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HISTOPATHOLOGICAL ANALYSIS OF PROSTATE CANCER GROWTH PATTERNS AND ROLE OF IMMUNOHISTOCHEMISTRY IN GRADING AND IDENTIFYING RARE HISTOLOGICAL VARIANTS

Histopathology

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ABSTRACT

Background- Prostate cancer comprises a heterogenous group of tumors having a range of clinical outcomes. Histopathological examination is the gold standard for accurately assessing them, but nevertheless sometimes diagnosing can be challenging particularly when rare variants are encountered. In such scenarios immunohistochemistry plays an immense aid in exact categorisation of the lesions. **Aim-** This study aims to understand the histological patterns of prostate carcinoma and the value that immunohistochemistry adds in establishing a diagnosis and grading, with special emphasis on rare variants. **Setting And Design-** Department of Pathology. Prospective observational study. **Material And Methods-** An institutional based prospective observational study was conducted on 31 TURP chippings positive for prostate cancer for a period of 1 year (June 2023-May 2024). Gleason score was assigned and relevant immunohistochemistry panel was used. Sensitivity and specificity of AMACR was calculated. The expression of serum PSA was correlated with ki-67 expression. **Statistical Analysis-** Data was gathered and entered in Microsoft excel spreadsheet, tabulated, and calculated using suitable software. **Results-** the most common age of presentation was in the 7th decade. Mean PSA level was 20.2129±4.997 ng/ml in the 31 primary prostate cancer cases. Prostatic acinar adenocarcinoma accounted for 92.322% cases and the others comprised primary urothelial carcinoma, sarcomatoid carcinoma and primary prostate lymphoma. Gleason score 7 emerged as the most common score. AMACR sensitivity and specificity was 92.86% and 100% respectively. Majority (90.32%) of the cases showed positive expression of ki67. The association between increased serum PSA value and Ki-67 index was not statistically significant. **Conclusion-** As an adjunct to histopathology, the judicious use of immunomarkers adds a diagnostic value and helps alleviate diagnostic challenges.

KEYWORDS

Gleason score, Immunohistochemistry, Prostate cancer, Rare variants

INTRODUCTION

Prostate cancer comprises a heterogeneous group of aggressive and non-aggressive tumors, having a range of clinical outcomes.[1] Despite having subpar sensitivity and specificity, elevated serum prostate specific antigen is utilized for early cancer screening. One of the best prognostic and predictive variables for prostate cancer is the Gleason scoring system.[2] Histopathological examination is the gold standard for identifying prostate lesions.[3] Nevertheless, the interpretation of biopsy specimens can be difficult, as morphological mimickers, subtle histological abnormalities and rare variants might result in an underdiagnosis or an incorrect diagnosis.[4] Addition of immunomarkers offers more details regarding positive cores, as well as help overcome diagnostic dilemmas.[5]

MATERIAL AND METHODS

Study Population:

An institutional based prospective observational study was conducted for a period of 1 year from June 2023 to May 2024. Following approval from the Ethics Committee, and mandatorily taking informed consent from the patients, the study was conducted on TURP (Transurethral Resection of Prostate) chippings, fulfilling the inclusion and exclusion criteria, that were received in the Department of Pathology. Radical prostatectomy specimens were excluded from the study as number of cases were less.

Procedure:

Relevant history and investigations, including serum PSA level, were taken as per the data collection form. The specimens were fixed in 10% NBF (neutral buffered formalin), and was processed. Slides were stained with haematoxylin and eosin (H&E) stain, and immunohistochemical stains. Following this, thorough histopathological evaluation was done, and a diagnosis was made after reviewing by two senior pathologists.

Immunohistochemical Analysis:

Immunohistochemical staining with AMACR, p63, HMWCK, Ki-67 (BioGenex) and other relevant markers was done. Non-streptavidin-biotin proprietary micropolymer-complex technology was used. Cytoplasmic or luminal, granular or diffuse staining was considered positive for AMACR. Cytoplasmic staining was considered positive for HMWCK. Nuclear staining was considered positive for p63. Granular nuclear staining was interpreted as positive for ki-67.

Statistical Analysis:

The data were collected and entered in Microsoft Excel spreadsheet and tabulated. Charts and tables were prepared according to the variables considered related to the objective. Percentages, rates, confidence interval, mean, standard deviation, etc. were obtained using SPSS IBM version 21. Chi square test was used to compare the categorical variables. The level of significance was set at .05 for all the tests.

RESULTS

Out of the total 204 TURP specimens, 169 were diagnosed as BPH. Of the remaining 35 cases, 4 were metastatic carcinoma and 31 were primary prostate cancer. This study focussed on the 31 primary malignant cases of prostate. A positive family history was seen in 3 patients.

