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***Corresponding author**

Pinuccia Faviana, Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Via Roma 57, 56126 Pisa, Italy

Intraductal Prostate Carcinoma an Aggressive Variant. Histopathological Analysis and Evaluation of the Correlation with erg and p63

Pinuccia Faviana[1], Riccardo Bartoletti[2], Marco Panichi[2], Francesca Manassero[2], Fabiola Farci[1], Annamaria Bartolucci[1], Simona Ortori[2], Luca Galli[3], Ramona Baldesi[2], Cesare Selli[2] and Laura Boldrini[1]

[1]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Italy
[2]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy
[3]Department of Oncology, Azienda Ospedaliero-Universitaria Pisana and University of Pisa, Italy

Abstract

Objective: Intraductal Carcinoma of the prostate (IDC-P) is a malignant lesion characterized by an expansive proliferation of malignant prostatic epithelial cells within ducts and acini. TMPRSS2-ERG is the most common ERG gene fusion in prostate cancer, and represents an early event in prostate cancer progression in particular as regard IDC-P. P63 is a homologue of the p53 tumor suppressor gene. We evaluated the presence of IDC-P and its putative correlation with other pathologic features, including ERG and p63 expression.

Method: The series consisted of 79 prostate cancer cases. IDC-P was classified on hematoxylin and eosin-stained. Two unstained tissue sections were collected for IHC, staining with anti-p63 and TMPRSS2- ERG.

Results: ERG expression was seen in 43.03% (34/79): it was widely positive, with negative immunostaining for p63, in the intraductal component of 12 /13 (92.3%) in the high grade cases with relapse, of 18/29 (62%) in the high grade group within relapse, and of 4/7 (57.15%) in the low grade group with relapse. In our study, IDC–P and high ERG expression was associated with aggressive disease (higher Gleason grade, pathologic stage and preoperative PSA) and adverse clinical outcomes (biochemical and disease recurrence).

Conclusions: ERG over expression in IDC-P was much more common in peripheral zone prostate cancers than in the transitional zone. In our hands, ERG immune positivity was related either to aggressive local tumor characteristics or to a worse outcome. Further studies will be required to identify the subgroup of prostate cancers in which TMPRSS2/ERG fusion may be prognostically important.

Introduction

Intraductal Carcinoma of the prostate (IDC-P) is a malignant lesion characterized by an expansive proliferation of malignant prostatic secretory epithelial cells within prostatic ducts and acini and demonstrates significant architectural and cytological atypia [1]. The presence of IDC-P in a specimen is frequently associated with large tumor volume, advanced disease stage, high Gleason score, and increased risk of recurrence [2]. The diagnostic criteria and clinical significance of this entity continue to evolve as more studies are undertaken, and advances

in the understanding of its' pathogenesis are supported by immunohistochemical and genetic markers. IDCP was historically a term used variably to describe prostatic acinar adenocarcinoma, prostatic ductal adenocarcinoma and urothelial carcinoma extension into prostatic ducts and acini [3]. Now, IDC-P is a term that refers specifically to prostatic adenocarcinoma extending into and proliferating within preexisting prostatic ducts, first detailed by Kovi et al in 1985 [4]. All intraductal lesions that appear more atypical either architecturally or cytologically than typical HGPIN should be evaluated carefully for the presence of IDC-P. The definition of IDC-P relies a series of morphological criteria that have been evaluated by different authors [5-6] it can exhibit a variety of growth patterns, including loose or dense cribriform, solid, micropapillary and rarely, flat architecture. The cells exhibit cuboidal or columnar cytological features with significant nuclear enlargement [7]. Several similar diagnostic criteria schemes for the morphologic diagnosis of IDC-P have been proposed: [8] the major diagnostic criteria for IDC-P include 1) solid or dense cribriform architecture (defined as atypical cells spanning greater than 50% of the glandular lumina), 2) marked nuclear atypia or pleomorphism with nucleomegaly (≥six times normal) and 3) non-focal comedonecrosis [9]. The presence of any of these criteria is considered diagnostic for IDC-P in conjunction with the presence of medium to large sized ducts or glands with at least partial preservation of an identifiable basal cell layer. Minor criteria for IDC-P that are often present and helpful but not diagnostic include 1) involvement of greater than six glands and/or ≥1 mm size, 2) atypical glands that are irregular or branching at right angles, 3) increased mitotic activity with frequently identified mitotic figures and 4) two distinct cell populations comprising of an outer layer of pleomorphic, mitotically active cells and a central component of cuboidal, monomorphic cells without mitotic activity [9-11]. In IDC-P with two morphologically distinct cell populations, the outer layer of pleomorphic cells does not stain strongly with Prostate-Specific Antigen (PSA), whereas the inner monomorphic cells demonstrate strong PSA positivity [12]. Immunohistochemistry (IHC) is also considered helpful in establishing a diagnosis of IDC-P in terms of confirming the presence of at least an incomplete or partial basal cell layer around the atypical glands. Since the initial studies by Kovi et al [4] and McNeal et al [5] several other studies have investigated IDC-P in radical prostatectomy and consistently found that the presence of IDC-P correlated with other adverse pathologic features, including higher Gleason score, larger tumor volume and greater probability of extraprostatic extension, seminal vesicle invasion and pelvic lymph node metastasis. It also correlated with decreased progression-free survival and with postsurgical, biochemical recurrence [12-14]. Cohen et al studied a small series of radical prostatectomy specimens with matching preoperative needle biopsy specimens and found that the inclusion of IDC-P in prostate biopsies in a preoperative model could improve the prediction of the pathologic stage of the radical prostatectomy specimens. Furthermore, the presence of IDC-P on biopsy correlated strongly with biochemical failure [12] . Recurrent gene fusions involving ERG are the most frequent genetic alteration in prostate cancer and result in overexpression of the nuclear transcription factor ERG [13-15]. TMPRSS2-ERG is the most common ERG gene fusion in prostate cancer, occurring in approximately 40-50% of tumors and when present, this gene fusion represents an early, clonal event in prostate cancer progression, in particular as regard IDC-P.

