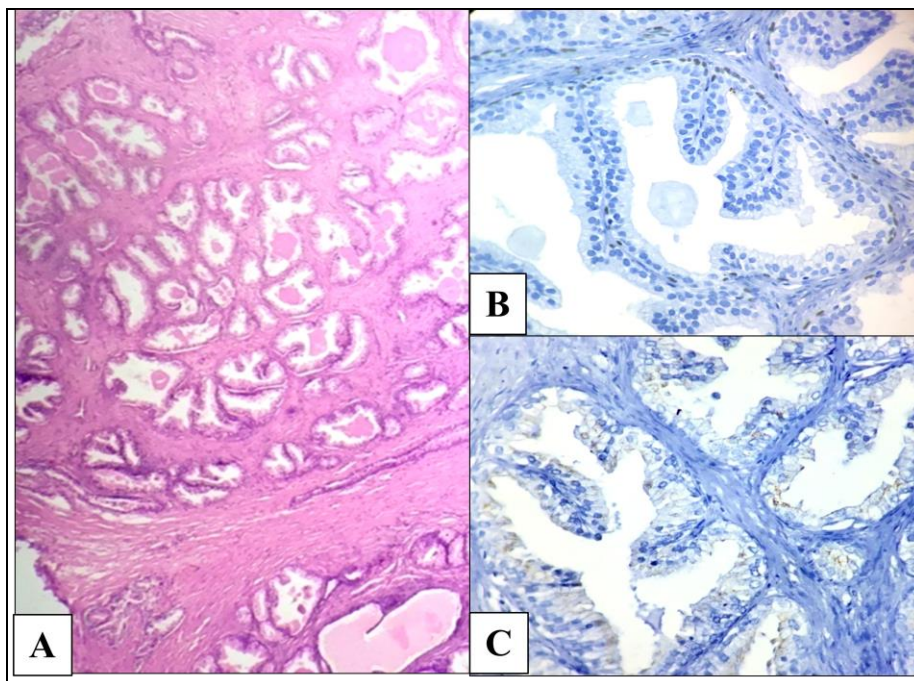


Fig. 1 : A) Benign prostatic hyperplasia of prostate (H&E, 10x); B): BPH with p63 positivity (40x); C): BPH with luminal AMACR positivity due to over staining (40x)

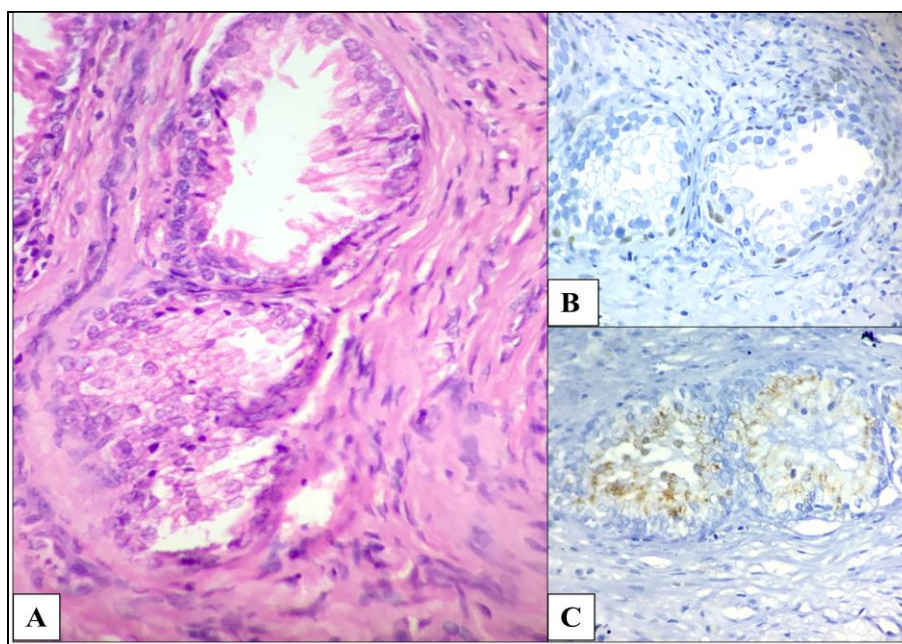


Fig. 2: A) High Grade Prostatic Intraepithelial Neoplasia (HGPIN) with prominent nucleoli and intact basal cell layer (H & E, 40x); B): HGPIN patchy p63 positivity (40x); C): HGPIN AMACR positivity-Grade2 (40x)

