International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 9; Issue 06(A); June 2020; Page No.22375-22379
DOI: http://dx.doi.org/10.24327/ijcar.2020. 22379.4410

Research Article

EXPRESSION OF IMMUNOHISTOCHEMICAL MARKERS ERG AND P63 IN PROSTATIC NEOPLASM AND ITS CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS

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A R T I C L E I N F O

Article History:
Received 4th March, 2020
Received in revised form 25th April, 2020
Accepted 23rd May, 2020
Published online 28th June, 2020

Key words:
Immunohistochemistry, ERG, P63, Prostatic Neoplasm

A B S T R A C T

Background: Immunohistochemistry (IHC) based on phenotypic expression in a prospective clinical setting is expected to provide the differential status of ERG and p63 expression in benign and malignant prostatic biopsy which could be utilized as adjunct to conventional clinicopathological parameters of diagnosis, prognosis and management.
Aim: To assess the combined diagnostic utility of ERG and p63 immunohistochemistry markers expression and correlate with clinicopathological parameters in the prostatic neoplasm.
Materials &Methods: In present study, total number of 70 cases of benign prostatic hyperplasia (BPH), benign prostatic hyperplasia with prostatic intraepithelial neoplasia (BPH with PIN), prostate carcinoma was included in this study. ERG and p63 immunohistochemical staining were applied as per standard protocol on formalin fixed paraffin embedded tissue sections of prostate neoplasm and serum Prostate Specific Antigen (PSA) level was done in all the cases.
Results: Seventy cases of prostate neoplasm were included in the study. Out of 70 cases 24 (34.29%) were diagnosed as Benign Prostatic Hyperplasia, 20 (28.57%) as Prostatic Intraepithelial Neoplasia and rest 26 (37.14%) as Carcinoma Prostate. After immunohistochemical evaluation of ERG and p63, finally 21 cases of BPH, 21 cases of PIN and 28 cases of carcinoma prostate were diagnosed. ERG and p63 immunohistochemical staining as an adjunctive test along with histopathological examination increase the diagnostic accuracy almost up to 100% in our study.
Conclusion: We conclude that ERG and p63 IHC staining in prostate neoplasm also helps in early diagnosis of prostatic intraepithelial neoplasia and carcinoma prostate cases.

INTRODUCTION

Prostate cancer was the second most common cancer diagnosed among men worldwide and fifth most common cancer overall as part of GLOBOCON series published by the international agency for research on cancer in year2008.[1] A recent study has shown overall false negative prostate biopsies (biopsies previously reported as benign but containing prostate adenocarcinoma or atypical small acinar proliferation) were estimated to be 2.4%, 1.1% for prostate cancer and 1.3% for atypical small acinar proliferation.[2]Immunohistochemistry (IHC) plays an important role in the differentiation among benign, premaligant and malignant lesion of prostate.

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Thus it would help in selecting the most appropriate treatment plan so the patient with favorable outcome would not need intensive therapy, whereas patient with high risk of early metastasis would be placed in the group of more intensive therapy and follow up.[3]

Aim: To assess the diagnostic utility of ERG and p63 IHC markers expression and to correlate immunohistochemical expression with clinic pathological parameters in benign and malignant neoplasm of prostrate.

MATERIAL AND METHODS

The study was conducted in the department of pathology and in the collaboration with urology department. This study was approved by Ethical Clearance Committee. Suspected cases of benign prostatic hyperplasia underwent transurethral

resection of prostate and suspected cases of carcinoma prostate underwent transrectal prostatic true cut needle biopsy.

Study Design: Prospective study

Study Duration: One year

Sample Size: Total number of 70 cases, 24 cases of BPH, 20 cases of PIN, 26 cases of prostate carcinoma was included in this study. Inclusion criteria: Patient who gave consent to enroll in the study and availability of clinical detail at presentation. Exclusion criteria: Patient who were not willing to give consent to be the part of study. Cases in which tissue was lost during antigen retrieval or insufficient tumor tissue.

