Intraductal Carcinoma of the Prostate: Precursor or Aggressive Phenotype of Prostate Cancer?

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BACKGROUND. Although the term ''intraductal carcinoma of the prostate'' (IDC-P) was introduced almost 40 years ago, there is still the lack of appreciation that this entity represents a clinically aggressive disease that continues to be misreported under the diagnostic category of high grade prostatic intraepithelial neoplasia (HGPIN).
METHODS. Recent data obtained from histological, molecular, and clinical studies were reviewed to demonstrate that IDC-P significantly differs from HGPIN, and has a major impact in terms of diagnosis, prognosis and therapy of prostate cancer (PCa).
RESULTS. HGPIN is the only accepted precursor of PCa. Its diagnosis in prostate biopsies has no prognostic implications, and does not dictate therapeutic decisions. By contrast, IDC-P correlates with a worse pathological and clinical outcome. IDC-P differs from HGPIN by distinct histological and molecular features. Recent clinical studies report that IDC-P is associated with neoadjuvant androgen deprivation therapy (ADT) and, chemotherapy (CT) failure as well as early disease recurrence after external beam radiation. Finally, IDC-P is associated with TMPRSS2-ERG gene fusion, which was reported to be regulated by estrogens and their receptors.
CONCLUSIONS. IDC-P is an aggressive phenotype of prostate cancer and predicts poor response to ADT, CT, and external beam radiation. IDC-P should be separated from HGPIN and should be reported in prostate biopsies and prostatectomy specimens. *Prostate* © 2012 Wiley Periodicals, Inc.

KEY WORDS: **intraductal prostate cancer; HGPIN; prognosis; androgen deprivation; chemotherapy; radiation therapy**

INTRODUCTION

The term ''intraductal carcinoma of the prostate'' was introduced first by Rhamy et al. [1] almost 40 years ago. McNeal and Yemoto, however, were the first to provide detailed morphological and clinical correlations and proposed the unifying term intraductal carcinoma of the prostate. IDC-P was identified as an independently significant variable in the prediction of pathological stage, tumor volume, and treatment failure [2]. Although the prognostic significance of IDC-P was confirmed by several subsequent studies [3–12], this entity remains controversial.

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Since the introduction of the concept ''High grade prostatic intraepithelial neoplasia (HGPIN)'' by Bostwick and Brawer in 1987, all intraductal neoplastic lesions of prostatic origin, including IDC-P, fall under the unifying term of HGPIN. As a consequence, the diagnosis of IDC-P is frequently not reported, as many pathologists summarize these intraductal malignancies under the diagnostic category of HGPIN [13–15].

Despite its morphology in part resembling HGPIN, IDC-P was considered to represent the intraductal spread of adenocarcinoma [2] and is an unlikely candidate for a premalignant neoplastic condition. While HGPIN is often present in prostate glands that have not yet developed invasive carcinoma, IDC-P is almost always associated with invasive cancer [7,8,16]. IDC-P on prostate biopsies is frequently associated with high-grade cancer and poor prognostic parameters at radical prostatectomy as well as advanced disease following other therapies [2–12,17].

The current review includes current histopathological, molecular, and clinical aspects of IDC-P and highlights the importance of reporting IDC-P in prostate specimens.

RESULTS

Histopathological Criteria

Prostatic intraepithelial neoplasia (PIN) consists of architecturally benign prostatic ducts and acini lined by cytologically atypical cells and is dichotomized into low- and high-grade PIN. At low magnification, PIN glands are of normal caliber, have undulated contours and are lined by epithelial cells that have a typical basophilic appearance, which is due to a combination of nuclear crowding, enlargement, and hyperchromasia, along with amphophilic cytoplasm [18]. 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 [2–12,17] (Table I). The hallmark of IDC-P are large caliber smooth contoured acini and ducts (greater than twice the diameter of normal peripheral zone gland structures) surrounded by basal cells, and filled with cytological malignant cells that, in contrast to those of HGPIN, by definition always span the gland lumen except when associated with necrosis (Fig. 1a,b). The common architectural patterns observed in IDC-P include solid, dense cribriform, loose cribriform, and complex papillary growth pattern (Fig. 1c). In the solid pattern, sheets of malignant epithelial cells fill large acini or prostatic ducts. In the dense cribriform pattern, malignant epithelial cells form closely packed cribriform structures with small rounded and punched out lumens, where solid areas predominated over luminal spaces. In contrast, the loose cribriform pattern contain larger lumina with relatively less epithelium [7].Because of potential morphological overlap between the loose cribriform and micropapillary pattern with HGPIN (Fig. 1d), Epstein et al. required additional features for the diagnosis of IDC-P, that is, marked pleomorphism with large hyperchromatic nuclei (six times larger than those in adjacent normal glandular cells; Fig. 1f), or comedonerosis [7]. IDC-P frequently has two cell populations (Fig. 1e): an outer perimeter cell group that is tall, pleomorphic, and mitotically active (proliferative layer) that stain poorly for prostate-specific antigen (PSA); and a central monomorphic cell group with bland nuclei, abundant cytoplasm containing abundant PSA and occasional extracellular mucin (secretory layer) [8].