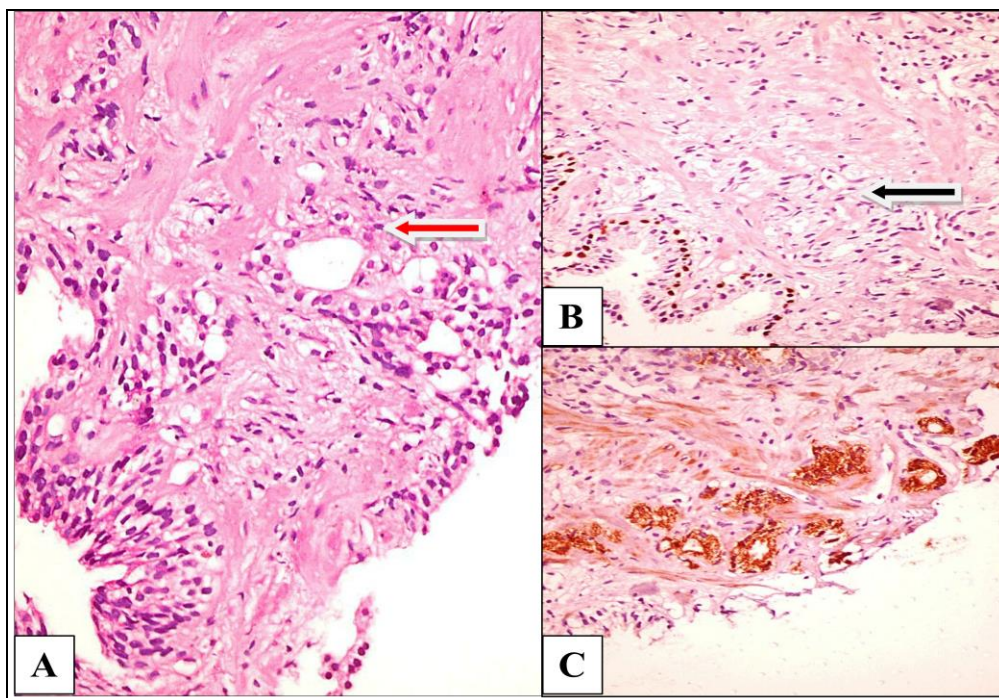


Fig. 3: A) Photomicrograph of a suspicious case showing atypical small acinar proliferation (red arrow) (H& E, 40x); B): Malignant glands (black arrow) with p63 negativity and benign glands with p63 positivity (40x); C): Malignant glands with Grade 3 AMACR positivity (40x)