The most common age of presentation was in the 7th decade (51.613%), with an age range from 55 to 85 years, the mean age being 71.7097±2.565 years [Chart 1]. Retention of urine was the most common complaint. 20.2129±4.997 ng/ml was the mean serum PSA. The lowest PSA value was 2.5ng/ml and highest was 63ng/ml.

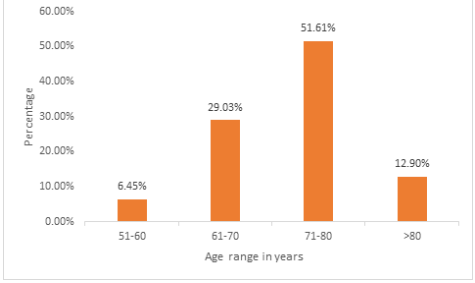

Chart 1: Age distribution of all cases

The most common malignant lesion encountered was prostate acinar adenocarcinoma (around 90%). Rare variants including primary

urothelial carcinoma, sarcomatoid carcinoma and primary prostate DLBCL comprised the remaining malignant lesions [Chart 2].

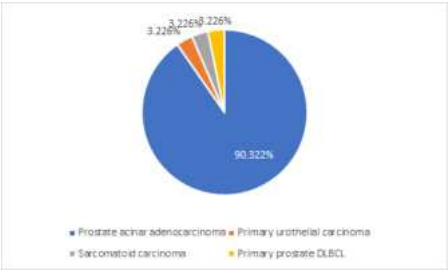

Chart 2: Distribution of all lesions

The prostate acinar adenocarcinoma cases were assigned a gleason score based on the predominant pattern and corresponding grade [Table 1].

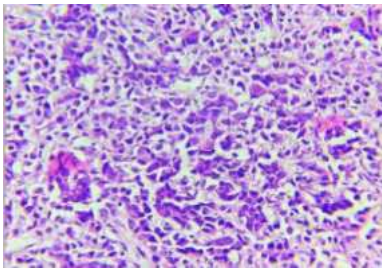

Figure 1: Prostate acinar adenocarcinoma [X400]

Table 1: Distribution Of Gleason Score And Grade Of All Lesions

Gleason Score		Gleason Grade	Frequency	Percentage
6	3+3	1	3	10.714%
7	3+4	2	6	21.429%
	4+3	3	4	14.286%
8	4+4	4	3	10.714%
	3+5		3	10.714%
	5+3		2	7.143%
9	4+5	5	4	14.286%
	5+4		3	10.714%
10	5+5		0	0%
Total			**28**	**100%**

The most common pattern was gleason 3+4 (21.429%) and, 7 (35.715%) was the most common score. Immunohistochemical staining with AMACR, HMWCK and p63 was done to exclude any dilemma and increase the diagnostic accuracy. The most common pattern comprised of fused glands [Chart 3].

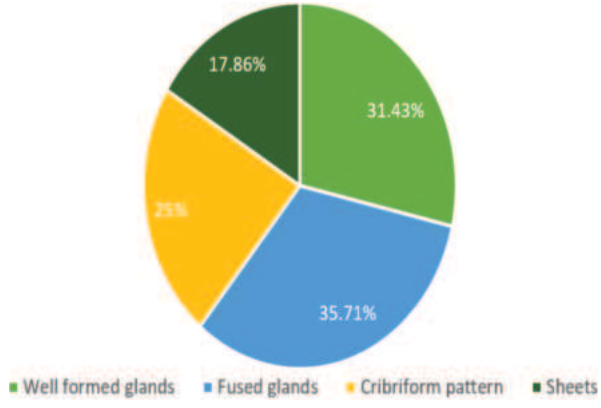

Chart 3: Distribution of lesions based on predominant pattern

There was a discrepancy between designated BPH with HGPIN and well differentiated carcinoma in 6 cases. IHC was done, and well differentiated carcinoma was confirmed in 4 cases.

IHC showed 1+ AMACR positivity, HMWCK and p63 were negative, confirming it to be carcinoma.

AMACR expression was positive in 26 of 28 (92.86%), and negative in 2 of 28 (7.14%) prostate acinar adenocarcinoma cases [Table 2]. Majority (53.571%) showed 3+ positivity. The sensitivity of AMACR was 92.86%, with a 100% specificity. HMWCK and p63 expression was lost in all the malignant lesions.

Table 2: AMACR expression with respect to gleason grade

Gleason	AMACR Expression (%)				Total
Grade	0 (0%)	1+ (1-10%)	2+ (11-50%)	3+ (>51%)	
1	1	1	1	0	3
2	0	1	2	3	6
3	0	0	1	3	4
4	1	0	3	4	8
5	0	0	2	5	7
Total	2	2	9	15	**28**
Percentage	7.143%	7.143%	32.143%	53.571%	**100%**

Ki-67 immunolabelling was done to study the aggressiveness of the lesions. Majority (90.32%) cases showed positive expression. In majority of the cases (11) a moderate (2+) expression was noted, followed by 3+, 1+ and 0. Seven cases on routine H&E stain showed a low mitotic count, and subsequently after Ki-67 immunolabelling, 3 cases showed weak, and 4 cases showed moderate expression. The expression was correlated with serum PSA [Table 3]. In this study, we found no significant association between increased serum PSA value and Ki-67 index. It was not statistically significant (p-value- .75591) at p-value <.05.

