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To Study the Role of P53 and KI-67 in Differentiating Benign and Malignant Prostatic Lesions: A Study of 81 Cases at LLRM Medical College, Meerut

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Abstract: ***Introduction: Immunohistochemistry can play an important rolein diagnostic surgical pathology and prognosis of prostatic lesions. Role of IHC markers p63, CKbE12 is well established and p53 and KI-67 are bring evaluated for their role as predictive or prognostic markers. Aims and objectives: To evaluate the immune-expression of p53 and ki-67 in benign and malignant prostatic lesions and their clinicopathological correlation. Material and methods: This study was done in LLRM Medical College attached to SVBP hospital Meerut, which included 81 patients with their detailed demographic data and clinical features of patients were studied with cystoscopic findings, serum Prostate specific antigen levels, histopathology and immunohistochemistry. Results: In our study, maximum cases were benign 52cases (64.2%), around 11cases (23.5%) were pre malignant and 18 cases (22.2%) were malignant. Stronger immune-positivity for p53 and Ki-67 was seen in higher grade of prostate cancer. Most common Gleason grade 2 (score 3+4) was seen in 08 cases (44.5%).***

Keywords: P53, KI-67, Prostatic Lesion

1. Introduction

Prostate cancer is a major health problem being second most frequently diagnosed cancer and fifth leading cause of cancer death in males[1]. Incidences increase from 20% in men in their fifties to approximately 70% in men at the age of 70 year. Estimated new cases of prostatic carcinoma is approximately 1, 276, 106 worldwide causing 358, 989 deaths (3.8% of all deaths caused by cancer in men) [2, 3]. The incidence rate in India is 9-10/100000 population. Age is a single most important risk factor for prostatic carcinoma. Tumorgrade serves an important prognostic factor along with other IHC markers=CK34bE12, p63, Ki-67 and p53. Prostatic lesions are routinely diagnosed by biopsies (TURP), needle biopsies which calls for need for reliable prognostic markers which correlates with Gleason scoring to point towards a positive diagnosis of carcinoma.

The tumor protein p53 (TP53) is the popular on cosuppressor gene and is located on chromosome 17p 13.1[4]& is mutated in all human cancer. Inactivating mutations in TP53 occur in the most of the human cancer including prostatic cancer & most mutations are detected in the central DNA-binding domain, thereby incapacitating the function of p53 as a transcription factors. . Inactivation of TP53 predicts an unfavourable patient outcome, early metastatic dissemination, and resistance to next-generation antiandrogens. Therefore, TP53 perturbations have a strong potential as a marker to identify patients with a high risk for lethal disease outcome who could benefit from more intensified treatment.

Ki-67 is a DNA-binding nuclear protein, which is expressed in proliferating but not quiescent (G0) cells during the cell cycle. Expression of the Ki67 protein (pKi67) is associated with the proliferative activity of intrinsic cell populations in malignant tumors including that of prostate, allowing it to be used as a marker of tumor aggressiveness[5.]

It serves as a marker of cell proliferation and immunohistochemical expression of Ki-67 to predict tumor proliferative behaviour and thus biological aggressiveness.

Aims and objective:

1) To study the expression of p53 and ki-67 in benign prostatic hyperplasia and prostate cancer.
2) To correlate the expression of P53 and Ki-67 with Gleason's grading of prostate cancer.

2. Materials and Methods

The present study was done in Department of Pathology, LLRM Medical College, Meerut in collaboration with department of Surgery, LLRM Medical College, attached to SVBP Hospital, Meerut. All cases attending the inpatient and outpatient department of surgery with complaints of urgency, hesitancy and dribbling of urine, frequency of micturition and nocturia were evaluated. Total 81 patients were included in the study. Detailed history, Clinical examination, Routine investigations, serum PSA level and Cystoscopic findings were all taken. At time of Cystoscopic examination, TRUS guided biopsies were taken and sent to Department of Pathology. Department of At Department of pathology, specimens received were in the form of TURP chips, prostatectomy specimens or trucut biopsies. Received specimens were subjected to gross examination. TURP chips, biopsies were completely submitted and representative sections from prostatectomy specimen were submitted for routine processing and Hematoxylin and Eosin (H & E) staining for histopathological examination.