Clinical assesment: Age, symptoms, per rectal findings, serum PSA level, ultrasound of prostate were recorded on a structured proforma from the clinical data sheets of patients. Not in all cases, follow up of 20 patients was possible, 13 were alive, 5 were deteriorating and 2 patients were dead. After 4 months follow-up of patients was not possible.

Laboratory assesment: Immunohistochemical examination of prostate biopsies were done on formalin fixed paraffin embedded tissue after H&E staining as per "Biopsy Interpretation of the prostate" Epstein JI & Natto, JG, 4TH edition 2008. Gleason's grading of prostate cancer was done according to guideline of 2005, International Society of Pathology Consensus Conference. Immunohistochemical workup for ERG and p63 were done on cases with adequate paraffin embedded tissue after routine case work up. Immunohistochemical staining was done by streptavidin biotin immunoperoxidase method, using anti-human ERG monoclonal rabbit antibody-ready to use (DAKO-code IR659) and anti-human p63 protein monoclonal mouse antibody-ready to use (DAKO-code IR 662) as per standard protocol. Positive control used for p63 was breast tissue and negative control was carcinoma prostate and positive tissue control for ERG was blood vessels and negative control was benign prostatic hyperplasia.

Statistical Analysis: Done by using SPSS (Statistical Package for Social Sciences) version 15.0 statistical analysis software. The values were represented in Number (%) and Mean ±SD, Chi square test and p value (Level of significance).

RESULTS

A total of 70 histologically diagnosed cases of prostate neoplasm were included in the study. Overall age of patients included in the study was 46 to 88 years and mean age was 66.67+9.56 years. Most common symptoms were increased frequency, weak urine stream, intermittency, nocturia, urgency, and retention of urine and less common symptoms were hematuria, weight loss and backache. The higher proportion ($p<0.05$) of patients of carcinoma prostate as compared BPH and PIN show weight loss (15.38% vs 0.0% & 0.0%) and backache (15.38% vs. 0.0% & 0.0%) which was statistically significantly.

On digital rectal examination, firmness and tenderness of prostate was found in higher proportion in BPH (29.17%) cases as compared to PIN (25.00%) and carcinoma prostate (19.23%), but nodularity and hardness of prostate was found in statistically significant ($p<0.001$) carcinoma prostate cases (84.62%,88.46%) as compared to cases of PIN (15.00%,10%) and BPH (0.00%,00.0%). Prostate gland was firm to hard and adherent in carcinoma prostate cases (38.46%) which was statistically significant ($p<0.001$) as compared to none of the cases of PIN (0.00%) and BPH (0.00%).

The PSA level was higher in BPH cases as compared to PIN and carcinoma prostate, having PSA levels <4 (45.83% vs. 50.00% & 3.85%) and PSA levels 4-10 (50.00% vs. 40.00% & 3.85%) while cases with PSA levels >10 was higher in carcinoma prostate (92.31%) as compared to PIN (55.00%) and BPH (4.17%). A statistically significant difference in PSA levels with different histopathological diagnosis of prostate was observed ($p<0.001$) [Fig1].

Mean prostate volume of cases of PIN 75.89+33.76 cc) was maximum followed by cases of BPH (61.21+25.33 cc) and minimum in cases of carcinoma prostate (49.38+19.11 cc). Difference in mean prostate volume of cases with different histopathological diagnosis was found to be statistically significant ($p=0.005$).

Histological diagnosis of 5 (7.14%) cases was BPH, 19 (27.14%) was BPH with Chronic Prostatitis, these 24 cases were included as BPH. 20 (28.57%) cases had histopathological diagnosis of BPH with PIN, they all 20 cases were included as PIN and rest 26 (37.14%) cases of carcinoma prostate were included as carcinoma prostate cases. Of the 26 carcinoma prostate cases, majority (n=16; 61.54%) had Gleason's score 6-8 and rest of the 10 (38.46%) cases had Gleason's score 9-10. No statistically significant association of Gleason score and PSA levels was found in cases of carcinoma prostate ($p=0.368$) [Fig2].