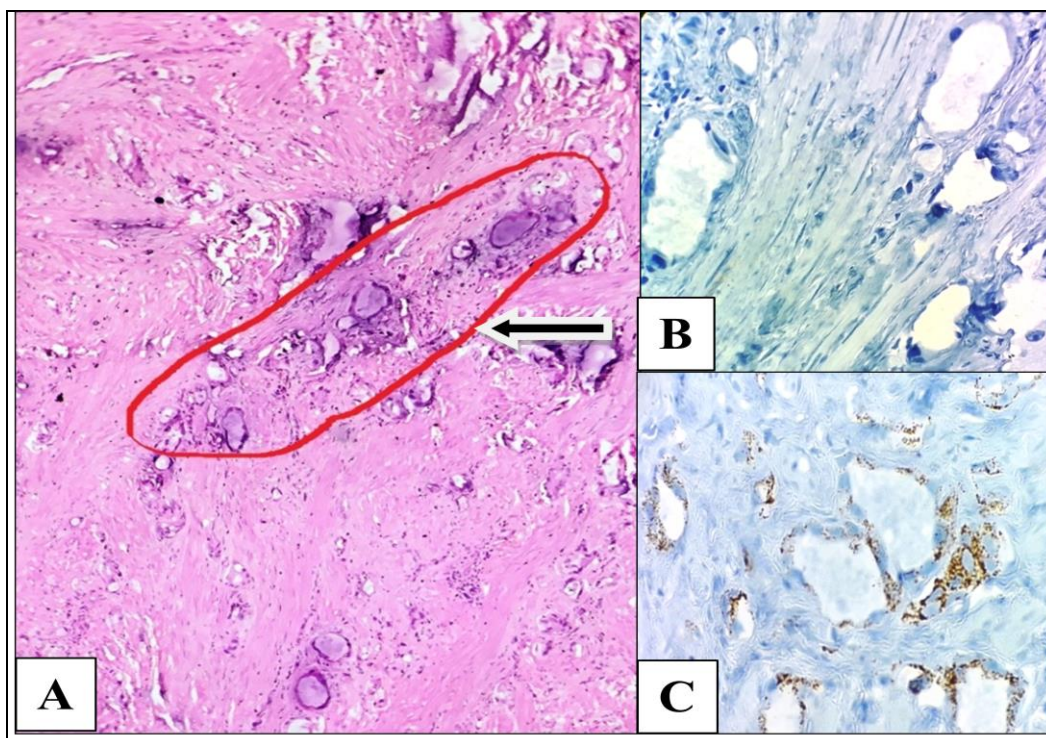


Fig 4: A): A suspicious case showing atypical small acinar proliferation (black arrow) (H& E, 10x); B): Atypical glands with p63 negativity (40x); C): AMACR positivity in malignant glands (40x)

