European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 2, Winter 2023

ORIGINAL RESEARCH

Histomorphological Spectrum of Prostatic Lesions and Usefulness of Immunohistochemistry in Differentiating Benign Mimickers from Prostatic Adenocarcinoma

[1]Dr. Prerana Choudhary, [2]Dr. Subhash Chandra Sharma, [3]Dr. Deepika Hemrajani

[1]Assistant Professor, [2]Associate Professor, [3]Professor, Department of Pathology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India

Corresponding author
Dr. Prerana Choudhary
Assistant Professor, Department of Pathology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India
Email: jhajharia.drprerana@gmail.com

Received: 12 January, 2023 Accepted: 27 February, 2023

ABSTRACT

Introduction: Prostatic specimens have a wide histological spectrum of benign and malignant lesions. With benign mimickers of prostatic adenocarcinoma, it can be diagnostically challenging in some cases. The present study was conducted to observe the histomorphological spectrum of prostatic lesions, and to evaluate the usefulness of basal cell specific anti-cytokeratin antibody for HMWCK (34ßE12) immunostaining in differentiating benign mimickers from prostatic adenocarcinoma.

Materials and Methods: Histomorphology of 229 consecutive prostatic specimens received over a period of six months was studied in this retrospective study. Immunohistochemical staining using basal cell specific antibody high molecular weight cytokeratin HMWCK (34ßE12) was done on 33 cases. Prostatic adenocarcinoma cases were graded according to ISUP 2014 Modified Gleason grading system.

Results: Both benign and malignant lesions had a peak incidence in seventh decade of life. Benign lesions accounted for majority of cases (88.21%), of which benign prostatic hyperplasia was the commonest lesion (84.71%). The incidence of prostatic adenocarcinoma was 11.79%. In cases of adenocarcinoma, maximum number of cases were of grade group 5 (40.8%). IHC using HMWCK was useful in 90.9% cases where it either confirmed (81.8%) or changed (9.1%) the diagnosis, thereby improving overall diagnostic efficacy.

Conclusion: Morphological spectrum of prostatic lesions is wide. Histopathology remains the cornerstone of diagnosis in most cases. Immunohistochemistry with basal cell specific marker HMWCK is valuable as an adjuvant to histopathology in diagnostically challenging cases.

Keywords: Benign Prostatic Hyperplasia, Benign Mimickers of Prostatic Adenocarcinoma, Prostatic Adenocarcinoma, Modified Gleason Grading, HMWCK.

INTRODUCTION

Prostatic diseases have a vast spectrum ranging from inflammatory to neoplastic conditions. Benign prostatic hyperplasia (BPH) and prostatic adenocarcinoma (PA) are increasingly frequent with advancing age. While BPH is the most common benign lesion; incidence of

prostate cancer in India is rising over the past few decades[1]. It is currently among the top five leading cancers in Indian males[1] with highest incidence above 65 years of age[2].

Understanding of prostate pathology is increasing over time. Ever expanding list of benign mimickers has broadened the differential diagnosis of PA[3]. Recognition of new entities and subtypes as well as updates in diagnostic criteria in current WHO classification[4] along with advancements in prognosis assessment including grading modifications[5,6] and identification of many molecular aberrations in recent years has impacted the diagnosis and management of PA drastically.

Histomorphological assessment remains the cornerstone in diagnosis of prostatic lesions. However, benign mimickers of prostatic adenocarcinoma, as well as relative paucity of tissue in needle biopsies pose a diagnostic dilemma in some cases. Immunohistochemistry (IHC) as an adjuvant using a cocktail of basal cell specific markers such as high molecular weight cytokeratin 34 beta E12 (HMWCK) or p63 and prostate carcinoma-specific marker alpha-methylacyl coenzyme A (coA) racemase (AMACR) aids in diagnosis of these cases. The combination of AMACR positivity with negative staining for basal cell-associated markers supports a malignant diagnosis[7].

The aim of the present study was to observe the histomorphological spectrum of prostatic lesions, and to evaluate the usefulness of basal cell specific anti-cytokeratin antibody for HMWCK (34ßE12) immunostaining in differentiating benign mimickers from PA.