In our study among 70 cases, p63 expression was positive in 31 cases, negative in 28 cases and focal loss was seen in 11 cases. In 24 histologically diagnosed cases of BPH, 21 cases (87.50%) were p63 positive, 3 cases (12.50%) showed focal loss of p63 and not a single case was p63 negative. Among 20 histologically diagnosed PIN cases, 10cases (50%) were p63 positive, 8 cases (40%) showed focal loss of p63 and 2 cases (10%) were p63 negative while in 26 histologically diagnosed cases of carcinoma prostate, all 26 cases (100%) were p63 negative, not a single case of carcinoma prostate showed p63 positivity.

On immunohistochemical examination with ERG , proportion of ERG positive expression cases was higher in carcinoma prostate (69.23%) as compared to PIN (35.00%) and BPH (8.33%). Difference in ERG expression in different histopathological diagnosis of cases which was found to be statistically significant ($p<0.001$)[Table1/Fig3]. Focal loss of p63 expression was observed in higher proportion of PIN cases (40.00%) as compared to BPH cases (12.50%) and carcinoma prostate cases (0.0%) [Fig4]. P63 expression was positive in majority of cases of BPH (87.50%) and PIN (50.00%) while none of carcinoma prostate cases (0.0%). P63 expression was negative in all the cases of carcinoma prostate (100.00%) and 10.00% cases of PIN. Difference in p63 expression with different histopathological diagnosis was found to be statisticallysignificant ($p<0.001$) [Table2].No statistically significant association of ERG intensity and Gleason's score was observed as well as association between PSA levels and ERG intensity was not found to be statistically significant in carcinoma prostate cases. Out of 24, histopathologically diagnosed BPH cases, final diagnosis of 3 (12.50%) cases were changed in to PIN after immunohistochemical staining evaluation, and rest of 21 (87.50%) cases diagnosis were remains the same.Among 20, histopathologically diagnosed

PIN cases, final diagnosis of 2 (10.00%) cases were changed in to Carcinoma prostate after immunohistochemical staining evaluation, and rest of 18 (90.0%) cases diagnosis were remain same and 3 cases also added as PIN. While 26 Carcinoma Prostate cases, final diagnosis after immunohistochemical staining evaluation, were remain same and 2 cases also added [Table3/Fig5].
Diagnostic accuracy of histopathological diagnosis was 92.86% which was found to be almost perfect agreement (κ=0.892). This agreement was found to be statistically significant (p<0.001)[Table3].

However, very small number of Carcinoma prostate cases showed perineural invasion and necrosis, there was no significant correlation was seen with ERG and p63 expression. Proportion of ERG positive cases was higher as compared to ERG negative cases for outcome Alive (76.92% vs. 42.86%) while proportion of ERG negative cases was higher as compared to ERG positive for outcome Deteriorating (42.86% vs. 15.38%) and Expiry (14.29% vs. 7.69%).The diagnosis of the small foci of prostate cancer in needle biopsy specimen is one of the major diagnostic challenge in surgical pathology. ERG and p63 IHC staining in prostate neoplasm helps in early diagnosis of PIN and Carcinoma prostate cases. Knowledge of patterns on routine microscopy along with the judicious use of immunohistochemistry will lead to arrive at a confident and correct diagnosis and avert a false positive interpretation.

Table 1 Comparison of ERG expresssion with Histopathological Diagnosis of Study Population (Chi-square test)

ERG Positivity	Total (N=70)	BPH (n=24)		PIN (n=20)		Ca Prostate (n=26)	
		No.	%	No.	%	No.	%
Negative	43	22	91.67	13	65.00	8	30.77
Positive	27	2	8.33	7	35.00	18	69.23
χ^2=19.684 (df=2); p<0.001							

