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To study ERG expression in benign, pre-neoplastic, and neoplastic lesions of prostate

Rishabh Chaudhary[1], Pradeep Tandon[2], Anubhav Raj[3], Nausheen Khan[4]

[1]Senior Resident, [2]Professor and Head, Department of Pathology, Hind Institute of Medical Sciences, Barabanki, [3]Ex Associate Professor, Department of Surgery, Integral Institute of Medical Sciences and Research, Lucknow, [4]Associate Professor, Department of Pathology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India

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ABSTRACT

Background: Prostate cancer (PCa) is the second most common malignancy in men and the sixth leading cause of death. Clinical course of PCa is highly variable and current clinico pathological parameters are unable to predict accurately the course of the disease because of genetic heterogeneity seen in this tumor. **Aims and Objectives:** The aim of the study was to study the prevalence of E26 transformation-specific-related gene (ERG) expression in benign and malignant lesions of prostate in Northern Indian patients. Whether ERG expression using immunohistochemical (IHC) methods can also be used for differentiating various lesions of the prostate gland is also evaluated. **Materials and Methods:** This is an observational study conducted on 50 biopsy specimens encompassing different lesions of prostate. The study was carried out in the Department of Pathology at Integral Institute of Medical Sciences and Research, Lucknow, India, during the period January 2020–September 2022. **Results:** Amongst 50 cases of prostatic lesions included in the study, there were 20 cases of benign prostatic hyperplasia (BPH), 17 cases of benign mimicker lesions and 13 cases of PCa. ERG expression was absent in all cases of BPH and benign mimicker lesions. ERG expression was seen in 38.5% of cases of PCa. **Conclusion:** In our study, none of the patients of BPH or benign mimicker lesion expressed ERG on IHC, while 38.5% of patients of PCa showed positive staining. This figure differs from reports from other parts of the world. ERG expressions can be a potential therapeutic target for personalized treatment in a subset of patients of PCa. However, it was not found to be a sensitive marker for the diagnosis of PCa.

Key words: ERG; Prostate cancer; Benign mimicker lesions of prostate

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INTRODUCTION

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are common diseases in adult and elderly males. Across the world, PCa is the second most common malignancy in men. In India, this disease constitutes 6.78% of all cancers and is the third most common malignancy in males.[1] Recent Indian studies reveal an increasing trend of PCa, with mean annual percentage change ranging from 0.14% to 8.6%.[2] Clinical course of PCa is highly variable and current clinicopathological parameters are unable to predict accurately the course of the disease.[3]

Tomlins et al., in 2005, demonstrated the presence of gene rearrangements in tissues obtained from patients of prostate adenocarcinoma (PCA).[4] This was the first instance when gene rearrangement abnormality was demonstrated in solid carcinomas. Earlier, it was believed that gene rearrangements occur mostly in hemato-lymphoid malignancies or sarcomas. Their discovery of recurrent (>50%) genetic rearrangements involving transmembrane protease serine 2 (TMPRSS2), with v-ets erythroblastosis is virus E26 oncogene homolog (avian). E26 transformation-specific-related gene (ERG) in PCa prompted molecular categorization of PCa into distinct molecular subtypes. Subsequently, the discovery of genetic rearrangements involving TMPRSS2 with other members of erythroblastosis virus E26 transformation-specific (ETS) transcription factor family such as ETV1, ETV4, or ETV5, prompted further classification of PCa.[5] Due to

Address for Correspondence:
Dr. Pradeep Tandon, Professor and Head, Department of Pathology, Hind Institute of Medical Sciences, Barabanki, Uttar Pradesh, India.
Mobile: +91-8840280751. **E-mail**: tandonp72@yahoo.co.in

clinical and molecular heterogeneity seen in PCa, challenges exist in diagnosing and treating patients of this disease. Since not all patients with identical clinical profile respond likewise to the same treatment, a proper understanding of PCa based on its molecular profile may help in selecting personalized management of the disease.

Diagnosis of PCa is usually established by histological examination. Differentiating benign mimicker and pre-cancerous lesions from PCa is sometimes challenging, especially when a small amount of tissue is available for examination – as in core needle biopsies. Markers like alpha methylacyl coenzyme A racemase (AMACR) and P_{63} have been employed for making this distinction. However, results with these markers are not 100% specific or sensitive.[6] There exists a need for evaluating new markers that may help in making this distinction. Lately, ERG expression in prostatic lesions is being explored for this purpose. Recent studies report ERG expression in 44–61% of cases of PCa compared to its expression in 1% of cases of BPH.[7,8] Significant racial and ethnic differences have been documented for ERG expression in PCa from the world over, but very few studies from India have investigated this issue. The present study was planned with the aim of evaluating ERG expression in prostatic lesions in Indian patients. Whether ERG expression can be a useful marker for differentiating benign from malignant prostatic lesions is also explored.