MATERIALS AND METHODS

This retrospective observational study was conducted at a tertiary care centre in Northern India. A total of two hundred twenty-nine consecutive prostatic specimens including 200 transurethral prostatic resection (TURP) specimens and 29 transrectal ultrasound (TRUS) guided prostatic needle biopsies received over a period of six months were included. Relevant clinical and demographic details were collected in all cases.

Tissue sections stained with hematoxylin and eosin (H&E) were thoroughly examined microscopically and detailed histological findings were recorded. IHC with HMWCK (34ßE12) was done on 33 selected cases. Expression of HMWCK was assessed in terms of cytoplasmic positivity as well as continuity of basal cells.

Cases of prostatic adenocarcinoma were analysed and graded according to ISUP 2014 Modified Gleason grading system[5]. A Gleason score was derived from primary, secondary and tertiary patterns. Depending upon the Gleason score, cases were assigned to grade groups 1-5, following ISUP-2019 consensus conference recommendations[6] and 2016 WHO classification of tumours of urinary system and male genital organs[8].

RESULTS

The present study included a total of 229 prostatic biopsies, comprising 200 TURP specimens and 29 prostatic needle biopsies.

All cases were classified into benign/non-neoplastic and malignant categories based on the morphological assessment. Benign and non-neoplastic lesions constituted the majority and accounted for 202 of the 229 cases (88.21%). The remaining 27 cases (11.79%) were categorised as malignant. Benign prostatic hyperplasia was the most frequent lesion overall and was present in 194 out of 229 cases (84.71%). Detailed spectrum of prostatic lesions in present study and their frequencies are depicted in Table1.

Table 1: Spectrum of Prostatic lesions (n- 229)

Histomorphological Lesion	Number of cases	Percentage
BPH	194	84.71%
With Prostatitis	76	33.18%
Without Prostatitis	118	51.53%

Metaplasia*	48	20.96%
Squamous metaplasia	42	18.34%
Transitional metaplasia	5	2.18%
Oncocytic metaplasia	1	0.44%
Atrophy (Benign prostatic atrophy) *	18	7.86%
Post atrophic hyperplasia	5	2.18%
Cystic atrophy	5	2.18%
Lobular atrophy	6	2.62%
Sclerotic atrophy	2	0.87%
Basal cell hyperplasia*	11	4.80%
Non-specific Granulomatous prostatitis*	10	4.37%
Atypical adenomatous hyperplasia*	8	3.5%
PIN*	14	6.11%
Low grade PIN (LGPIN)	9	3.93%
High grade PIN (HGPIN)	5	2.18%
Prostatic adenocarcinoma	27	11.79%
Miscellaneous*	3	1.31%
Sclerosing adenosis	1	0.44%
Seminal vesicle	1	0.44%
Rectal mucosa	1	0.44%

*****all cases had associated BPH ***Except*** 3 cases of non-specific granulomatous prostatitis, 4 cases of PAH, 6 cases of LGPIN, 4 cases of HGPIN and 1 case of lobular atrophy. BPH: Benign Prostatic Hyperplasia; PIN: Prostatic Intraepithelial Neoplasia.

The age range of benign lesions was 41-90 years with an average age of 64 years while the adenocarcinoma cases were distributed between 52-88 years of age with an average age of 65 years. Among both benign and malignant lesions, maximum number of cases were seen in the seventh decade of life. The age wise distribution of benign and malignant cases is depicted in table 2.

Table 2: Age distribution of patients-

Age in years	Benign n (%)	Malignant n (%)
41-50	25 (12.4%)	0 (0%)
51-60	50 (24.8%)	8 (29.6%)
61-70	77 (38.1%)	14 (51.9%)
71-80	46 (22.7%)	4 (14.8%)
>80	4 (2.0%)	1 (3.7%)
Total	202 (100%)	27 (100%)

Cases of BPH (n=194) were further subcategorised depending upon the relative proportions of glandular and stromal components. Majority of BPH cases were of fibro adenomyomatous type (72.16%), followed by fibroadenomatous type (18.04%), fibro muscular type (8.76%) and fibrous type (1.04%).