Table 2 Comparison of p63 expression with Histopathological Diagnosis of Study Population (Chi-square test)

p63 expression	Total (N=70)	BPH (n=24)		PIN (n=20)		Ca Prostate (n=26)	
		No.	%	No.	%	No.	%
Focal loss of p63	11	3	12.50	8	40.00	0	0.00
Negative	28	0	0.00	2	10.00	26	100.00
Positive	31	21	87.50	10	50.00	0	0.00
χ^2=71.032 (df=4); p<0.001							

Table 3 Comparison of Histopathological Diagnosis and Final Diagnosis after ERG and p63 immunohistochemical evaluation (Chi-square test)

Histopathological diagnosis	Immunohistochemical evaluation(IHC)					
	BPH (n=21)		PIN (n=21)		Ca Prostate (n=28)	
	No.	%	No.	%	No.	%
BPH (n=24)	21	87.50	3	12.50	0	0.00
PIN (n=20)	0	0.00	18	90.00	2	10.00
Ca Prostate (n=26)	0	0.00	0	0.00	26	100.00
Final Diagnosis after IHC	21		21		28	

(κ=0.892), (p<0.001)

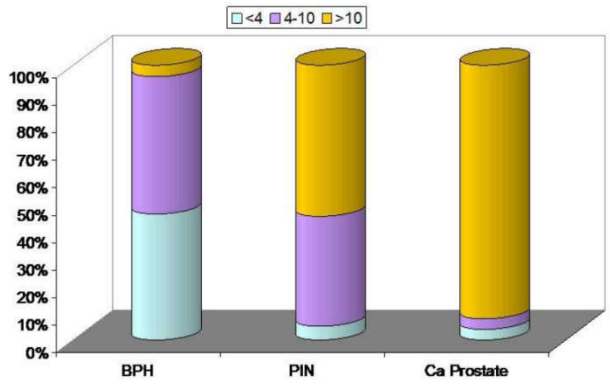

Fig 1 Comparison of PSA levels with histopathological diagnosis of Study Population

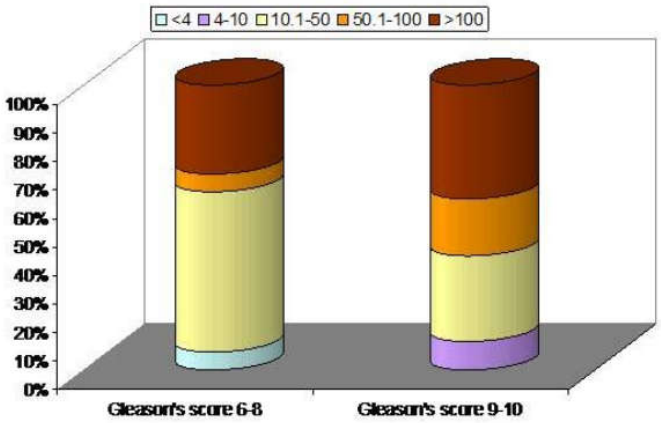

Fig 2 Association of PSA level with Gleason's Score of study population in Ca Prostate

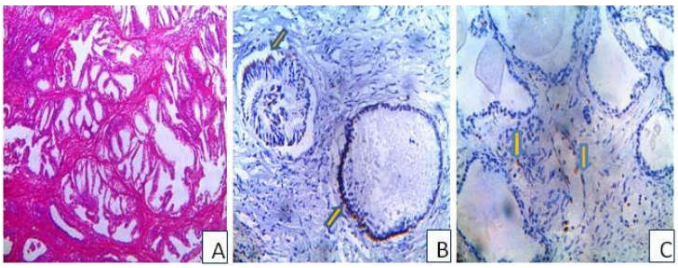

Fig 3 A: Section showing glandular hyperplasia in BPH (H&E stain, X10), B: positive nuclear p63 expression inbasal cell layer of gland in BPH (IHC, X20), C: negative ERG expression in BPH, arrow shows ERG positivity in endothelial cells of blood vessel and lymphocytes (IHC, X20).