Aims and objectives

The primary aim of the study was to investigate ERG expression in different premalignant and mimicker lesions of the prostate. Its utility for differentiating benign and mimicker lesions from PCa will also be studied.

MATERIALS AND METHODS

The study was conducted in the Department of Pathology at Integral Institute of Medical Sciences and Research (IIMSR), Lucknow, after obtaining approval from the Institutional Research and Ethics Committee (Approval no: IEC/IIMS&R/2021/35). The study period was from January 2020 to September 2022. A total of 50 cases of prostatic tissue showing BPH, benign mimicker lesions, premalignant, or malignant lesions of prostate were included in the study. Patients of prostatic cancer who received adjuvant chemo/radiotherapy before surgery were excluded from the study. The specimens were collected in 10% neutral buffered formalin and processed as per standard protocol. Tissue sections stained by Haematoxylin and Eosin stain were evaluated for initial histological diagnosis. Immunohistochemical (IHC) demonstration of ERG antigen using rabbit monoclonal antibody against ERG (clone EP111, Diagnostic Biosystems) was carried out by PAP technique. P_{63} immuno-staining was employed for the demonstration of basal cells in problematic cases (using clone DBR-16.1 of Diagnostic Biosytems as the primary antibody). Following staining protocol was used for immune-histochemical demonstration of ERG and P_{63}. Sections of 2–3 micron thickness from formalin-fixed paraffin-embedded tissue blocks on charged microscopic slides were heated for 60 min at 60°C. Sections were subsequently deparaffinized in three changes of xylene for 10 min each, followed by sequential immersion in a graded series of ethyl alcohol (100–70% concentration) for 3 min each. Antigen retrieval was done by immersion in 10× Tris-EDTA retrieval buffer (pH 9.0) for 20 min at 95°C. After rinsing in wash buffer, endogenous peroxidase activity was blocked using a 4% solution of hydrogen peroxide in methanol for 10 min. This was followed by the application of primary antibody (60 min at room temperature), three changes of wash buffer (3 min each), application of secondary antibody-conjugated polymer (incubation for 12 min at room temperature), two changes of rinsing in wash buffer and incubation in diaminobenzidine chromogen (5 min at room temperature). After rinsing in three changes of wash buffer (3 min each), sections were counter-stained with hematoxylin and eosin (10 min). Slides were dried and mounted using DPX mountant. Positive staining for ERG appeared as brown nuclear staining. Staining of endothelial cells within the prostatic tissue served as a built-in control for positive ERG staining. A section of benign breast lesion was used as a positive control for P_{63}. ERG staining was graded as negative, weak positive (1+), or strong positive (2+).

RESULTS

Amongst 50 cases of prostatic lesions included in the present study, BPH was seen in 40% of cases (20 cases), benign mimicker lesions were seen in 34% of cases (17 cases) and malignancy was observed in 26% of prostatic lesions (13 cases). In the malignant group, there were 10 cases of invasive adenocarcinoma. For the purpose of analysis, three cases of PIN were also included in the malignant group (Table 1). Among benign mimicker lesions, there were five cases of basal cell hyperplasia, four of simple atrophy, three

Table 1: Age-wise distribution of different lesions

Age in years	BPH	Mimickers	PCa
40–50	0	01	1
51–60	05	07	04
61–70	08	06	04
71–80	06	03	04
81–90	01	0	0
Total	20	17	13

BPH: Benign prostatic hyperplasia, PCa: Prostate cancer

of post atrophic hyperplasia, and five cases of adenosis. In conjunction with histomorphological changes, all cases showing positive staining for P_{63} were labeled as BPH or benign mimicker lesion.

Age-wise distribution of different lesions included in our study is shown in Table 1.

ERG expression in different prostatic lesions in our study is shown in Table 2.

As shown in Table 2, all cases of BPH (Figure 1a and b) and benign mimicker lesions were negative for ERG expression (Figure 2a and b). In the malignant group, one out of three cases of PIN (Figure 3a and b) and four out of 10 cases of invasive PCa were positive for ERG expression (Figure 4a and b). As shown in Figure 3b, ERG positivity Grade 1+ was seen in the case having HGPIN. Patient of carcinoma prostate had ERG positivity ranging from Grade 1+ (Figure 4b) to 2+.