Several BPH associated features were also recorded. Prostatitis was the most frequently associated finding with BPH and was observed in 76 out of 194 BPH cases in the form of chronic inflammation (59 cases), acute on chronic inflammation (10 cases) and non-specific granulomatous inflammation (7 cases). Other associated findings included infarction (75 cases), Von Brunn nests (53 cases), squamous metaplasia (42 cases), low grade PIN (3 cases) and high grade PIN (1 case).

Benign prostatic atrophy was observed in 18 cases (7.86%), out of which 13 cases were associated with BPH. Atrophy cases were subcategorised into post atrophic hyperplasia,

cystic atrophy, lobular atrophy and sclerotic atrophy, based on morphology.

Metaplastic changes in the epithelial lining were a common finding (20.96%). Squamous metaplasia was the commonest and was seen in association with infarction in all cases. None of the metaplastic changes were associated with malignancy.

Prostatic intraepithelial neoplasia (PIN) was found in 14 cases (6.11%) including 9 cases of low grade PIN (LGPIN) and 5 cases of high grade PIN (HGPIN). Six of the LGPIN cases (66.6%) and 4 HGPIN cases (80%) were associated with adenocarcinoma.

All malignant lesions in our study were prostatic acinar adenocarcinoma (n=27). Different growth patterns of adenocarcinoma observed were fused glandular pattern in 19 cases (70.37%), sheeting pattern with lack of glands in 15 cases (55.55%), well formed, round to angulated glands in 14 cases (51.85%) and cribriform pattern in 5 cases (18.51%). One case showed presence of comedonecrosis (3.7%) while perineural invasion was seen in 11 cases (40.8%).

Adenocarcinoma cases were graded according to ISUP 2014 modified Gleason grading system. Most frequent Gleason grade was grade 4 for both primary (37%) and secondary pattern (51.85%). Grade groups 1-5 were assigned based on Gleason scores derived from primary, secondary and tertiary patterns, as per ISUP-2019 consensus conference recommendations and 2016 WHO classification. Maximum number of cases (40.8%) were categorised as grade group 5. Detailed Gleason scores and grade groups are given in Table 3.

Table 3: Grade groups according to WHO classification of tumors of the urinary system and male genital organs, 2016-

Grade Group	Gleason Score	Number of Cases
1	3+3	3 (11.1%)
2	3+4	5 (18.5%)
3	4+3	2 (7.4%)
4		6 (22.2%)
	4+4	5
	5+3	1
5		11 (40.8%)
	4+5	3
	5+4	4
	5+5	4
Total		27

Benign mimickers of PA were recognised in 70 cases (30.56 %). These included basal cell hyperplasia (11 cases), cribriform pattern of BPH and non-specific granulomatous prostatitis (10 cases each), atypical adenomatous hyperplasia (8 cases), lobular atrophy (6 cases), post atrophic hyperplasia, cystic atrophy and transitional metaplasia (5 cases each), small glandular pattern of BPH (4 cases), sclerotic atrophy (2 cases), sclerosis adenosis, oncocytic metaplasia, seminal vesicle and rectal mucosa (1 case each) in decreasing order of frequency. All benign mimickers had associated BPH and were present as small foci among benign glands, *except* 4 cases of post atrophic hyperplasia, and one cases of lobular atrophy. Incidence of benign mimickers of PA is given in Table 4.

Table 4: Incidence of Benign Mimickers of Prostatic Adenocarcinoma (n- 229)

Lesion	Number of cases	Percentage
Basal cell hyperplasia	11	4.80 %
Cribriform pattern of BPH	10	4.37 %
Non-specific granulomatous prostatitis	10	4.37 %
Atypical adenomatous hyperplasia	8	3.5 %
Lobular atrophy	6	2.62 %
Post atrophic hyperplasia	5	2.18 %

Cystic atrophy	5	2.18 %
Transitional metaplasia	5	2.18 %
Small glandular pattern of BPH	4	1.75 %
Sclerotic atrophy	2	0.87 %
Sclerosing adenosis	1	0.44 %
Oncocytic metaplasia	1	0.44 %
Seminal vesicle	1	0.44 %
Rectal mucosa	1	0.44 %
Total	**70**	**30.56 %%**