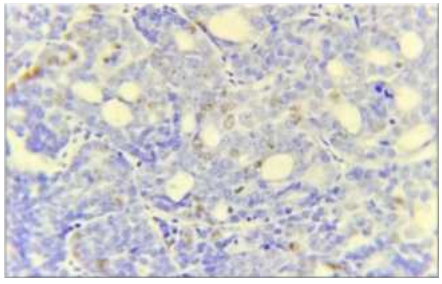

Figure 2: Prostate acinar adenocarcinoma showing Ki67 positivity

Table 3: Expression of ki-67 with respect to serum PSA

PSA (ng/ml)	Ki-67 Expression				
	0 (<3%)	1+ (3-25%)	2+ (26-50%)	3+ (>50%)	Percentage of positive expression
1-10	2	3	1	2	21.43%
11-20	1	3	4	2	32.14%
21-30	0	1	4	3	28.57%
>30	0	1	2	2	17.86%
Total	**3**	**8**	**11**	**9**	**100%**

We encountered 3 rare cases. They comprised sarcomatoid carcinoma, primary urothelial carcinoma and DLBCL. Relevant immunohistochemical panel was used to confirm these cases. Sarcomatoid carcinoma was positive for vimentin, AE3, PSA and negative for desmin and p63. Primary urothelial carcinoma was showed CK7, p63, GATA3 positivity and was negative for PSA. Primary prostate DLBCL displayed CD20, BCL2, BCL6 positivity, and was CD3, CD10 negative.

DISCUSSION

Prostate cancer ranks fourth globally. It is the eighth leading cause of cancer related death worldwide. They are most commonly diagnosed in men older than 50 years. Acinar adenocarcinoma accounts for approximately 95% of cases. Established risk factors include advancing age, family history, genetics and race (higher in black men). In our study 3 patients had a positive family history. The diagnosis is established by histopathological evaluation of prostate samples.[6]

In the present study, most patients presented in the 7th decade, with an age range of 55 to 85 years, the mean age being 71.7097±2.565 years. The age range was similar to the study done by Kumari K et al[7], with their age range being 50-85 years. Most patients presented in the 7th decade, which is comparable [Table 4] to the study done by Kumari K et al,[7] whereas Deshmukh BD et al[8] found maximum cases in the 8th decade. A Petterson et al[9] found a similar mean age of 71 years. Retention of urine was the most common complain, similar to the study published by Gangwar S et al.[10]

Table 4: Comparison Of Mean Age With Other Studies

Study	A Petterson et al[9]	Kumari K et al[7]	Mahadev KS et al[11]	Rathod SG et al[12]	A Josepine [13]	Present study
Mean age in years	71	68.3	66.6	65	68.8	71.709

Table 5: Comparison Of Gleason Score With Other Studies

	Ranjitham, Bheemarao[3]	Popescu T et al[2]	Azad S, Bahal N, et al[17]	Deshmukh B et al [8]	Rathod S et al[12]	Present study
Most common gleason score	7	6	9	9	7	7
Gleason score breakup	3(3+4), 2(4+3)	(3+3)			(4+3)	6(3+4), 6(4+3)
Percentage	5 (45.45%)	109 (33.1 %)	11 (45.8%)	6 (33.34 %)	19 (47.5%)	10 (35.715 %)

Prostate specific antigen (PSA) is expressed by normal, non-neoplastic and neoplastic prostatic tissue. It is a glycoprotein, and its half-life is 2.2 days [14]. when the integrity of the cell is damaged, it causes a rise in PSA.[15] The mean serum PSA in the present study was 20.2129±4.997 ng/ml, almost comparable to the study by Antony T et al[14] who found it to be 17.6 ng/ml. The studies by Ngwu PE et al[16] and Kumari K et al[7] found a higher value of 52.3±37.5 ng/ml and 101.2 ng/ml respectively.

Tumor aggressiveness has been identified by the Gleason score, which is determined by the morphology of the main tumor pattern plus secondary tumor pattern.[1] The most common gleason score was 7 in our study, comparable to other studies as shown in Table 5.