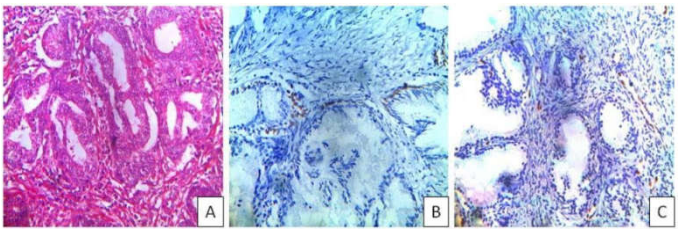

Fig 4 A: Section showing nuclear stratification & enlargement anisonucleosis, hyperchromasia, & prominent nucleoli in majority of cells in PIN (H&E stain, X20), B: focal loss of p63 expression in basal cell layer of PIN (IHC, X20), C: negative ERG expression in secretory cell layer of PIN, and showed ERG positivity in endothelial cells of blood vessel and ERG positivity in lymphocytes (IHC, X20).

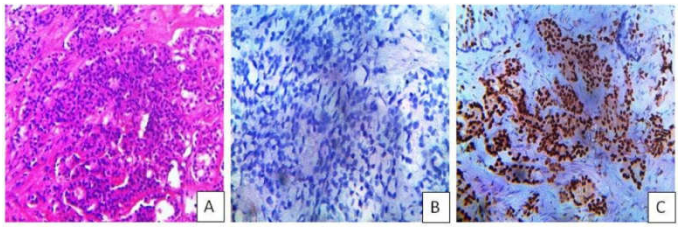

Fig 5 A:Section showing small acini arranged in back to back fashion in adenocarcinoma prostate (H&E stain, X20), B: negative p63 expression in adenocarcinoma prostate (IHC, X20), C: positive nuclear ERG expression in adenocarcinoma prostate (IHC, X20).

DISCUSSION

Prostate carcinoma and benign prostatic hyperplasia are the two principal conditions that involve the prostate; they account for more than 90% of all prostatic disease. Prostate cancer is the most common and second leading cause of death in the men in the United States. [4] Early detection of cancer and better understanding of the premalignant lesions offer practical methods of reducing morbidity and mortality. Prostatic carcinoma may arise in any zone of prostate, but the relative distribution is different in different zone; about 68% of the carcinomas arise in the peripheral zone, 24% in the transition zone and 8% in the central zone.[5] Donald F. Gleason in 1966 created a unique grading system for prostate carcinoma based solely on the architectural pattern of the tumors. In this system, prostate cancers are stratified in to five grades on the basis of degree of glandular differentiation and growth pattern of tumor in relation to stroma as evaluated on low power view. Gleason grading on histological examination is the best prognostic indicator in prostate cancer, however interobserver variation can occur, grading on biopsy may not correlate with the prostatectomy specimen because of sampling problems, and cases of morphological identical prostate cancer can behave differently.[6] Patients with low grade PIN are at no greater risk of having carcinoma with repeat biopsy.[7] Pathologist cannot reproducibly distinguish between low grade PIN and BPH. [8] So low grade PIN should not be commented on biopsy.

High grade PIN is associated with 23 to 35% risk of carcinoma on subsequent biopsy. [9] There is an increase in the size and number of high grade PIN foci in prostate with cancer as compared with prostate without cancer.[10] It appears that high grade PIN is a precursor lesion of carcinoma prostate. High grade PIN is intermediate between benign prostate lesions and adenocarcinoma of the prostate.It is important to use a combination of positive and negative markers for immunohistochemical analysis to assist in the diagnosis of prostate cancer. It has been shown that using a positive marker like ά-methylacyl coenzyme a racemase or anti ERG antibody in association with negative markers like traditional basal cell marker e.g., 34βE12 or p63 can help to confirm the diagnosis when small atypical glands are identified by routine H&E staining. [11,12,13,14] The p63 and ERG immunostain combines the high sensitivity of p63 for basal cells and high specificity of ERG for secretory cells may be a potential useful marker in the work-up of difficult prostate biopsies. The high specificity of ERG in secretory cells for the presence of prostate adenocarcinoma may have important implications for prostate biopsy interpretation and need to be further validated in larger prospective studies. [14]