For immunostaining for p53 and ki-67.--: 3-4 μm micrometer thin sections were cut and placed on poly L lysine coated slides,, deparaffinised and rehydrated through graded concentrations of ethanol. For antigen retrieval, the slides were incubated with Tris EDTA for 20 min in

pressure cooker after washing with tris buffer saline (TBS) Incubated in hydrogen peroxide. Primary antibody was put.

p53 and Ki-67 immunostaining was performed using Rabbit Monoclonal p53 and Rabbit Monoclonal Ki-67 antibody for 1 hr. (Diagnostic BioSystems 6616 Owens Drive Pleasanton, CA 94588 USA). Then secondary antibody was put for 30 minutes followed by DAB solution (Diaminobenzidine) for 45 minutes counterstaining was done with 10% Hematoxylin and mounted with DPX.

Inclusion Criteria:
All cases attending the inpatient and outpatient department of surgery for of complaints urgency, hesistancy, dribbling of urine, frequency of micturition and nocturia were included in the study.

Exclusion Criteria:
Tissue sections with inadequate study material were excluded from the study.

For positive control-colonic carcinoma tissue (for p53) and chronic tonsillitis tissue (for Ki-67) were used.

p53and Ki-67immunoexpression: The cutoff value was 20% and divided into three categories as:

- Immunonegative
- < 20% as Low expression
- > 20% as High expression for p53

3. Observations and Results

Table 1: Distribution of total cases according to Histopathological Diagnosis (n=81)

S. No.	Histological Diagnosis	No. of cases	%
A.	**BENIGN**	**52**	**64.2**
1.	Nodular hyperplasia of prostate (NHP)	22	27.1
2.	NHP with chronic prostatitis	12	14.8
3.	Stromal nodule	06	7.4
4.	NHP with basal cell hyperplasia	05	6.1
5.	NHP with acute prostatitis	02	2.4
6.	Sclerosing adenosis	01	1.2
7.	NHP with squamous metaplasia	01	1.2
8.	Infarct	01	1.2
9.	NHP with granulomatous prostatitis	01	1.2
B.	**PRE-MALIGNANT**	**11**	**13.5**
1.	Low gradient raepithelialneoplasia	07	8.6
2.	High gradient raepithelialneoplasia	04	4.3
C.	**MALIGNANT**	**18**	**22.2**
1.	Acinar adenocarcinoma	12	14.8
2.	Ductal adenocarcinoma	02	2.4
3.	Prostaticurothelialcarcinoma	02	2.4
4.	Adenosquamous carcinoma	02	2.4
5.	Intraductaladeno carcinoma	00	00
6.	Basal cell carcinoma	00	00
	Total	**81**	**100**

Above table showed that out of total 81 prostate cases, 52cases (64.2%) were of benign nature followed by 18cases (22.2%) of malignant and 11 cases (13.5%) of premalignant lesions. Out of total 52 benign cases, 22 (27.1%) cases were of nodular hyperplasia of prostate followed by 12cases (14.8%) of nodular hyperplasia of prostate with chronic prostatitis, 06cases (7.4%) of stromal nodule, 05cases (6.1%) of nodular hyperplasia of prostate with basal cell hyperplasia, 02 cases (2.4%) of nodular hyperplasia of prostate with acute prostatitis and 01 case (1.2%) each of infarct and nodular hyperplasia with granulomatous prostatitis.

Out of total 18 malignant cases, 12cases (14.8%) were of acinaradeno carcinoma in which one of the case shows arcomatoid features 02cases (2.4%) each of ductal adenocarcinoma, prostaticurothelial carcinoma and adeno-squamouscarcinoma. Inductaladeno carcinoma, we found cribriformand papillary pattern.

Table 2: Correlation of Ki-67 and p53 Immunoexpression with Gleason's Grading (n=18)

S. no.	Gleason's grade	Ki-67 immunoexpression				p53 immunoexpression			
		Low (<20%)		High (>20%)		Low (<20%)		High (>20%)	
		Cases No.	%	Cases No.	%	Cases No.	%	Cases No.	%
1	1 (n=03)	1	33.3	1	33.3	2	66.6	0	0
2	2 (n=08)	3	37.5	5	62.5	3	37.5	5	62.5
3	3 (n=04)	1	25	3	75	1	25	3	75
4	4 (n=02)	0	0	2	100	0	0	2	100
5	5 (n=01)	0	0	1	100	0	0	1	100

In view of p53, above table showed that out of total 18 cases of prostatic carcinoma 11 cases showed higher immune expression, 06cases showed low immune-expression and 01 case was immune-negative for p53.

In relation to Gleason grade100% positivity was seen in grade 4 and grade5 followed by 75%in grade 3.

Regarding, Ki-67 higher immune-expression was observed in 12 cases out of total 18 cases. And in relation to Gleason grade 100% immune-positivity was seen in Grade 4&5 followed by Grade 3.

Combined immune-positivity of p53 and ki-67 was seen in 66.6% of total cases.

