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BENIGN MIMICKERS OF PROSTATIC CARCINOMA: INCIDENCE, CORRELATION WITH PSA LEVELS AND THE DIAGNOSTIC DILEMMAS

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ABSTRACT

Background: There are several benign proliferations and normal histoanatomical structures of prostate which mimic malignancy and their awareness is essential to avoid diagnostic pitfalls. Establishing, or ruling out, the diagnosis of carcinoma of prostate has been a well-known challenge for pathologists for many years. A**im:** To assess the morphological spectrum of benign mimickers of prostatic carcinoma, their incidence and correlations with serum PSA levels. **Materials and Methods:** This study included a total of 180 cases of prostatic biopsies. All the lesions were graded into non-neoplastic and neoplastic lesions. Cases with foci where malignancy was questioned and which upon expert review the entire case was determined to be benign were included as benign mimickers of prostatic carcinoma. Immunohistochemical (IHC) were used in suspicious and atypical cases for a confirmative diagnosis. The histological features were correlated with serum PSA levels. **Results:** Non-neoplastic lesions were common in this study with 39.4% associated with benign mimickers. 71 cases(39.4%) formed the group benign mimickers of prostatic carcinoma which included basal cell hyperplasia (21.6%), small acinar proliferation (8.89%), atrophy (6.1%), adenosis (3.3%), granulomatous prostatitis (1.67%) and inflammatory atypia (0.6%). IHC was essential in 24 (13.3%) cases for correct diagnosis. Majority of the benign mimickers of prostate had higher PSA levels >4ng/ml (81.6%). Basal cell hyperplasia and Small acinar proliferation had PSA level >10ng/ml. **CONCLUSION:** Basal cell hyperplasia and small acinar proliferation are the most common benign changes causing diagnostic difficulty. Careful examination of H&E sections usually suffices to diagnose these benign mimickers. However in 13.3% of cases IHC was essential for a conclusive diagnosis. Using a panel of immunostains including AMACR, 34βE12 and p63 (positive AMACR immunostaining along with negative basal cell markers) is recommended in the differentiation of prostatic cancer and benign mimickers.

KEYWORDS: *Benign mimickers, Prostatic carcinoma, PSA, Basal cell hyperplasia, Small acinar proliferation.*

INTRODUCTION

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 next to lung cancer and the sixth leading cause of cancer death among men worldwide.[1] There are several benign proliferations and normal histoanatomical structures of prostate which mimic malignancy in histopathology and their awareness is essential to avoid diagnostic pitfalls.[2] Establishing, or ruling out, the diagnosis of carcinoma of prostate has been a well-known challenge for pathologists for many years.

OBJECTIVES

To assess the morphological spectrum of benign mimickers of prostatic carcinoma, their incidence and correlations with serum PSA levels. Histopathological diagnosis was supplemented with histochemistry and immunohistochemistry in suspicious or atypical cases.

Study Design: Analytical and descriptive (Prospective).

Study Sample: A total of 180 cases of prostatic biopsies received in the Histopathology division in the Department of Pathology, Karuna Medical College, Palakkad, Kerala, India during the time period June 2015 to July 2018.

Exclusion Criteria: Prostatectomy done with radical cystectomy was excluded. Also cases with serum PSA assay unavailable.

Study Method: All the lesions were graded into non-neoplastic and neoplastic lesions. Cases with foci where malignancy was questioned and which upon expert review the entire case was determined to be benign were included as benign mimickers of prostatic carcinoma. Special stains like Alcian blue, periodic acid schiff (PAS) and Ziehl Neelson were performed wherever necessary. Immunohistochemical (IHC) study for High molecular weight cytokeratin (HMWCK), p63, leucocyte common antigen(LCA), Alpha-methylacyl-CoA racemase (AMACR) were used in suspicious and atypical cases for a confirmative diagnosis. The histological features were correlated with serum PSA levels.(TABLE1)

Statistical Analysis: Significance of changes between groups **Chi square test / Fisher's exact test** whichever was applicable**.** Relationship between different variables were assessed using Pearson or Spearman correlation coefficient. All tests were two-sided and performed at a significance level of α=.05.The statistical software namely SPSS 20 and Systat 8.0 were used for the analysis of the data.