p63 is a homologue of the p53 tumor suppressor gene. The knowledge that basal cells are invariably absent from the malignant glands of prostatic adenocarcinoma and the ability of immunohistochemical staining for high molecular weight cytokeratin to detect basal cells have proven to be diagnostically invaluable [16-19]. This is particularly true for small foci of carcinoma commonly seen in needle biopsy specimens. From a biological perspective, it has been postulated that the basal cells represent the reserve cell compartment within the prostatic epithelium [20-24] and that interruption and loss of the basal cell layer are important steps in the genesis of invasive carcinoma from the putative precursor lesion, prostatic intraepithelial neoplasia or IDC-P [25-27]. However, the presence of clearly identifiable basal cells in a gland or duct does preclude the diagnosis of carcinoma for that structure.

Cases and Clinical Information

The series consisted of 79 prostate cancer cases which were retrieved from Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa.

All patients undergoing radical prostatectomy in this series were operated upon by a single surgeon at Urological surgery between 2004 and 2015 and had received adjuvant or neoadjuvant hormone therapy or adjuvant radiotherapy. Serum Prostate-Specific Antigen (PSA) levels were drawn within 1 month before surgery (preoperative PSA level). All cases had been previously diagnosed by pathologists subspecialized in urologic pathology. According to previous reports [25,26], biochemical recurrence was defined as serum PSA ≥ 0.2 ng/ml after a previously undetectable serum PSA value.

Histological Evaluation

Hematoxylin and eosin stained (HE) slides that had been prepared from Radical Prostatectomy (RP) specimens were re-evaluated by a genitourinary pathologist. The following pathological parameters were analyzed for each patient: Gleason score, Surgical Margin (SM); and the presence of IDC-P, Extraprostatic Extension (EPE), Seminal Vesicle Invasion (SVI) and Lymph Node Metastasis (LN). bGS was also revaluated according to the 2016 International Society of Urological Pathology (ISUP) grading system.

Intraductal carcinoma

IDC-P was defined according to the McNeal criteria [5], which, in brief, are well-circumscribed lesions bound by an intact basal cell and distended by overtly malignant-appearing epithelial cell populations. These lumen-spanning lesions are found almost exclusively in close proximity with invasive cancer (Figure 1).

Immunohistochemistry

IHC analysis was done; sections were cut with four microns thickness from paraffin embedded, formalin fixed blocks. Two unstained tissue sections were collected for IHC, staining with anti-p63 (4A4, Ventana) mouse monoclonal primary antibody, and TMPRSS2-ERG, (EPR3864 anti-ERG, Ventana) rabbit monoclonal

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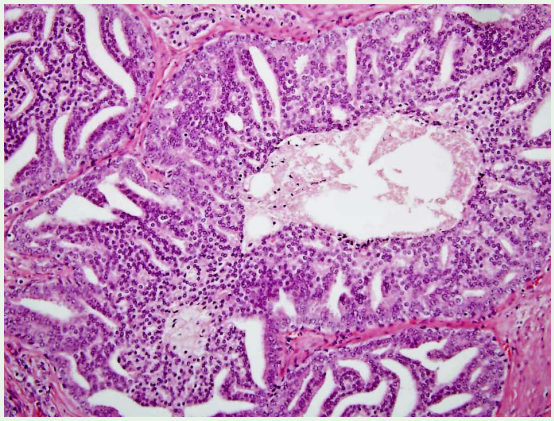

Figure 1: Histological features of intraductal cancer of theprostate (IDC-P). Large caliber smooth contoured ducts surrounded by basal cells.