Table 2: ERG expression in different prostatic lesions

ERG expression	BPH	Benign mimickers lesions	PCa*
Negative staining	20/20	17/17	8/13
Weak (1+) staining	0	0	2**
Strong (2+) staining	0	0	3

*PCa includes cases of invasive PCa as well as PIN, ** 1 case of invasive carcinoma and 1 case of PIN, BPH: Benign prostatic hyperplasia, PCa: Prostate cancer, ERG: E26 transformation-specific related gene

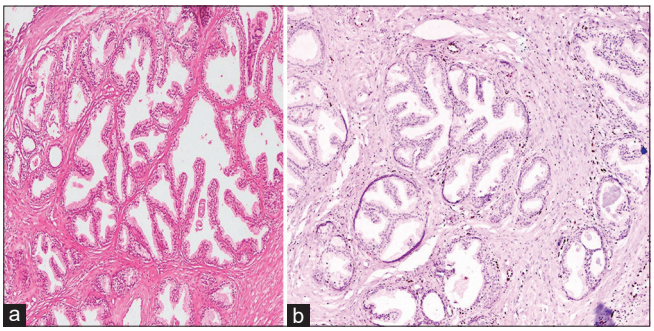

Figure 1: (a) H and E-stained slide of benign prostatic hyperplasia (×100). (b) Case of benign prostatic hyperplasia illustrated in Figure 1a showing the absence of E26 transformation-specific-related gene staining on immunohistochemical (×100)

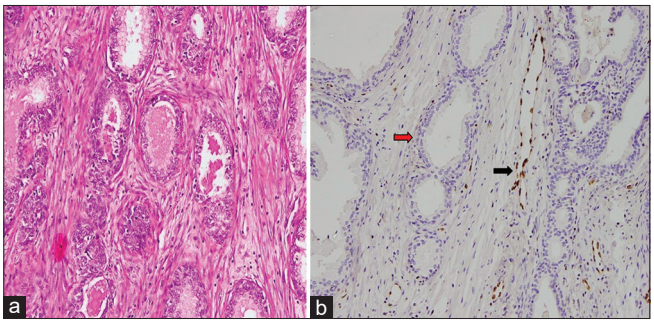

Figure 2: (a) H and E-stained section of a case showing atypical adenosis (×200). (b) Case illustrated in Figure 2a with negative E26 transformation-specific related gene staining of glandular epithelium (red arrow). Vascular endothelium (internal positive control) showing positive E26 transformation-specific-related gene staining (black arrow) (×200)

DISCUSSION

PCa is one of the most common cancers worldwide and currently, it is the second most common cause of cancer-related deaths among men. Clinical course of PCa is highly variable from purely indolent to highly aggressive. Unfortunately, current clinicopathological parameters can foretell the unpredictable behavior of PCa to a limited extent only. They also fail to provide adequate information for selecting optimal treatment in an individual patient. Hence, novel prognostic and predictive tools are needed to institute personalized therapy in patients of PCa. Lately, it has become evident that PCa shows remarkable genetic heterogeneity and this can help in explaining the variability of clinical response to currently administered treatment. Compared to other cancers, PCa shows a low mutation rate and few chromosomal gain and loss events; but gene fusion, caused by chromosomal rearrangements

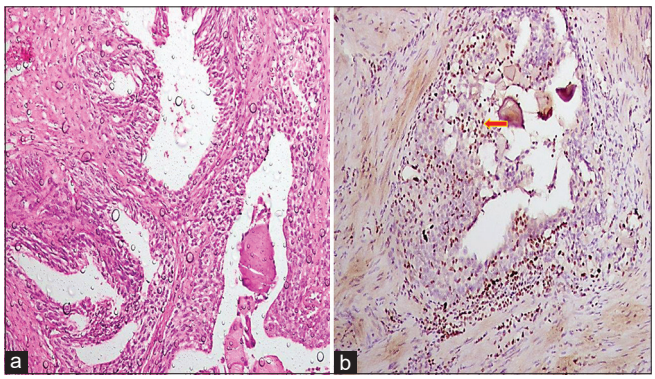

Figure 3: (a) H and E-stained section of high-grade PIN (Negative for P63) (×200). (b) A case of high-grade PIN illustrated in Figure 3a showing positive E26 transformation-specific-related gene staining (red arrow) (×200)