Immunohistochemistry was done only when a definitive diagnosis couldn't be reached on the basis of morphology alone. Total 33 cases were selected for IHC with HMWCK antibody. Twenty seven of these 33 cases were benign mimickers of PA, while one case each was of HGPIN and poorly differentiated urothelial carcinoma. Two cases each of BPH and PA were included as positive and negative controls respectively. In the case of urothelial carcinoma, a panel of HMWCK and PSA was used. IHC confirmed the histomorphological diagnosis in 27 (81.8%) of these cases. In 5 of the remaining six cases where IHC results were discordant/inconclusive, specimen was prostatic needle biopsy. In 3 of these cases (9.1%) the diagnosis was changed. These included 2 cases of basal cell hyperplasia and one case of urothelial carcinoma, which were reported as BPH and prostatic adenocarcinoma respectively following IHC. The results of IHC were inconclusive in 3 cases due to loss of representative tissue at the level of immunostaining. Results of IHC are summarised in Table 5.

Table 5: Summary of IHC results

Histopathological diagnosis	**No. of cases**	**IHC results**	
		Concordant	**Discordant / Inconclusive**
Basal cell hyperplasia	13	10	3; 2 BPH, 1 inconclusive
Atypical adenomatous hyperplasia	6	4	2 inconclusive
Post atrophic hyperplasia	2	2	
Small glandular pattern of BPH	4	4	
Transitional metaplasia	2	2	
BPH	2	2	
HGPIN	1	1	
Prostatic adenocarcinoma	2	2	
Urothelial carcinoma	1	0	1 Prostatic adenocarcinoma
Total	33	27	6

Figure 1: Benign prostatic hyperplasia: A- Mixed glandular and stromal proliferation (H&E, 10X);
B- Benign prostatic glands- showing continuous lining of basal cells (HMWCK Immunostaining, 10X)

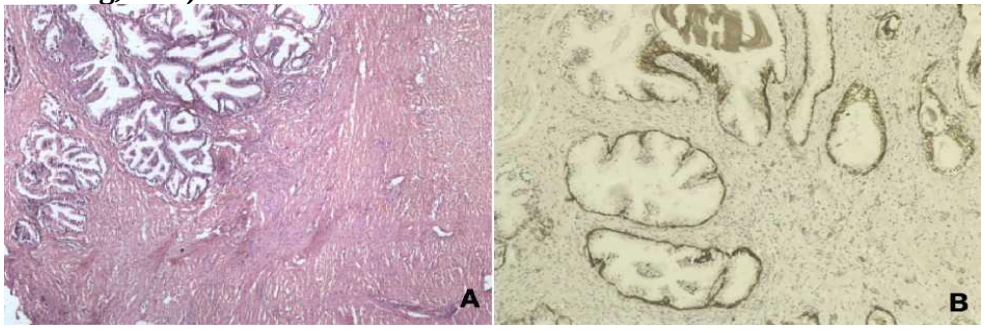


Figure 2: Benign mimickers of prostatic adenocarcinoma: A- Seminal vesicle showing enlarged, hyperchromatic nuclei with degenerative atypia (H&E, 40X); B- Small glandular pattern of BPH (H&E, 10X); B- Cribriform pattern of BPH (H&E, 10X); D,E,F- Atypical adenomatous hyperplasia, D- Well circumscribed proliferation of small to medium sized glands (H&E, 4X), E- Back to back glands with bland cytological features (H&E, 10X), F- HMWCK shows a discontinuous basal cell layer (HMWCK, 40X); G- Basal cell hyperplasia, showing 2-3 cell thick layer of proliferating basal cells (H&E, 10X), H- Incomplete basal cell hyperplasia with preservation of secretory cell layer (H&E, 40X), I- HMWCK highlighting increased thickness of basal cell layer (HMWCK, 40X). BPH- benign prostatic hyperplasia, HMWCK- high molecular weight cytokeratin.