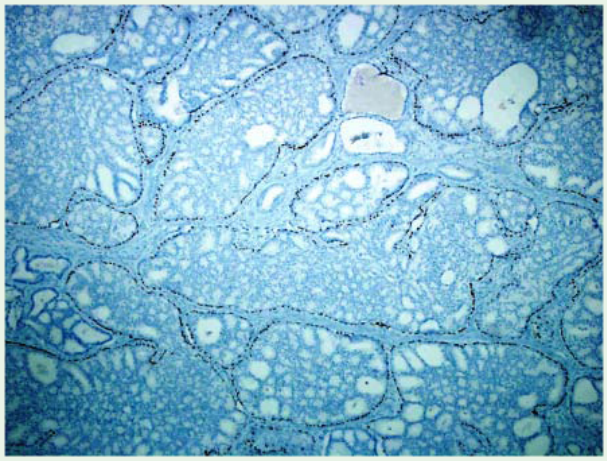

Figure 2: Complete positivity of P63.

primary antibody. Also, there were a negative internal control for p63 and ERG, the same tissue without primary antibody (p63 and ERG staining is nuclear).

All IHC staining slides were evaluated with light microscope. Nuclear staining for p63 (Figure 2) was determined to be negative when completely absent, positive, strongly complete, or focally. With regard to nuclear staining for ERG (Figure 3) because ERG-positive tumors showed positivity in over 75% of cells and intensity was uniform, we expressed the results of staining as positive or negative ERG.

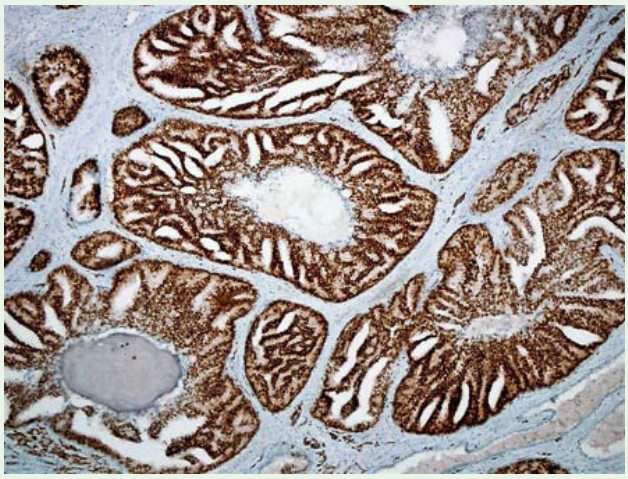

Figure 3: Strong nuclear expression of ERG.

Follow-up

Complete baseline and follow-up data were available for all the 79 patients. PSA was measured every 3 months after prostatectomy. CT or MRI was performed at least every 6 months after patients were diagnosed. Bone scintigraphy was also performed when bone metastases were suspected. Clinical progression was defined as

Table 1: Clinical and pathological characteristics.

	N°	GS	TNM	IDC-P
High Grade with relapse	13	9-Aug	3 (pT2c)	Present
			4 (pT3a)	
			6 (pT3b)	
High grade no relapse	29	14: (4+3)	1 (pT2a)	Present (18)
		10:08	1 (pT2b)	Absent (11)
		5:09	6 (pT2c)	
			10 (pT3a)	
			11 (pT3b)	
Low grade with relapse	7	4 (3+4)	6 (pT2c)	Present focally (4)
		3 (3+3)	1 (pT3a)	Absent (3)
Low grade no relapse	30	15 (3+4)	1 (pT2a)	Absent
		15 (3+3)	3 (pT2b)	
			23 (pT2c)	
			3 (pT3a)	

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Table 2: Valuation of ERG and p63 expression in the intraductal component of prostate cancer.