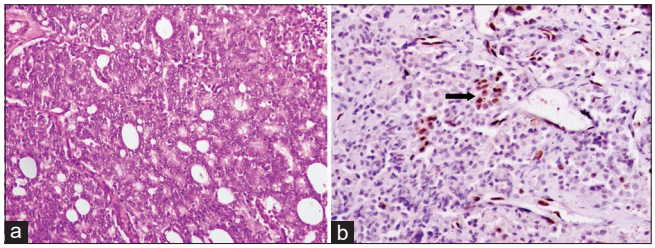

Figure 4: (a) H and E-stained section of a case of adenocarcinoma prostate (×200). (b) Case illustrated in figure 4a showing E26 transformation-specific related gene positivity (black arrow) (×400)

is found in approximately half of the patients.[19] The most frequent gene fusion seen in PCa (in >90% cases) involves 5' untranslated promoter region of TMPRSS2 (serine protease transmembrane protease 2) with coding region of the transcription factor, v-ets avian erythroblastosis virus E26 oncogene homolog (ERG) of the ETS gene family.[20] ETS family represents a large family of 28 human transcription factors. Definitive evidence of the causal role of ETS factors in human malignancy was first discovered in Ewing's sarcoma that revealed recurrent translocations between the EWSR1 gene on chr 22 (one of the members of ETS family) and the FLI1 gene on chr 11.[21] In morphologically normal prostate epithelial cells, ERG proto-oncogene is dormant and ERG transcript or protein products are undetectable.[4,8] TMPRSS2-ERG fusion in PCA results in unscheduled expression of ERG fusion transcript with resultant production of ERG oncoprotein. ERG oncoprotein shows deletion of 32 amino acids at the N terminal end.[20] In the absence of these amino acid sequences, ERG becomes more stable due to increased resistance. ERG becomes more stable due to increased resistance to ubiquitin- proteasomal degradation. This results in uncontrolled cell proliferation.

Toubiquitin-proteasomal degradation. This results in uncontrolled cell proliferation.[22] TMPRSS2-ERG gene fusion is found in 40–60% of PCa patients of Caucasian origin with low prevalence among African-Americans and Asians. Apart from the oncogenic potential of ERG activation in PCa tumorigenesis, its usefulness in diagnosis, prognostication, and potential therapeutic stratification of patients is also being investigated.[23] In large cohort studies among African Americans, Caucasian Americans, and Chinese men lower Gleason score and lower clinical T-stage was reported among ERG positive PCa patients. Thus, ERG-negative PCa patients are more likely to have an adverse outcome.[24,25]

Studies indicate that considerable variation exists in different ethnic and racial groups as far as TMPRSS2–ERG genomic fusions and/or ERG protein expression is concerned.[26] There are very few studies from India which have investigated ERG expression in prostatic lesions and they show conflicting results. In one study of Indian patients with PCa, the prevalence of ERG gene rearrangement was found to be similar to that observed in the Caucasian population but differed from the results seen in Japanese and Chinese patients.[5] In another study, the prevalence of TMPRSS2-ERG genetic rearrangement was seen in only 27% of Indian patients.[17] Earlier detection of TMPRSS2–ERG fusions using fluorescence *in situ* hybridization (FISH) was cumbersome and impractical for routine use. The development of ERG-specific antibodies has made rapid evaluation of ERG possible by IHC methods.[20] Results of ERG oncoprotein detection using immunohistochemistry are highly concordant with FISH and are more applicable for clinical use.[27] In view of greater role, ERG detection may play in personalized therapy of PCa in the future, the present study was planned to evaluate ERG expression in patients of prostatic diseases seen in our institution. It utility in differentiating benign, benign mimicker, and malignant lesions of prostate was also analyzed.

In our study, BPH was seen most commonly in the age group of 61–70 years. This is in concordance with other studies from India but differs from the study by Bhat et al.,[28] who found this disorder to be most common in the age range of 70–79 years. In our study, PCa was seen equally distributed 6th–8th decades. However, the number of cases is not large enough to reach any definite conclusion. In our study, the expression of ERG in BPH in our study is compared with findings of some other researchers in Table 3.

ERG expression was not seen in any of our cases of BPH. This differs somewhat from the findings of Velaeti et al.,[11] and Tomlins et al.,[12] who found ERG expression in a very small percentage of their cases of BPH.

In Table 4, ERG expression in benign mimicker lesions in our study is compared with findings of some other workers. Results of our study concur with findings of other workers.