In present study age of patients diagnosed as BPH were between 50-85 years, mean age was 65.7±9.96 years, age of patients diagnosed as PIN were between 55 and 86 years with mean age of 68.15±9.30 years and age of patients diagnosed as Carcinoma Prostate were between 46 and 88 years with a mean age of 66.46±9.61year. Heinzer H *et al* (2009), showed 64% of new prostate cancer cases in the United States were diagnosed in men older than age of 65 years, and 23% in older than age 75 years.[15]It is important to use a combination of positive and negative markers for immunohistochemical analysis to assist in the diagnosis of prostate cancer. It has been shown that using a positive marker like ά-methylacyl coenzyme a racemase or anti ERG antibody in association with negative markers like traditional basal cell marker e.g., 34βE12 or p63 can help to confirm the diagnosis when small atypical glands are identified by routine H&E staining. [14]

In this study correlation of PSA level with gleason's score in carcinoma prostate cases was done, no statistically significant association was seen in between PSA level and gleason's score, however study of Sladana Zivkovic (2004) revealed statistically significant correlation between serums PSA with gleason score in patients of carcinoma prostate. [16]
In this study ERG expression was highly specific, almost 100% in detecting carcinoma prostate if diagnosis of high grade PIN was ruled out, sensitivity of ERG expression in carcinoma prostate was 69.23%, almost similar observation was also made in study of Furusato B *et al* [17] & Shah RB *et al*. [18] Thus this study showed that combined use of ERG (high specificity) and p63 (high sensitivity) immunohistochemistry had great utility in resolving diagnostic problems in case of prostate neoplasm in small needle biopsies containing small foci of suspicious cells(almost 100% sensitivity and 100% specificity) and early detection of premalignant lesion of prostate. Similar observation was also made in study of Yaskiv *et al*. [14] In our study PSA level, Gleason's score, tumor necrosis and perineural invasion, age and clinical outcome of patients of carcinoma prostate cases were not show any statistical significant correlation with ERG positive and negative cases. Similar observation was also made in study of Esgueva R *et al*.[19] while Mackinnon AC *et al* study showed increase ERG copy number to be correlated with higher clinical stage and more aggressive disease. [20] ERG positive carcinoma prostate cases may be associated with increased risk of tumor progression as compared to ERG negative cancer, it may help to decide treatment options ranging from medical treatment to aggressive management with radiation, chemotherapy or surgical removal of prostate and avoid side effect of prostate treatment like erectile dysfunction and urinary incontinence.

Although prognostic features of ERG expression in carcinoma prostate remain to be better understood, both positive and negative associations with clinicopathological parameters have been reported and reviewed by Kumar Sinha *et al* [21] and Clark and Cooper.[22] Diagnostic accuracy of histopathological diagnosis was 92.86%; ERG and p63 immunohistochemical staining as an adjunctive test along with histopathological examination increase the diagnostic accuracy almost up to 100% in our study. However, in our study there was no significant correlation was seen in between ERG expression and clinicopathological parameters of Ca prostate cases, further independent studies in larger and better defined cohorts are warranted to see the correlation between ERG expression and clinicopathological parameters of Ca prostate for

considering ERG as an authentic, and validated prognostic marker in prostate carcinomas.

CONCLUSION

However, in our study there was no significant correlation was seen in between ERG& p63 expression with clinicopathological parameters of Carcinoma prostate cases, further independent studies in larger and better defined cohorts are warranted to see the correlation between ERG expression and clinicopathological parameters of carcinoma prostate for considering ERG as an authentic, robust and validated prognostic marker in prostate carcinomas.

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How to cite this article:

Dr Anurag singh *et al* (2020) 'Expression of Immunohistochemical Markers Erg and P63 in Prostatic Neoplasm and its Correlation with Clinicopathological Parameters', *International Journal of Current Advanced Research,* 09(06), pp. 22375-22379. DOI: http://dx.doi.org/10.24327/ijcar.2020. 22379.4410

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