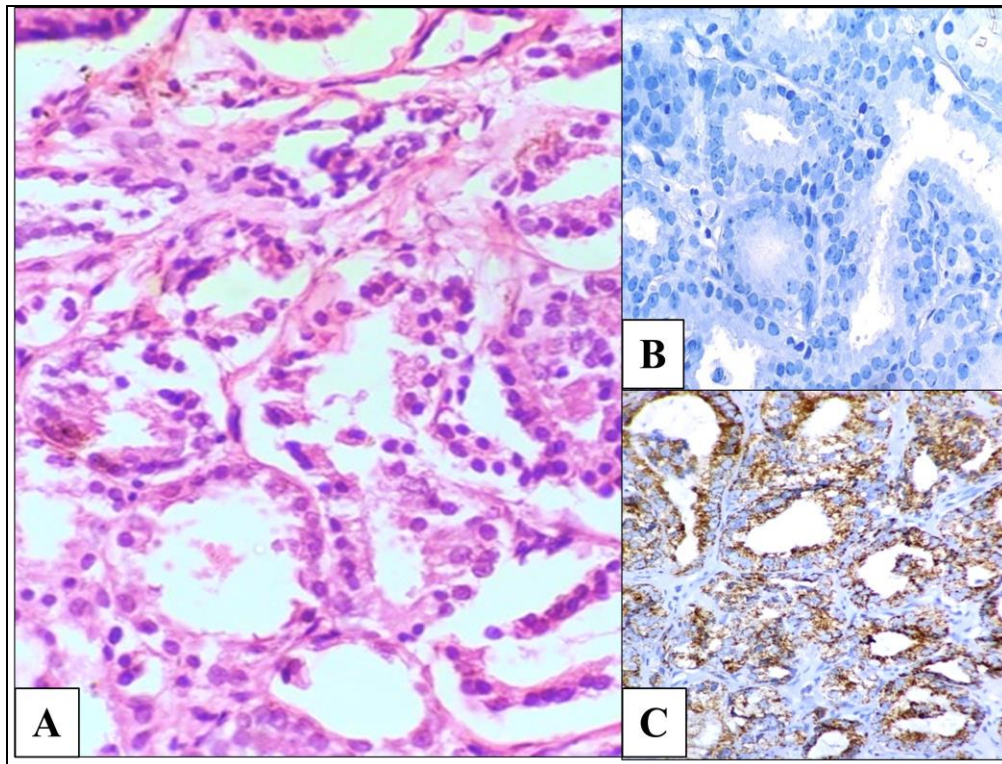


Fig. 5: A) Photomicrograph of a suspicious case showing closely packed small glands with bland nuclear features (H& E, 40x); B): Atypical glands with p63 negativity (40x); C): Grade 3 AMACR positivity (40x) in malignant glands.

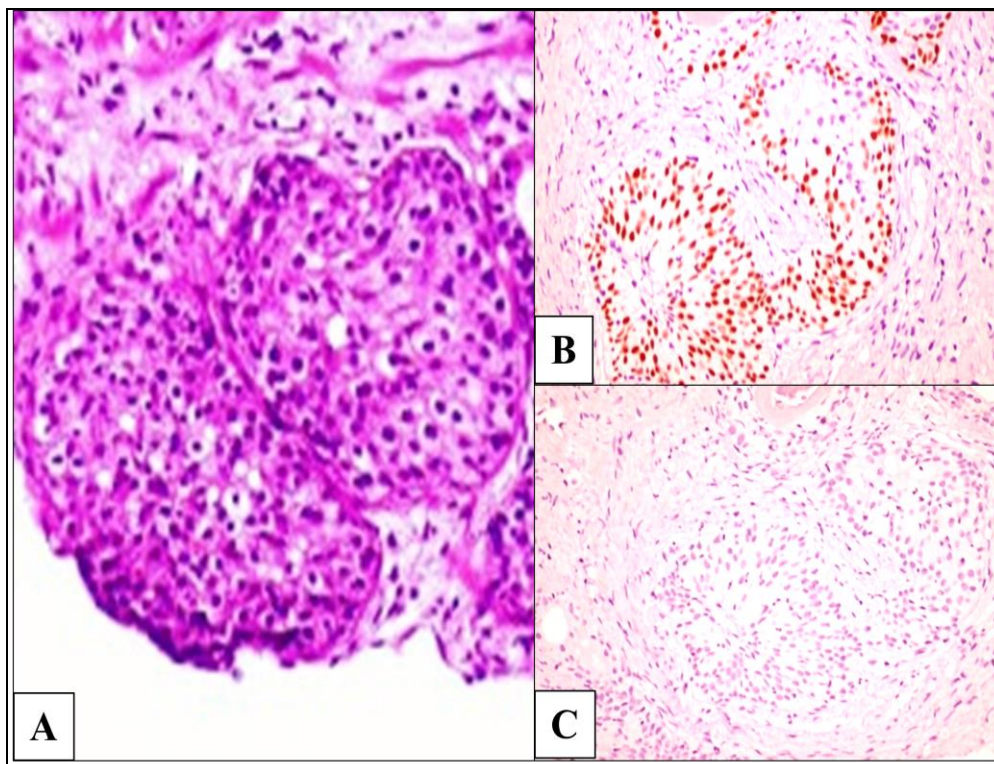


Fig. 6: A) Basal cell hyperplasia of prostate (H& E, 40x) B) showing p63 positivity (40x) and C) AMACR negativity (40x)

Discussion

The histomorphology was studied in 60 cases of prostate specimens with special emphasis given to morphologically suspicious cases. Maximum cases were of benign prostatic hyperplasia (73.3%) occurring in 60-69yrs, similar Haroun et al¹³ and Jasani et al.¹⁴ Prostate adenocarcinoma was found to be the most common prostate malignancy in men, encountered in 7th decade of life, with a mean age of 69yrs. The histopathology of lesions was as follows:

Microscopy and Histopathological Patterns

In the present study among the inflammatory lesions, chronic prostatitis was more common while acute prostatitis was not observed. Benign prostatic hyperplasia (BPH) is hyperplasia of glandular and stromal tissue with papillary buds, in folding and cysts. Glandulostromal pattern of hyperplasia was the most frequent histological pattern. BPH with co-existing chronic prostatitis was observed in 15 cases similar to a study conducted by Dr. Ashish Joshee, Dr. Kaushal C.L. Sharma.¹⁵ Granulomatous prostatitis is thought to represent an initially immune-mediated process accompanied by a reaction to the prostatic secretions released from obstructed ducts. On microscopic examination, large nodular aggregate of histiocytes, epithelioid cells, lymphocytes, and plasma cells were seen. In our study, incidence of granulomatous prostatitis was 1.6% similar to Mohan et al study.¹⁶ Basal cell hyperplasia (BCH) is usually seen in the transitional zone, but it may also occur in the peripheral portion of the gland. Microscopically, it appears as small, solid nests of benign appearing epithelial cells with a somewhat clear cytoplasm. Prominent nucleoli may or may not be present in BCH. BPH with BCH was observed in two (3.3%) cases. Squamous metaplasia can be seen at the periphery of infarcts, after TURP or as a result of hormonal manipulation. BPH with squamous metaplasia was seen in two (3.3%) cases. There was one case of AAH and two cases of atrophy, constituting 1.6% and 3.3% of the total cases, respectively. This is comparable to the reported incidence of less than 1% by Hameed and Humphrey¹⁷ who stated that AAH is invariably an incidental histological finding. The peculiarity of these two processes is that they may be confused with the diverse patterns of prostatic adenocarcinoma.

Present study showed 13.3% of low grade PIN and 18.3% of high grade PIN in 60 cases. HGPIN in Pacelli and Bostwick¹⁸ was 4.2%. Rekhi et al¹⁹ found LGPIN in 18.6% cases of BPH and 5.8% of cases of adenocarcinoma. The present study showed that all eight cases of LGPIN were associated with BPH. HGPIN was observed in 3.5% of the cases of BPH and 87.5% of the cases of adenocarcinoma. This variation could be due to small sample size of this study. Adenocarcinoma constituted 16.6% of cases which could be easily diagnosed on H&E, having characteristic infiltrative pattern, small and crowded glands with prominent nucleoli, nuclear enlargement, hyperchromasia, mitotic figures, apoptotic bodies, amphophilic cytoplasm with sharp luminal border. Incidence of adenocarcinoma is comparable with Djavan et al study.²⁰ Gleason's score was

2-4, 5-7 and 8-10 in 14%, 29% and 57% cases respectively. Perineural invasion is regarded as pathognomonic of prostate cancer if there is circumferential or intraneural invasion by the tumor cells.²¹ In our study perineural invasion was seen in 7 out of 10 cases.

We used p63 and AMACR IHC markers in all 44 benign (BPH) and 10 malignant (adenocarcinoma) controls, low grade and high grade prostatic intraepithelial neoplasia to study expression of AMACR and p63 in the various lesions. Basal cells in all BPH cases were positive for only p63, similar to Kruslin et al study.²² AMACR was positive in two cases of BPH which correlated with Jiang et al²³ study. According to Evans et al,⁶ pseudo neoplasms also (atypical adenomatous hyperplasia, atrophy, post atrophic hyperplasia and basal cell metaplasia) shows positive AMACR immunoreactivity. According to Leav et al²⁴ a phenomenon called "Field effect" plays a role in such positive BPH cases. The other phenomenon which was suggested by Yang et al⁹ is the process of "Over staining". Both the BPH cases which were positive for AMACR were again subjected to p63 staining which was positive. LGPIN was negative for AMACR markers. All cases of HGPIN were positive for both AMACR and p63 similar to Kruslin et al²² study. All cases of adenocarcinoma were positive for AMACR only, which correlated with Jiang et al.²³