In Table 5, the expression of ERG in PCa in our study is compared with the findings in some other studies from outside India.

Our findings of ERG expression in PCa are similar to the overall results reported by Kelly et al., and Liu et al., but differ significantly from the findings of Bismar et al. However, in the study of Kelly et al., although the overall rate of ERG positivity was 39.2%, in their Malaysian-Indian cohort, the positivity rate was 63%.

In Table 6, we have compared our findings of ERG expression in PCa with some other studies from India.

As shown from Table 6 above, in our study, ERG expression in PCa is more than what is reported in the series by Rawal et al., and Bhanushali et al., Rawal et al.,[17] and Bhanushali et al.,[18] employed FISH technique and Ateeq et al.,[5] employed IHC for demonstration of ERG expression. Previous studies indicate that methodology used for detection of TMPRSS2: ERG fusion can have an effect on the detection rate; it being highest by reverse transcription polymerase chain reaction (52%) and IHC (52%) and lesser for FISH (42%).[29]

Table 3: Comparison of ERG expression in BPH in some studies

S. No.	Study	BPH (n)	ERG expression (n)	%age of cases with positive expression
1	Present study	20	0	0
2	Ibrahim et al.[9]	17	0	0
3	Lee et al.[10]	31	0	0
4	Velaeti et al.[11]	115	3	2.6
5	Tomlins et al.[12]	162	2	1.2

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

Table 4: ERG expression in benign mimicker lesions of prostate in some studies

S. No.	Study	Mimickers (n)	ERG expression (n)	%age of cases with positive expression
1	Present study	17	0	0
2	Lee et al.[10]	31	0	0
3	Liu et al.[13]	18	0	0
4	Green et al.[14]	45	0	0

ERG: E26 transformation-specific-related gene

Table 5: Comparison of ERG expression in PCa in some studies

S. No	Study	PCa (n)	ERG expression (n)	% age of cases with positive expression
1	Present study	13*	05**	38.5
2	Kelly et al.[15]	120	47	39.2
3	Liu et al.[13]	90	40	44
4	Bismar et al.[16]	136	22	16.1

*PCa includes cases of invasive PCa as well as PIN, **Four cases of invasive carcinoma and one case of PIN, PCa: Prostate cancer, ERG: E26 transformation-specific related gene

Table 6: ERG expression in PCa in studies from India

S. No	Study	PCa (n)	ERG expression (n)	% age of cases with positive expression
1	Present study	13	05	38.5
2	Ateeq et al.[5]	94	46	48.9
3	Rawal et al.[17]	30	8	27
4	Bhanushali et al.[18]	102	27	26

PCa: Prostate cancer, ERG: E26 transformation-specific-related gene

In conclusions, we found that ERG expression is not a very sensitive marker for the detection of PCa as such but it may have potential as a diagnostic biomarker in patients with ambivalent results with P_{63} and AMACR. Further, its evaluation identifies a subset of PCa patients and indicates genetically heterogeneous nature of this disease. This will have implications in triaging patients for evolving therapies targeting ERG. Although prognostic value of this fusion in PCa patients is unclear as yet, in few studies, it has been linked with favorable prognosis[30] and with recurrence and aggressiveness in others.[31] Some studies indicate a high association between ERG-positive high-grade PIN and PCa. This prompts better follow-up of ERG-positive high-grade PIN patients for the detection of subsequent development of PCa.[10]

Limitations of the study

Lack of follow-up data of patients and correlation between ERG expression and prognosis.

CONCLUSION

We found that ERG is expressed in 38.5% cases of PCa. Its expression is absent in benign and mimicker lesion of the prostate. We conclude that ERG expression is not a very sensitive marker for detection of PCa. However, it may be useful as diagnostic marker in patient with ambivalent result with P63 and AMACR.

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Author's Contribution:
RC- Design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation; **PT-** Concept, design, definition of intellectual content, manuscript preparation, manuscript editing, manuscript review; **AR**-Definition of intellectual content, manuscript reviewing; **NK-** Definition of intellectual content, manuscript reviewing.

Work attributed to:
Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India.

Orcid ID:
Rishabh Chaudhary - https://orcid.org/0009-0009-2784-5154
Pradeep Tandon - https://orcid.org/0000-0002-4976-6707
Anubhav Raj - https://orcid.org/0009-0005-0638-3780
Nausheen Khan - https://orcid.org/0000-0001-5693-0061

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