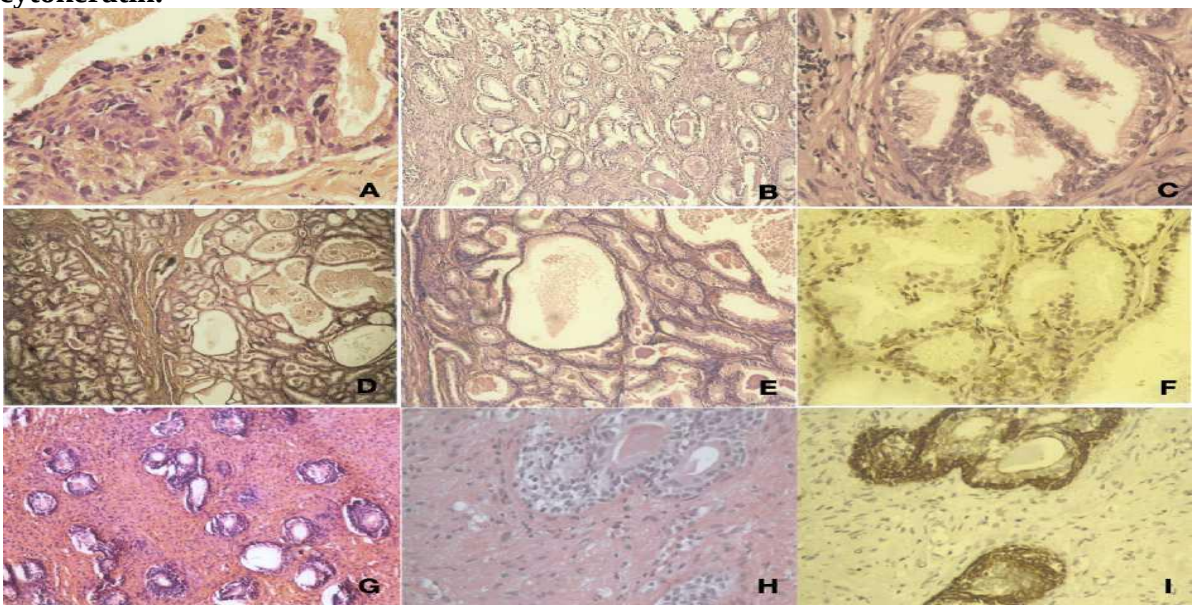
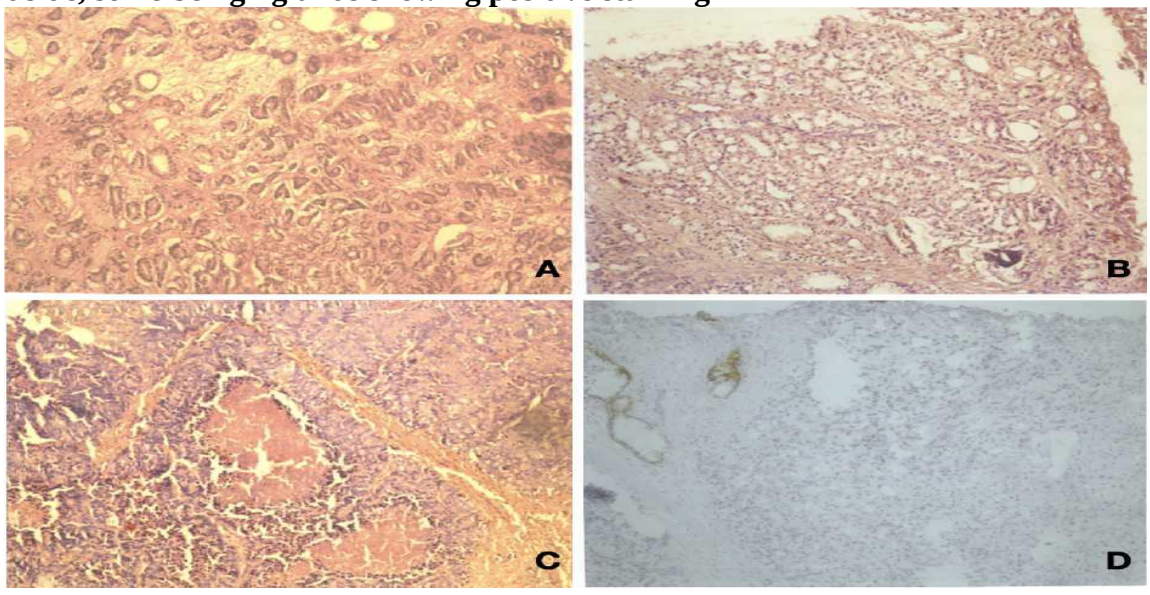