RESULTS

Non-neoplastic lesions were common in this study with Nodular hyperplasia(83.9%) with 29% associated with prostatitis, 39.4% associated with benign mimickers (graph 1). 71 cases(39.4%) formed the group benign mimickers of prostatic carcinoma which included basal cell hyperplasia (21.6%), small acinar proliferation (8.89%), atrophy (6.1%), adenosis (3.3%), granulomatous prostatitis (1.67%) and inflammatory atypia(0.6%). (Fig 1 – 5)

Histochemistry for mucinous differentiation were analysed. 65.4% cases of ADENOCARCINOMA showed acidic mucin in the lumens as demonstrated by Alcian blue [pH1] and all the cases of LOBUAR ATROPHY showed negativity for Alcian Blue.(Table2)

IHC was essential in 24 (13.3%) cases for correct diagnosis. Majority of the benign mimickers of prostate had higher PSA levels >4ng/ml (81.6%). Basal cell hyperplasia (53.3%) and Small acinar proliferation (23.3%) had PSA level >10ng/ml.(graph 2)

Table 1: Criteria used for PSA value assessment in prostatic diseases.

PSA[ng/ml]	
0-4	Normal
4-10	Mild elevation
>10	Significant elevation

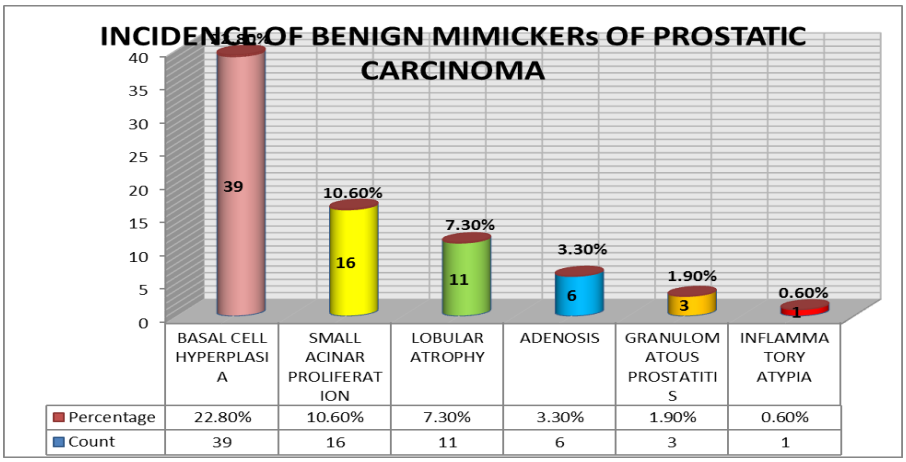
Table 2: Mucinous differentiation of Adenocarcinoma and lobular atrophy with Alcian blue staining.

MUCINOUS DIFFERENTIATION				
Mucinous Pool	H&E-Stain		After Alcian Blue stain	
	No. Of Cases	%	No. Of Cases	%
Adenocarcinoma	9	34.6%	17	65.4%
Lobular atrophy	10	40.1%	0	0

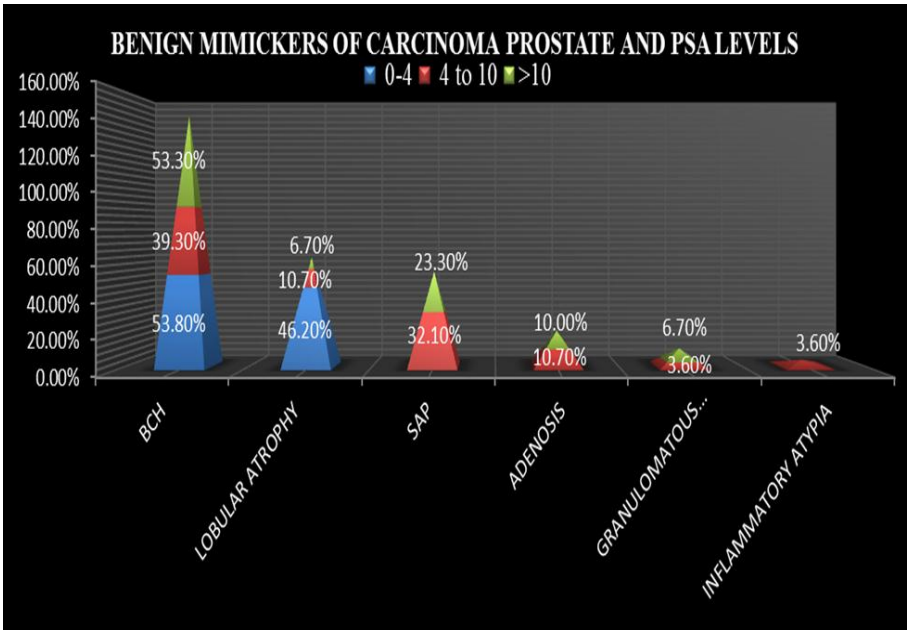
Table 3: Comparative incidence of mimickers of prostatic carcinoma.

