RESEARCH ARTICLE

ERG expression in BPH vs prostatic adenocarcinoma and its correlation with Gleason grade group

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Abstract

Objective: To evaluate immunohistochemical expression of erythroblast transformation-specific-related gene in prostate carcinoma and benign prostate hyperplasia, and its association with Gleason grade groups.

Method: The retrospective, comparative, cross-sectional study was conducted from January to December 2022 at the Department of Histopathology, Pakistan Navy Ship Shifa Hospital, Karachi, and comprised prostate samples from January 2019 to January 2020. All tissue specimens were subjected to immunohistochemical staining with erythroblast transformation-specific-related gene. The expression of immunohistochemical and its association was determined in benign prostate hyperplasia and prostate carcinoma groups. Data was analysed using SPSS 23.

Results: Of the 60 cases with mean age 72±7.4 years (range: 58-88 years), 33(55%) had prostate carcinoma and 27(45%) had benign prostate hyperplasia Of the prostatic carcinoma cases, 20(60.6%) showed positive nuclear staining, while 13(39.4%) showed no nuclear staining. Weak positive staining was observed in 3(9.1%), and moderate in 3(9.1%) cases. Strongly positive ERG expression was found in 14(42.4%) patients. The erythroblast transformation-specific-related gene was equally expressed in low and high Gleason grade groups of prostate carcinoma (p>0.05). All 27(100%) cases of benign prostate hyperplasia showed negative immunohistochemical expression for erythroblast transformation-specific-related gene.

Conclusion: The erythroblast transformation-specific-related gene expression was found to be associated with prostate carcinoma compared to benign prostate hyperplasia cases, and could be used as a diagnostic tool for distinguishing between the two.

Keywords: Prostate carcinoma, Benign prostatic hyperplasia, BPH, ERG protein, Immunohistochemistry.

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Introduction

Prostate carcinoma (Ca prostate) is one of the major cancers prevalent in males globally. According to the Global Cancer Observatory (GLOBOCAN) report of 2020, there were over 1.4 million newly-diagnosed Ca prostate cases. The number of deaths reported from Ca prostate in the year 2020 was 375,304. Every seventh man in the United States and every 25th worldwide is diagnosed with Ca prostate. According to the American Cancer Society, 192,000 new cases and 33,330 Ca prostate-related deaths were documented in 2020 in the US, accounting for 10.6% of all new cancer diagnoses. In Pakistan, 4,550 new cases and 2188 deaths were documented in men in 2020 due to Ca prostate, according to GLOBOCAN. The annual registry of the Shaukat Khanum Memorial Cancer Hospital and Research Centre in 2019 reported Ca prostate as the second most common adult male malignancy, with 11.4 per 100,000 male population getting diagnosed with it. Several risk factors are associated with increased susceptibility to Ca prostate, including obesity, age, genetics, sedentary lifestyle, hypertension, certain consumable products, medications and levels of hormones. Among all of these, obesity has been found to be associated with high mortality in Ca prostate.[1]

Adenocarcinoma prostate is the most common histological type of Ca prostate. The most widely accepted grading system for adenocarcinoma prostate is Gleason scoring system which is based on the evaluation of the most predominant microscopic glandular pattern, ranging from grade 1, which is the most well-differentiated, to grade 5, which is the most undifferentiated pattern. Gleason score (GS) is obtained by adding primary and secondary patterns.[2] This grading system was upgraded by the International Society of Urological Pathology (ISUP), and, according to the Epstein grading system, GS 3+3=6 is Grade Group (GG) 1, GS 3+4=7 is GG-2, GS 4+3=7 is GG-3, GS 4+4=8, 3+5=8, 5+3=8 are GG-4, and GS 9-10 is GG-5.2 Together with other parameters, GS or GG predict prognosis of Ca prostate, with higher scores indicating more aggressive cases having a poor prognosis.

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A noncancerous enlargement of prostate gland is known as benign prostatic hyperplasia (BPH). The onset of BPH is usually seen in men with advancing age. Most of the males are affected at or over 50 years of age. This frequency increases with increasing age, and around 90% of males are affected after the age of 70.[3]

Besides histological features, there are certain immunohistochemical (IHC) markers for the diagnosis of Ca prostate and its differentiation from BPH. These IHC markers are especially helpful in cases where limited number of suspicious glands obtained by needle biopsies make the definitive diagnosis of prostatic adenocarcinoma challenging for the pathologist.[4]