Prostatic biopsies occasionally contain proliferative foci of small atypical acini that display some but not all features diagnostic of adenocarcinoma. Such foci have been described by a wide variety of terms which are synonymous like suspicious, atypical focus, and atypical small acinar proliferation (ASAP) suspicious but not diagnostic of malignancy. ASAP include lesions such as HGPIN, benign mimickers of cancer, reactive atypia and many cases that in retrospect show minute carcinoma but contain insufficient cytological or architectural atypia to establish a definitive diagnosis of cancer. The likelihood of prostate cancer on subsequent biopsy in men with a diagnosis of ASAP on initial biopsy is 21-49%.²⁵

Amongst the benign mimickers atypical adenomatous hyperplasia, basal cell hyperplasia, sclerosing adenosis and partial atrophy are commonly misdiagnosed as prostate carcinoma.⁵ In such cases, basal cell markers like HMWCK (34 β E12) and CK 5/6 and p63 are very useful for demonstration of basal cells as their presence hints against a diagnosis of invasive prostatic adenocarcinoma.²⁶ Some lesions such as atypical adenomatous hyperplasia (AAH), HGPIN, post atrophic hyperplasia (PAH) may show discontinuous or patchy p63 staining.²⁷ Hence, one must be cautious in interpreting negative basal immunostains as they are supportive of a diagnosis of prostate cancer in the appropriate H and E. Rarely early prostatic adenocarcinoma can express p63 and this is usually not a diagnostic problem, as AMACR is positive in the malignant cells.²⁸ Thus, it is important to recognize that the diagnosis of cancer is based on the absence of a detectable positive basal cell layer and a sensitive and specific additional positive adenocarcinoma

specific marker is required for confirmation of the diagnosis.

AMACR is a sensitive and specific IHC marker found to be consistently up regulated in PCa.²³ However there are varied reports regarding the expression of AMACR in prostate cancer which ranges from 62% to 100% respectively.^{11,29,30} Kunju et al²⁹ were able to resolve 27 (93%) of 29 atypical biopsies after immunostaining with AMACR and basal cell markers. Zhou et al³⁰ demonstrated that, of 115 prostate biopsies diagnosed as atypical by an expert pathologist, 34 (30%) were changed to a final diagnosis of cancer based on a positive AMACR immunostain. In one Indian study by Kumaresan et al,³¹ they could resolve 49 of the 50 atypical cases (98%), using HMWCK and AMACR. Thus, proving its diagnostic efficacy in small core biopsies especially when the foci in question is <1mm in maximum dimension or due to the many benign mimickers of malignancy.

In our study, AMACR and p63 were found to be very sensitive markers for excluding a malignancy but AMACR showed a lower specificity than p63 (Table 3). We have utilized these two monoclonal antibodies in combination to solve atypical/suspicious foci. IHC was done on the six suspicious cases in literature, the incidence of atypical biopsies ranged from 0.4% to 23% with a mean of 5.5%.³² In our study it was 10%. Of the six suspicious cases, there was a change of diagnosis in two cases from 'Suspicious for malignancy' to 'Adenocarcinoma'. In one case the diagnosis was changed from "AAH" to "Adenocarcinoma". Another case which was 'Suspicious for malignancy', after IHC was labeled as "Atrophic prostate". Similarly BCH and Cribriform type of HGPIN was easily differentiated from adenocarcinoma after the use of AMACR and p63 (Table 4). The reasons for the error in the provisional diagnosis may be either due to limited focus of cancer with very few malignant acini or because of diagnostic errors with benign mimickers of adenocarcinoma.

Conclusion

Hence, we conclude that the spectrum of diseases affecting prostate gland is Prostatitis, Benign lesions like BPH, Premalignant lesions like PIN and AAH, and Prostate carcinoma. Meticulous histopathological examination of all prostate biopsies is necessary in order to identify premalignant lesions and benign mimickers of malignancy. Although histopathology is the gold standard, a combination of immunohistochemical markers of p63 and AMACR is a great adjunct in combating the morphologically suspicious cases to reduce the chance of misdiagnosis.

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Conflict of Interest: None.

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