S.no	Benign Mimickers of Carcinoma Prostate	Herawi et al [106] (usa)	Monika Garg et al[2]	Mittal et al[24]	Sirishs et al[71]	Poonam Burdak et al[99]	Akhter et al[98]	Present Study
1	Basal cell hyperplasia	2.5	3.9	5.4	27.71	0.1	3.3	22.8
2	Small acinar proliferation	25.7						10.6
3	Atrophy	45.5	0.6	1.63				7.3
4	Adenosis	3.7	1.7	2.16	3	0.1		3.3
5	Granulomatous prostatitis	4.6	3.6	1.62	2	1.3	1.6	1.9
6	Inflammatory atypia	2.5					1.6	0.6

Values are presented as percentage unless otherwise indicated



Graph 1: Incidence of benign mimickers of prostatic carcinoma.



Graph 2: Benign mimickers of carcinoma prostate and serum PSA levels.

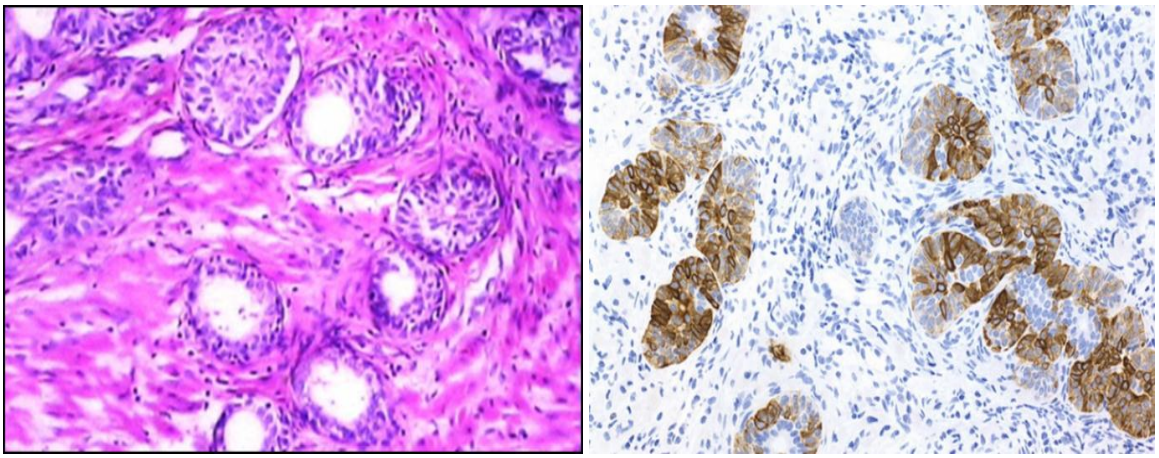


Fig 1: A)Basal cell hyperplasia, showing glands filled with small darkly staining basal cells with peripheral palisading. B)Diffuse strong staining with HMWCK in basal cell hyperplasia (H&E, 100X).