Figure 3: Prostatic acinar adenocarcinoma A: Gleason grade 3- Round to angulated glands; B: Gleason grade 4- Fused glands; C- Gleason grade 5- Comedonecrosis (H&E, 10X) ; D: Complete absence of HMWCK positive basal cells in adenocarcinoma. On the left side, some benign glands showing positive staining



DISCUSSION

Prostatic specimens have a wide histological spectrum of benign and malignant lesions, thus contributing significantly to histopathology workload. With benign mimickers of prostatic adenocarcinoma, it can be diagnostically challenging in some cases. This study was undertaken to observe the histopathological spectrum of prostatic lesions at our centre and to evaluate the usefulness of a basal cell marker HMWCK in differentiating benign mimickers from prostatic adenocarcinoma.

The present study included a total of 229 prostatic biopsies. The age of patients ranged from 41-90 years with an average age of 64 years in benign lesions and 65 years in malignant lesions. Both benign and malignant lesions were most frequent in seventh decade of life. These findings correlated well with studies by Farooq et al[9], Sharma et al[10], George and Thomas[11] while Garg et al[12] reported the highest incidence in 8th decade.

Benign lesions were more common in our study accounting for 88.21% cases. BPH was the most frequent lesion overall and was present in 84.71% cases. Prostatitis was seen in association with BPH in 33.16% cases and majority of these cases (77.6%) had chronic prostatitis. Other common associated lesions were basal cell hyperplasia (4.8%), non-specific granulomatous prostatitis (4.37%), and atypical adenomatous hyperplasia (3.5%) among others. These findings agree with other Indian studies[9,10,12].

Prostatic intraepithelial neoplasia was found in 6.11% cases including 3.93% cases with low grade PIN and 2.18% cases with high grade PIN. Similar prevalence of PIN has been reported in earlier studies[10,13,14]. High grade PIN is considered a precursor of adenocarcinoma and has shown high incidence of development of adenocarcinoma in long term follow up studies[14]. In the present study, 80% of HGPIN cases were associated with adenocarcinoma, which was in agreement with previous studies by Gaudin EB et al[13] and Sharma et al[10]. Higher prevalence of adenocarcinoma in association with HGPIN warrants a thorough examination of tissue sections and a close follow-up.

Prostatic adenocarcinoma constituted 11.79% of cases in the present study. Prevalence of PA was 12.44% in 433 cases in study by Farooq et al[9], while George and Thomas[11] reported a prevalence of 10.9% in 1163 prostatic biopsies.

Adenocarcinoma cases were graded according to ISUP 2014 modified Gleason grading system[5]. Most frequent Gleason grade was grade 4 for both primary (37%) and secondary pattern (51.85%). The commonest Gleason scores were score 9 and score 7 (25.9% each). Grade group 5 was the most common grade group (40.8%). Shah MB et al[15] made similar observations while Farooq et al[9] found Gleason score 7 (4+3) and grade group 3 to be the most common group. Garg et al[12] reported 51.5% cases intermediate grade with a Gleason score of 7-8.

Perineural invasion (PNI), defined as circumferential encirclement of nerves by malignant glands, is suggested to be associated with cancer aggressiveness and lethal prostate cancer[15]. PNI is more commonly seen in association with higher Gleason grade tumours and in slightly older age[15]. In our study, perineural invasion was seen in 11 cases (40.8%), out of which 8 cases were of Gleason grade 4 and above. Garg et al[12] and Zareba et al[16] have reported similar prevalence of PNI in PA cases.