Prostatic adenocarcinoma shows marked molecular heterogeneity, including transmembrane protease, serine 2 (TMPRSS2) and erythroblast transformation-specific-related gene (ERG), with TMPRSS2-ERG (T/E) fusion being the most predominant molecular alteration, and approximately 50% of the cases show its presence.[5] ERG is a member of an erythroblast transformation-specific (ETS) family of transcription factors, and is categorised as a proto-oncogene. It is the key regulator of embryonic development, cell proliferation, differentiation, angiogenesis, inflammation and apoptosis.[6] The protein encoded by this gene is mainly expressed in the nucleus. A cell surface protein, TMPRSS2 is primarily expressed by endothelial cells. It is expressed in normal prostate epithelial cells, and is needed for normal prostate function. The promoter region of TMPRSS2 becomes fused to the coding region of ERG in Ca prostate to form a fusion gene. Both genes are present on chromosome 21 and fusion is caused by chromosomal translocation between TMPRSS2 and ERG. The promoter of TMPRSS2 is under the control of androgen, and subsequently this fusion drives the overexpression of ERG in the presence of androgens.[7] A precursor of adenocarcinoma prostate is high-grade prostatic intraepithelial neoplasia (PIN), which has been occasionally found to contain the T/E fusion, and can thus express ERG.[5] Fusions have also been detected at low frequency in BPH. This indicates that T/E fusion is an early event in the development of Ca prostate, and its presence in BPH can increase the risk of developing carcinoma.[8] Moreover, the product of this fusion gene can be an important therapeutic target in Ca prostate. There are reports showing better response of ERG fusion positive prostatic adenocarcinoma to androgen deprivation therapy, helping in stratifying patients for clinical management.[5]

Detection of ERG fusion can be done by fluorescent in situ hybridisation (FISH) and IHC. The results of FISH and ERG IHC stain have been found to be highly concordant with a specificity of 96.5% and sensitivity of 95.7%.[5] The ERG IHC stain is an important surrogate marker of T/E gene fusion and has been reported as a potential marker for the diagnosis of prostatic adenocarcinoma.[5]

To our knowledge, the expression of ERG in Ca prostate and its association with GG groups have not been studied much in Pakistan. The current study was planned to fill the gap in literature by evaluating IHC expression of ERG in Ca prostate and BPH cases, and its association with GG groups.

Materials and Methods

The retrospective, comparative, cross-sectional study was conducted from January to December 2022 at the Department of Histopathology, Pakistan Navy Ship (PNS) Shifa Hospital, Karachi, and comprised prostate samples from January 2019 to January 2020. After approval from the ethics review committee of the Bahria University Medical and Dental College, Karachi, the sample size was calculated using OpenEpi version 3 with 95% confidence interval (CI), 5% confidence limit and prevalence 5.20% (0.052).[9] The formula used was: n=[DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1)+p*(1-p)]. Data was retrieved using a pre-designed proforma. Informed consent had been obtained from the patients at the time of the procedure. Prostatectomy and transurethral resection of prostate samples were retrieved using non-probability convenience sampling technique. Ca prostate and BPH cases regardless of age that had been diagnosed by histopathologists were included. Metastatic tumours, poorly fixed tissue and priorly treated samples were excluded.

The most representative sections were used for IHC analysis For which 3-5µm sections were taken from formalin-fixed paraffin-embedded (FFPE) blocks, and picked up on poly-L-lysine (PLL) coated slides. Retrieval solution (potential of hydrogen [pH] 6.0 citrate buffer 10x) in water bath at 98-99°C for 40 minutes was used for antigen retrieval. It was then removed from the water bath and cooled at room temperature for 15-20 minutes, and rinsed 2-3 times. Hydrogen peroxide (H_2O_2) blocking solution was used to block endogenous peroxide. Primary antibody ERG was applied. The ERG concentration was prepared according to Zeta corporation company-specified protocol and incubated for 1 hour at room temperature, followed by 10-minute incubation with horseradish peroxidase (HRP) polymer.[10] Chromogen was applied for 20 minutes before counterstaining, dehydrating and mounting. Phosphate buffer solution (PBS) was applied after each step. Nuclear staining of endothelial cells was used as positive internal control for ERG. The staining intensity in the nuclei of prostate adenocarcinoma cells were scored as negative (no staining=0), weak expression (1+), moderate expression (2+), and strong expression (3+).[11] IHC findings were subsequently interpreted.

Data was analysed using SPSS 23. Quantitative variables were expressed as mean±standard deviation, while qualitative variables were reported as frequencies and percentages. Chi square test was used where appropriate. P<0.05 was considered significant at 95% CI.

Results

Of the 60 cases with mean age 72±7.4 years (range: 58-88 years), 33(55%) had Ca prostate and 27(45%) had BPH. Of the Ca prostate cases, 20(60.6%) showed positive nuclear staining, while 13(39.4%) showed no nuclear staining. In contrast, all 27(100%) BPH cases showed negative IHC expression for ERG (Figure). The difference was statistically significant (p<0.05) (Table 1). Among the Cz prostate cases, weak positive staining was observed in 3(9.1%), and moderate in 3(9.1%). Strongly positive ERG expression was found in 14(42.4%) patients. Among the Ca prostate cases, 5(15.2%) were GG-1, 2(6%) were GG-2, 4(12.1%) were GG-3, 5(15.2%) were GG-4 and 17(51.5%) were GG-5. Strong expression of ERG was most prevalent in GG-5 group, but statistically significant association was not found between ERG expression and GG groups (Table 2).