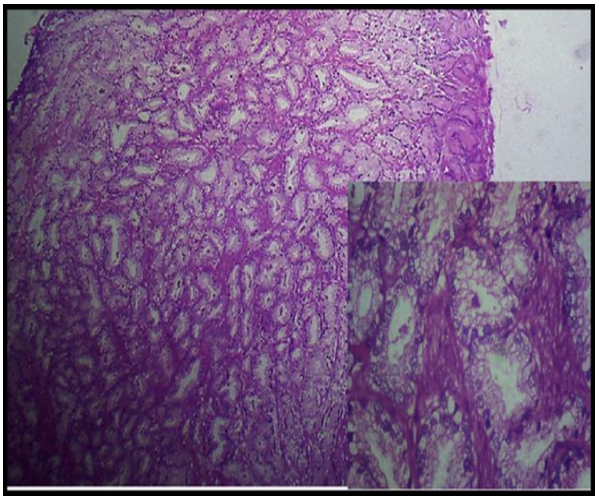


Fig 2: Photomicrography of Adenosis/Atypical adenomatous hyperplasia showing small gland proliferative pattern. High power shows mild anisonucleosis with prominent nucleoli. (H&E 40X, inset 400X)

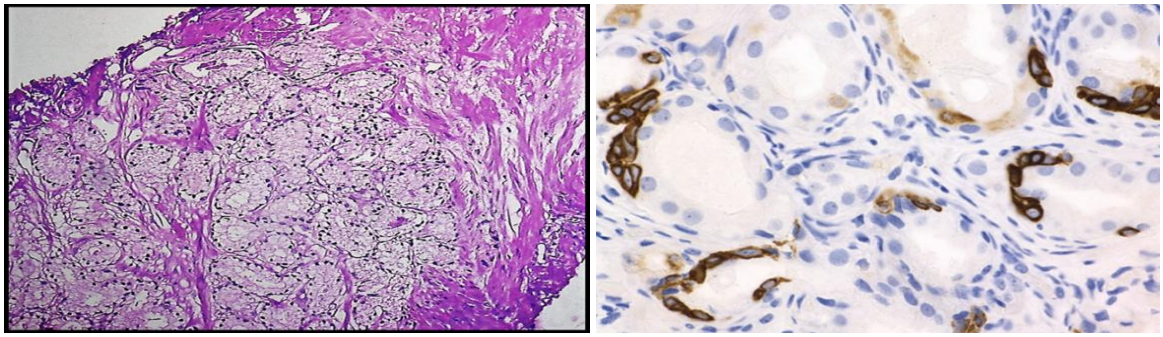


Fig 3: A) Showing closely packed benign glands in a case of Small Acinar Proliferation.(H&E 100X)B) Basal cells usually present at least focally / HMWCK(+)(IHC40)X).

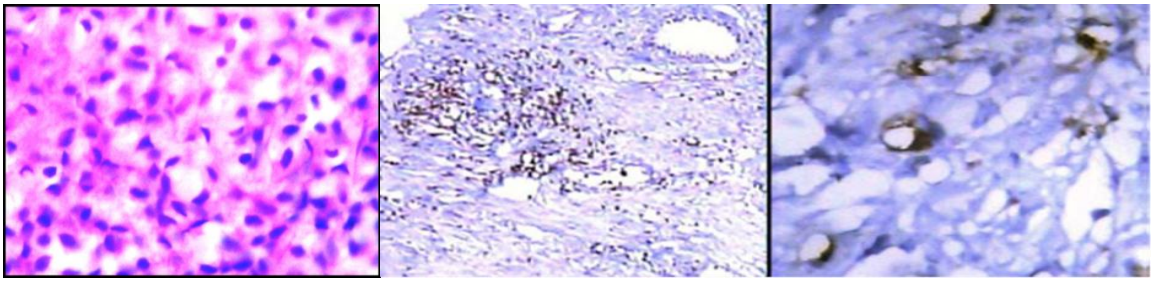


Fig 4: Artefactual change of lymphocytes in the stroma appearing as signet ring cells. Immunohistochemistry of leucocyte common antigen showing membrane positivity.(H&E 100x, 400X).