High grade with relapse (13)	ERG expression in intraductal component		p63 expression in intraductal component			Biochemical recurrence	Lymph node Metastasis
	Positive	Negative	Focal	Diffuse	Negative		
EPE : 4 (30,7%)							
VSI : 6 (46,15%)							
Margin+: 9 (69,2%)							
IDC-P: 12 (92,3%)	12 (92,3%)	1 (7,69%)		12 (92,3%)	1 (7,69%)	7 (53,8%)	6 (46,15%)
High grade within relapse (29)							
EPE : 10 (29%)							
VSI : 11 (37,9%)							
Margin+: 21 (72,4%)							
IDC-P: 18 (62%)	18 (62%)	11 (23,5%)		18 (62%)	11 (23,5%)		
Low grade with relapse (7)							
EPE : 0 (0%)							
VSI : 0 (0%)							
Margin+:3 (42,8%)							
IDC-P: 4 (57,14%)	4 (57,15)	3 (42,8%)		4 (57,15%)	3 (42,8%)	7	0
Low grade within relapse (30)							
EPE : 3 (10%)							
VSI : 0 (0%)							
Margin+:10 (33,33%)							
IDC-P: 0 (0%)							

[a]Values are shown as n. [b]p-values are assessed by χ^2 test.

verification of local recurrence, distant metastasis, and/or newly diagnosed lymph node metastasis by any of the above imaging studies.

Result

The clinical and pathological characteristics of the patients in this study are summarized in Table 1. The median age of patients was 69 years.

Intraductal carcinoma occurring with concurrent invasive tumor. ERG expression was seen in 43.03% (34/79): it was widely positive, with negative immunostaining for p63, in the intraductal component of 12 /13 (92.3%) in the high grade cases with relapse, of 18/29 (62%) in the high grade group within relapse, and of 4/7 (57.15%) in the low grade group with relapse (Table 2). IDC -P and high ERG expression was associated with aggressive disease (higher Gleason grade, pathologic stage and preoperative PSA) and adverse clinical outcomes (biochemical and disease recurrence) (Table 3).

Discussion

Prostate cancer is a highly heterogeneous disease, ranging from slow-growing indolent tumors to rapidly progressing fatal carcinomas associated with significant morbidity. Many studies have identified the presence of IDC-P as a prognostic factor for PSA failure after RP [27]. At first, in 1972, Rhamy et al. [1] described the intraductal spread of prostate carcinoma then, McNeal and Yemoto [5] labeled the term IDC-P to emphasize the unbeatable clinical and histological features of this entity. It showed that IDC-P was almost always correlated with adverse pathological characteristics and worse prognosis [27]. The main objective of the current study was to investigate whether ERG immunopositivity was associated with clinical and pathologic phenotypes of IDC-P and whether it could serve as a prognostic biomarker to predict recurrence and mortality. Numerous studies have been published, in the past decade, which generated conflicting results. ERG staining in prostate cancer as positive or negative, only 2 studies, to date, have evaluated the prognostic value of the intensity of ERG staining, which yield conflicting results [28]. Bismar et al [29] have shown a negative correlation between staining intensity and cancer-specific mortality, whereas Spencer et al [30] reported an increased risk of biochemical recurrence, metastasis, and cancer-specific death in prostatic cancer with high ERG intensity. In our hands, there was no association between staining intensity or H-score on one hand and any clinicopathologic or outcome parameters on another hand. In summary, the biological relationship between TMPRSS2/ERG fusion and clinicopathologic parameters, such as PSA level, Gleason score, pathologic stage and prognosis, is not well established, and the results of different studies lack consistency. That being said, the possibility that ERG status may only influence a small subset of prostate cancer cases bearing a unique histologic or molecular signature exists, and such a relationship would be diluted when all prostate cancers are pooled into different studies. In this work we have found that ERG over expression in IDC-P was much more

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Table 3: Correlations between ERG expression and the main clinicopathological characteristics of our 79 prostate cancer patients.

Characteristic	*ERG* expression[a]		p-value[b]
	neg	pos	
Age			
≤69 years	20	20	0.2
>69 years	25	14	
T			
T2 (T2a-T2b-T2c)	33	11	0.0002
T3 (T3a-T3b)	12	23	
N			
N0	10	16	<0.0001
N1	4	13	
Nx	31	5	
Gleason score			
Low (3+3)	17	0	<0.0001
High (7, 8, 9)	28	34	
Margins			
Negative	29	5	<0.0001
Positive	16	20	
Relapse			
Absent	41	18	<0.0001
Present	4	16	
Intraductal			
Absent	45	0	<0.0001
Present	0	34	

[a]Values are shown as n; [bp]-values are assessed by c2 test.

common in peripheral zone prostate cancers in comparison with those of the transitional zone. In our hands, ERG immunopositivity was partially unrelated either to aggressive local tumor characteristics or to a worse outcome. Further studies incorporating thorough morphologic and immunophenotypic features, or using advanced molecular techniques (eg, array-comparative genomic hybridization and next-generation sequencing) to allow the comparison of gene profiles, will be required to identify the subgroup of prostate cancers in which TMPRSS2/ERG fusion may be prognostically important.

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