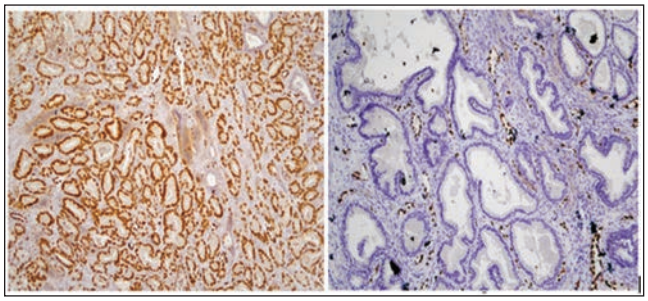

Figure : Prostate carcinoma Gleason grade group 4 showing strong ERG expression (left), and benign prostatic hyperplasia (BPH) showing no ERG expression (right). (immunohistochemical [IHC] staining x 400).

Table-1: ERG expression in BPH and prostate carcinoma (n=60).

ERG expression	Benign prostatic hyperplasia (n = 27)	Adenocarcinoma prostate (n=33)	p-*value*
Positive	0 (0%)	20 (60.6%)	0.000000154
Negative	27 (100%)	13 (39.4%)	

ERG: E26 transformation-specific-related gene, BPH: Benign prostatic hyperplasia.

Table-2: Association of ERG expression with prostate carcinoma grade groups (n=33).

Grade groups	Negative expression	Weak expression	Moderate expression	Strong expression	*p*-value
Grade group 1 (n=5)	5 (100%)	0	0	0	0.13
Grade group 2 (n=2)	0	0	0	2 (100%)	
Grade group 3 (n=4)	3 (75%)	0	0	1 (25%)	
Grade group 4 (n=5)	1 (20%)	0	1 (20%)	3 (60%)	
Grade group 5 (n=17)	4 (23.5%)	3 (17.7%)	2 (11.8%)	8 (47%)	

ERG: E26 transformation-specific-related gene.

Discussion

Ca prostate is the second most common adult male malignancy. The incidence of BPH and Ca prostate increases with age. Prostate-specific antigen (PSA) is used for screening purposes.[12]

The T/E fusion is the most prevalent molecular alteration in Ca prostate.[5] It is an initial step in prostate carcinogenesis. Literature shows that overexpression of ERG protein by IHC significantly correlates with the presence of the T/E fusion gene detected by FISH.[5]

The present study analysed cases of BPH and Ca prostate. The mean age of the sample was 72 years, which is in line with a cross-sectional study in Australia, which reported 71 years.[13] Another study reported it to be 69.02 years.[14]

In the current study, no expression of ERG was observed in BPHS cases. However, the expression of ERG in Ca prostate cases was 60.6%. The finding corresponded with those of an earlier Pakistani study which reported 62%, out of which 14.5% cases were GG-1, 41.93% GG-2-3 and 43.54% were GG-4-5.[5]

A study in Karachi evaluated 78 cases of Ca prostate for ERG expression, and ERG expression was noted in 31. Of them, 3, 10 and 18 cases were of low, intermediate and high ERG expression, respectively.[14]

The current results also corresponded to the study conducted in Canada with 340 Ca prostate cases from 1998 to 2012, where ERG expression and phosphatase and TENSIN homologue (PTEN) loss were noted in 42.7% of the total cases, and most were in the low-grade groups.[15]

In an Egyptian study, ERG expression was restricted to Ca prostate cases, and it was negative in BPH and prostatic intraepithelial neoplasia (PIN) (p<0.001).[16] The results are similar in the current study.

In the present study, most of the cases (17/33) belonged to GG-5, out of which 13(76.5%) expressed ERG. No statistically significant association was found between GG groups and ERG expression. This observation was in concordance with a study conducted in Saudi Arabia.[17] Likewise, a study in Turkiye also noticed no significant relationship between GG and ERG positivity (p=0.197).[18] A study in Iran also noted no significant correlation between the two.[19]

The current study has limitations as it had a small sample size raised from a single tertiary care hospital. Large-scale, multicentre studies are needed to validate the findings.

Conclusion

ERG expression was found to be significantly more in Ca prostate cases compared to BPH, and this can be used to differentiate between the two. Moreover, ERG expression can also be used as therapeutic target for Ca prostate.

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MQ: Concept, design, writing, literature review, results and discussion.
SS: Data interpretation.
BHN: Data collection.
EK: Data analysis.
NJ: Interpretation of results.