Alpha methyacyl CoA racemase (AMACR) is an enzyme, which plays a role in oxidation of bile acid intermediates and branched chain fatty acids. Its expression is increased in prostate cancer, hence is utilized as a positive immunomarker[18]. Our study showed a significant expression of AMACR, with a sensitivity of 92.86%, and 100% specificity. It was concurrent to studies conducted by Rathod S et al[12], with 90% sensitivity and 100% specificity. While studies by Singh V et al[18] concluded AMACR sensitivity and specificity to be 95% and 92.5% respectively.

High molecular weight cytokeratin (HMWCK) and p63 is expressed by basal cells. Their expression is lost in prostate cancer[12]. HMWCK and p63 showed negative staining in all malignant cases of prostate adenocarcinoma, in our study. Studies by Rathod S et al[12] and Shah et al,[19] also observed 100% negative staining of HMWCK. Similar results were observed by Rajhitham et al,[3] Signoretti et al,[20] Rathod S et al,[12] who found p63 negativity in 100%, 97% and 100% cases respectively.

We found no significant association between increased serum PSA value and Ki-67 index, in this study. Our finding corroborated with findings by Gangwar S et al,[10] Murti K et al[15] and Sulik M et al.[21] Whereas, Mahadev KS et al[11] found a significant increase in expression of Ki-67 with increase in PSA.

The patient with sarcomatoid carcinoma was 73-years old and presented with urinary hesitancy. Serum PSA was 4.8ng/ml. On H&E, there was a dilemma between sarcomatoid carcinoma and poorly differentiated carcinoma. An immunohistochemical panel aided in the diagnosis. The malignant mesenchymal component comprised majority of the lesion, and it was admixed with a minor malignant epithelial component.

Sarcomatoid carcinoma is a clinically aggressive tumor. It is biphasic and presents at a higher stage. Prognosis is poor. Usually occurs at an advanced age. In most patients the serum PSA is normal, causing a delayed diagnosis.[22] On microscopy, there is an admixture of carcinomatous and sarcomatoid components as per study by Zizi-Sermpetzoglou et al.[23] Immunohistochemistry shows vimentin and AE3 positivity with a negative PSA staining of the sarcomatoid component.

One case of primary urothelial carcinoma was encountered. It was initially thought to be metastasis from the urinary bladder. The patient was a 66-year-old, with PSA of 3.9 ng/ml. Cystoscopy was done to rule it out. The bladder was found to be normal on imaging. Immunohistochemical panel further validated the diagnosis of urothelial carcinoma. Primary urothelial carcinoma of prostate is a rare entity. Histopathological evaluation combined with immunohistochemistry is required for the diagnosis. Immunohistochemically, it shows CK7 and CK20 positivity, as per studies conducted by Zhou J et al.[24] It is associated with a poor prognosis.[25]

One case of DLBCL was encountered. The patient was an 83-year-old, who presented with incomplete voiding, and an enlarged prostate was felt on digital rectal examination. PSA was normal. TURP was done, and histopathological evaluation indicated it to be a lymphoma, which was confirmed by an immunohistochemical panel, leading to categorising it to DLBCL. According to study by Harley F et al primary DLBCL of the prostate occurs at an advanced age. It might mimic BPH on digital rectal examination. PSA is mostly within normal range. The diagnosis is done based on the immunohistochemical profile comprising CD20, BCL2, BCL6, CD3 and CD10. The prognosis is poor.[26]

A total of 18 patients were followed up for a period of 6 months to assess the prognosis. Metastasis had occurred in 2 cases with gleason score 9, and DLBCL. The patient with sarcomatoid carcinoma did not survive. Rest of the patients are currently under follow up.

When choosing treatments for prostate cancer, prognostic parameters such age, co-morbidities, and baseline urine function are considered in addition to clinical TNM stage, Gleason's score, and initial PSA level. Active surveillance, hormonal therapy, radiation therapy, chemotherapy, surgery, and cryotherapy are among the available treatment options. The characteristics of the tumor, PSA levels, grade, stage, and likelihood of recurrence all influence the therapy option. Radiation therapy and radical prostatectomy are possible treatments for low-risk prostate cancer. Hormonal therapy, often known as androgen-deprivation therapy, is advised for malignancies that have recurred or have progressed outside the prostate.[27]

There are a few limitations of our study. First, is the sample size being small. Second, is the limited study period, due to which extensive follow up could not be done.

CONCLUSION

Our study found that prostatic adenocarcinoma is rampant in our society and needs to be diagnosed early for a favourable prognosis. The adjunctive use of an immunohistochemical panel enhances diagnostic accuracy and reduces the likelihood of misdiagnosis in histopathology. It is particularly valuable in resolving diagnostic challenges posed by complex cases. By judiciously employing these panels, pathologists can effectively categorize rare variants and differentiate between primary and metastatic lesions. Identification of such rare variants is critical as they often correlate with poorer prognoses, thereby significantly augmenting both diagnostic precision and prognostic insight.

Conflict(s) Of Interest
None

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