The microscopic appearance of prostatic adenocarcinoma is mimicked by astounding number of lesions, all of which are benign in nature. Most mimics are readily recognisable on TURP and radical prostatectomy specimens but can be especially troublesome when limited tissue is available for evaluation as in needle biopsies[17,18]. These mimickers range from normal structures like seminal vesicle and rectal mucosa to atrophy and hyperplasias. Most of these lesions, such as atypical adenomatous hyperplasia, basal cell hyperplasia and seminal vesicle, have small glandular pattern and are included in the differential diagnosis of low grade PA. Inflammatory lesions such as granulomatous prostatitis and xanthogranulomatous prostatitis

may even simulate high grade PA[17,18]. Awareness to these patterns and a systematic approach on routine microscopy along with judicious use of ancillary tests such as immunohistochemistry prevents a false diagnosis of PA.

Benign mimickers of PA were recognised in 30.56% cases in our study and were present as small foci among benign glands in most cases. The commonest mimicker was basal cell hyperplasia (4.80%) followed closely by cribriform pattern of BPH, non-specific granulomatous prostatitis (4.37% each) and atypical adenomatous hyperplasia (3.5%). Similar findings were reported by Garg et al[12] and Nanda et al[19].

Immunohistochemistry using such as basal cell specific markers HMWCK (34ßE12) or p63 and positive markers such as prostate cancer specific AMACR is being increasingly used to differentiate benign mimickers from prostatic adenocarcinoma[20,21,22]. The loss of basal cells is considered a diagnostic hallmark of PA[20]. Absence of basal cell staining by IHC in a morphologically suspicious lesion with simultaneous positivity staining in adjacent benign glands strongly supports the diagnosis of malignancy.

In the present study, IHC with HMWCK (34ßE12) was done in 33 cases. IHC results were concordant with histomorphology in 81.8% of cases. Cases (9.1%) where IHC results were discordant included 2 cases of basal cell hyperplasia and one case of urothelial carcinoma, where diagnosis was changed to BPH and prostatic adenocarcinoma respectively. In the remaining 9.1% cases IHC was inconclusive due to loss of representative tissue during processing. HMWCK was useful in 90.9% cases where it either confirmed (81.8%) or changed (9.1%) the diagnosis, thereby improving overall diagnostic efficacy. In 2 of the three cases where IHC results were discordant, the prostatic specimens were needle biopsies. This further emphasised the utility of IHC to aid in the diagnosis of challenging cases where paucity of tissue can be a limiting factor.

A positive HMWCK staining excludes malignancy, however a negative staining requires caution in interpretation[7,20]. A combination of AMACR with HMWCK/p63 overcomes the pitfall of using a basal cell marker alone. The limitation of our study was the use of only a basal cell specific marker for IHC.

CONCLUSION

Prostatic specimens have a wide histological spectrum of benign and malignant lesions, ranging from non-neoplastic prostatitis to high grade PA. Accurate identification, and differentiation of benign mimickers and premalignant lesions from PA is of prime importance in determining treatment outcome. Histomorphology alone achieves the diagnosis in majority of the cases. However, factors such as paucity of tissue in prostatic needle biopsies, benign mimickers of PA and atypical small acinar proliferations among benign glands can make diagnosis challenging in some cases. We infer that IHC with basal cell specific marker HMWCK improves objectivity in diagnosis and is a valuable adjuvant to histopathology in such cases.

REFERENCES

1. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Global Oncology. 2020 Sep;6(6):1063–75.
2. ICMR-NCDIR, Clinicopathological Profile of Cancers in India: A Report of the Hospital Based Cancer Registries, 2021, Bengaluru, India
3. Goldblum JR, Lamps LW, Mckenney JK, Myers JL, Rosai J. Rosai and Ackerman's surgical pathology. Philadelphia, Pa: Elsevier; 2018.
4. Kench JG, Amin MB, Berney DM, Compérat EM, Cree IA, Gill AJ, et al. WHO Classification of Tumours fifth edition: evolving issues in the classification, diagnosis,

and prognostication of prostate cancer. Histopathology. 2022 Aug 2;

5. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. The American Journal of Surgical Pathology. 2015 Oct;40(2):1.
6. van Leenders GJLH, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. American Journal of Surgical Pathology. 2020 May 26;44(8):e87–99.
7. Paner GP, Luthringer DJ, Amin MB. Best Practice in Diagnostic Immunohistochemistry: Prostate Carcinoma and Its Mimics in Needle Core Biopsies. Archives of Pathology & Laboratory Medicine. 2008 Sep 1;132(9):1388–96.
8. Moch H, Humphrey PA, Ulbright TM, Reuter VE, eds. WHO Classification of Tumours of the Urinary System and Male Genital Organs, 4th ed. Lyon, France: IARC; 2016.
9. Farooq S, Bilal S, Khaliq BI, Sidieq F, Aslam H, Shah I. The Spectrum of Histopathological Patterns Observed in Prostate Specimens in a Tertiary Care Hospital in Kashmir. International Journal of Contemporary Medical Research [IJCMR]. 2019 Apr;6(4).
10. Sharma A, Sharma M, Gandhi S, Khajuria A, Goswami KC. Histomorphological spectrum of prostatic lesions: a retrospective analysis of transurethral resection of prostate specimens. International Journal of Research in Medical Sciences. 2017 May 27;5(6):2373.
11. George E, Thomas S. A histopathologic survey of prostate disease in the sultanate of Oman. Internet J Pathol. 2005;3(2).
12. Garg M, Kaur G, Malhotra V, Garg R. Histopathological spectrum of 364 prostatic specimens including immunohistochemistry with special reference to grey zone lesions. Prostate International. 2013 Dec;1(4):146–51.
13. Gaudin PB, Sesterhenn IA, Wojno KJ, Mostofi FK, Epstein JI. Incidence and clinical significance of high-grade prostatic intraepithelial neoplasia in turp specimens. Urology. 1997 Apr;49(4):558–63.
14. Pacelli A, Bostwick DG. Clinical significance of high-grade prostatic intraepithelial neoplasia in transurethral resection specimens. Urology. 1997 Sep;50(3):355–9.
15. Shah MB, Raju K, Kumar G H. Revisiting Prostate Biopsy with 2014 ISUP Modified Gleason Score and Gleason Grade – A Cross Section Study. Biomedical Research and Therapy. 2018 Dec 27;5(12):2918–25.
16. Zareba P, Flavin R, Isikbay M, Rider JR, Gerke TA, Finn S, et al. Perineural invasion and risk of lethal prostate cancer. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology [Internet]. 2017 May 1;26(5):719–26. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5413395/
17. Srigley JR. Benign mimickers of prostatic adenocarcinoma. Modern Pathology [Internet]. 2004 Mar 1;17(3):328–48. Available from: https://www.nature.com/articles/3800055
18. Trpkov K. Benign mimics of prostatic adenocarcinoma. Modern Pathology [Internet]. 2018 Jan [cited 2021 Aug 25];31(S1):22–46. Available from: https://www.nature.com/articles/modpathol2017136.pdf
19. Nanda A, Mahapatra Q, Mohanty P, Mohanty L. Histomorphological study of prostatic adenocarcinoma and its mimics. Indian Journal of Pathology and Microbiology. 2019;62(2):251.
20. Wojno KJ, Epstein JI. The Utility of Basal Cell—Specific Anti-Cytokeratin Antibody (34βE12) in the Diagnosis of Prostate Cancer. The American Journal of Surgical

Pathology. 1995 Mar;19(3):251–60.
21. Alampally S, Khadija Fatima S, G A. Histopathological spectrum of prostatic lesions and utility of p63 and Alpha-methylacyl-Co A racemase immunohistochemical markers in resolving suspicious cases. Indian Journal of Pathology and Oncology. 2019 Jun 15;6(2):275–83.
22. Hasan IA, Gaidan H, Al-kaabi M. Diagnostic Value of Cytokeratin 34 beta E12 (Ck34βE12) and α-Methylacyl-CoA racemase (AMACR) Immunohistochemical Expression in Prostatic Lesions. Iranian Journal of Pathology. 2020 May 1;15(3):232–8.