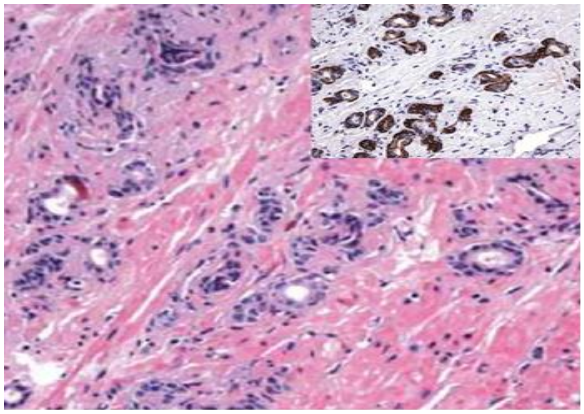


Fig 5: Lobular atrophy –infiltrating pattern. Inset-photomicrography of IHC showing basal cell marker HMWCK poisitivity. (H&E 100X)

DISCUSSION

There are several benign proliferations and normal histoanatomical structures of prostate which mimic malignancy and their awareness is essential to avoid diagnostic pitfalls. Currently, two premalignant lesions have been recognized: prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH), there is a need to determine their significance as there are many important unanswered questions.[3] A pattern-based approach to benign mimickers have been depicted by Srigley J.[4]

• A PATTERN-BASED APPROACH TO BENIGN MIMICKERS[4]

SMALL GLAND PATTERN	LARGE GLAND PATTERN
Seminal vesicle	(Clear cell) cribriform hyperplasia
Cowper's gland	Adenoid cystic-like basal cell hyperplasia
Atrophy	Reactive atypia
Post-atrophic hyperplasia	
Reactive atypia	**FUSED GLAND PATTERN**
Mucinous metaplasia	Paraganglioma
Nephrogenic metaplasia(adenoma)	Xanthogranulomatous inflammation (xanthoma)
Basal cell hyperplasia	Malakoplakia
Benign nodular hyperplasia Sclerosing adenosis	
Verumontanum	
Mucosal gland hyperplasia	**SOLID PATTERN**
Mesonephric gland hyperplasia	Usual prostatitis with crush artifacts
Atypical adenomatous hyperplasia	Idiopathic granulomatous prostatitis
	Signet ring-like change in lymphocytes and stromal cells

Association of BPH with common benign mimickers of prostatic carcinoma like basal cell hyperplasia, atypical adenomatous hyperplasia and atrophy were discussed by authors like Mittal et al.[5], Monika Garg et al[6] and Poonam Burdak et al[7] with an incidence ranging from 0.1 to 9.19[Table 3]. Our study showed a much higher incidence of 39.4%. Incidence of benign mimickers vary with different population. Basal cell hyperplasia is the most common finding in all the studies ranging from 0.1% (Poonam Burdak et al) to 27.7%(Sirish S et al). In our study BCH is the highest incident lesion with 22.8% which is in accordance with above range. Lobular atrophy of prostatic glands mimicking carcinoma occur from 0.6%(Monika Garg et al) to 45.5% (Herawi et al). Our 7.3% is slightly higher than the Indian studies but much lower than the study from USA. Granulomatous prostatitis is the second most common lesion with a range of 1.3%(Poonam Burdak et al) to 4.6%(Herawi et al). Our value of 1.9% is corresponding to above studies. Adenosis/Atypical adenomatous hyperplasia are seen ranging from 0.1%(Poonam Burdak et al) to 3.7%(Herawi et al).Our incidence of 3.3% is within the above range. Small acinar proliferation is reported only in one study by Herawi et al(25.7%). Our finding of 10.6% is less compared to above study.

Inflammatory atypia has been reprted in two other studies in 1.6%(Akhter et al) and 2.5% (Herawi et al). We reported a single case(0.6%) which required IHC to demonstrate the lymphocytes(LCA positive) in the stroma producing artefactual signet ring appearance.

We observed increased PSA in majority of benign mimickers; 4 -10ng/ml in 39.4% and >10ng/ml in 42.2% cases. There is only fleeting reference on this subject in studies like prognostic and predictive factors and reporting of prostate carcinoma in prostate needle biopsy specimens by Amin M et al.[8]

CONCLUSION

Our study shows that currently basal cell hyperplasia, lobular atrophy and small acinar proliferation are the most common benign changes causing diagnostic difficulty. Careful examination of H&E sections usually suffices to diagnose these benign mimickers. However in 13.3% of cases IHC was essential for a conclusive diagnosis. Using a panel of immunostains including AMACR, 34βE12 and p63 (positive AMACR immunostaining along with negative basal cell markers) is recommended in the differentiation of prostatic cancer and benign mimickers. More studies are needed especially in relation to benign mimickers and PSA to avoid false diagnosis of adenocarcinoma prostate.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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