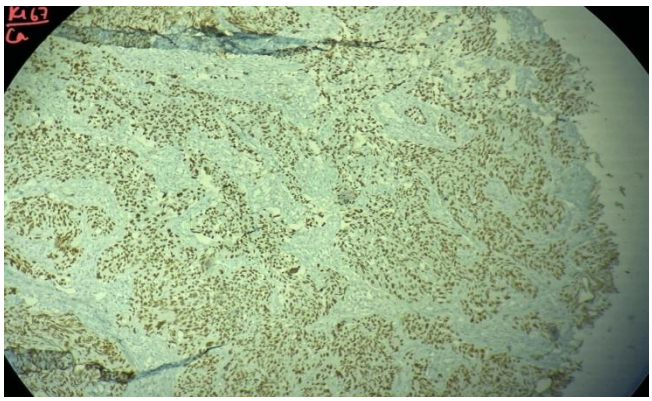

Figure 1: Strong ki-67 immunoexpression

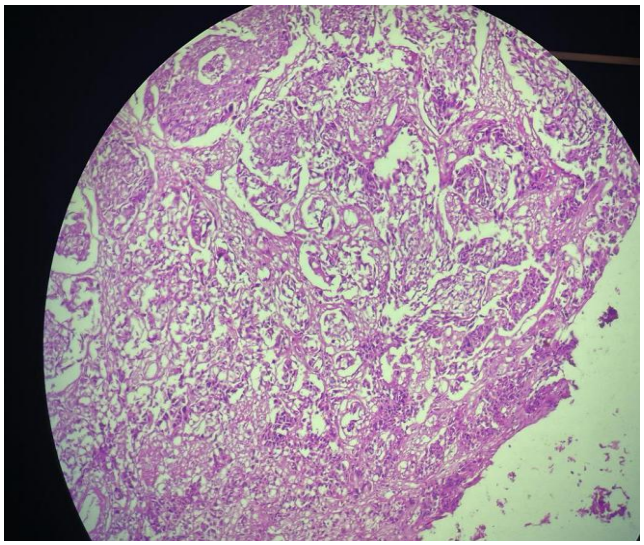

Figure 2: Gleason grade 4 H&E 40x

4. Discussion

The study was carried out total in 81 patients in LLRM Medical College, Meerut in collaboration with SVBP hospital in Department of Pathology. Results were noted and comparisons with other studies were undertaken as described below:

NHP and prostatic adeno carcinoma were the most common entities affecting the prostate gland.

In present study, malignant cases were 22.2% as compared to 64.2% of benign cases with ratio 1: 3 and 13.5% of premalignant lesion. The predominant lesion was NHP (64.2%) similar to the results of nehaangurana's et al[6] stated 64.3% of NHP and 32.1% of prostate carcinoma cases.

Carcinoma of prostate is the second most common malignancy in men, second only to lung cancers. Hormonal factors play important role in the development of prostatic carcinoma.5-10% of prostatic carcinoma have a genetic link.

In present study, carcinoma prostate was identified 18cases (22.2%) close to previous study. Adeno carcinoma was the most common histological type of cancer followed by ductal type of adeno carcinoma found in this study.

In context to Ki-67 in this study, 12 (66.6%) cases out of total 18 malignant cases show high ki-67 immunoexpression (>20%) while only 03cases (5.8%) out of total 52 BPH cases show high ki-67immunoexpressionalmost similar to 71.4% as reported by Madani et al[7], 67.76% by Zhong et al whereas a very high expression observed as 93% by Makarewicz et al. p53 expression show high positivity (>20%) in 55.7% cases of benign prostatic hyperplasia and 61.1%of prostatic carcinoma. These findings are similar to Jiang *et al*. in which positive staining rates of p53 protein were 51.1% and 10% respectively in patients with carcinoma and BPH ($P < 0.05$), whereas Sasor *et al*. and Petrescu *et al*. revealed lack of p53 immuno- reactivity in BPH.

5. Conclusion

Benign lesions are more common than malignant lesions. Among the histological patterns of prostatic lesions, nodular hyperplasia of prostate (NHP) was predominant type. It is necessary to study all prostate biopsy [Transurethral resection of prostate (TURP) and needle] in order to identify premalignant lesions, proliferative activity, and grade of inflammation.

Histopathological diagnosis and Gleason's grading plays a definitive role in the management of prostatic cancer

In practice Gleason grading system is a simple, easily understood, remembered and easily applied.

Both p53 and ki-67 were significantly up regulated in malignant lesions as compared to benign lesions and a strong relationship with Gleason grade was also noticed; hence these markers can be used along with other prostate cancer prognostic factors

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