The number of duct-spanning glands required for the diagnosis of IDPC-P remains contentious. A single duct- spanning gland with preseved basal cells

TABLE I. Diagnostic Criteria of Intraductal Cancer of the Prostate (IDC-P) and Distinction From High Grade Prostatic Intraepithelial Neoplasia (HGPIN)

Diagnostic criteria	IDC-P	HGPIN
Basal cells (34βE12, p63)	Always present	Always present
Cytological malignant cells	Always present	Always present
Intraluminal bridging	Always present	Never present
Solid growth pattern	Frequent	Never present
Dense cribriform pattern	Frequent	Never present
Loose cribriform pattern	Less frequent	Rare
Complex papillary pattern	Less frequent	Never present
Comedonecrosis	Frequent	Never present
Markedly enlarged nuclei	Less frequent	Never present
Two population of cells	Frequent	Never present

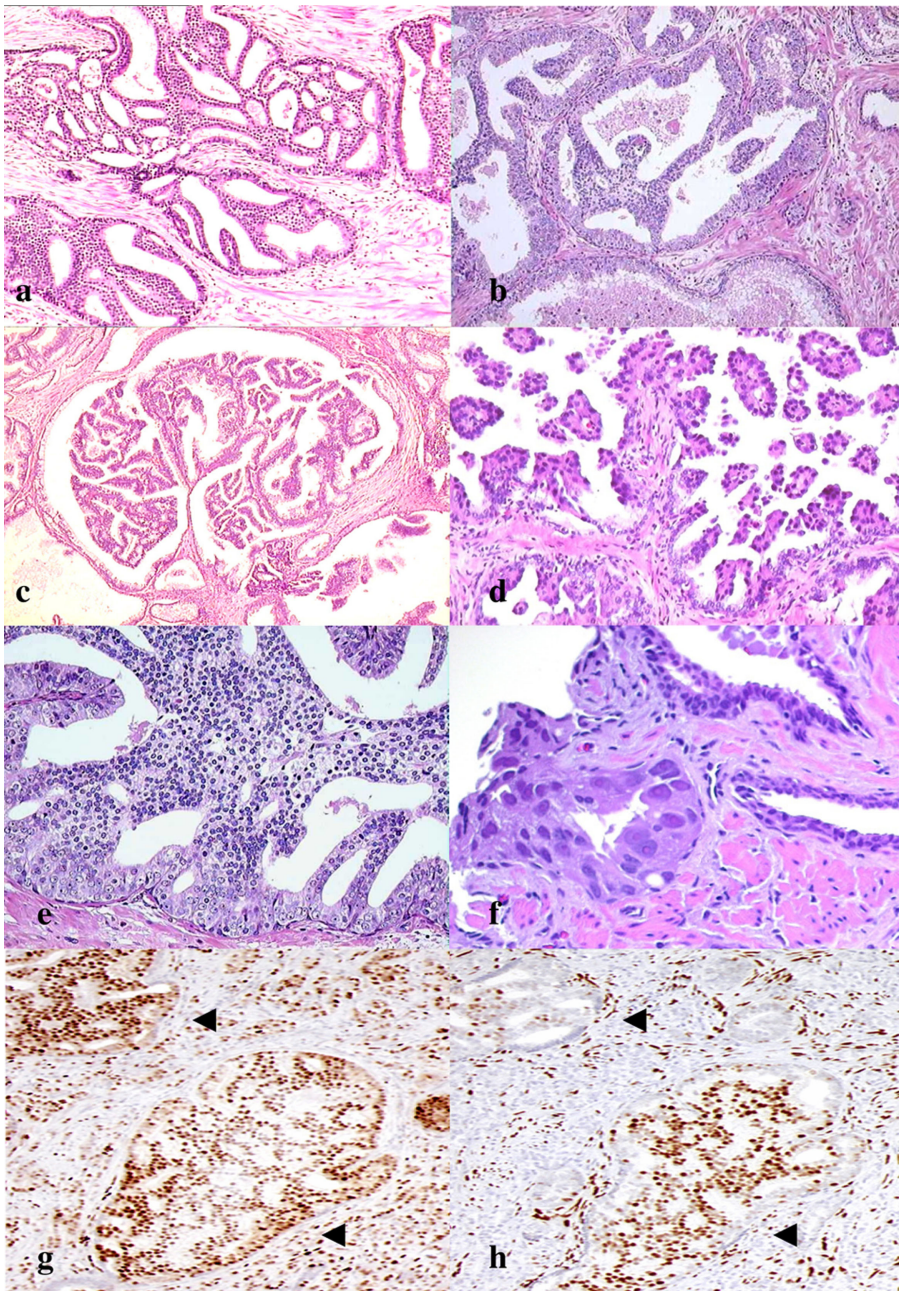

Fig. 1. Histological features of intraductal cancer of the prostate (IDC-P). Large caliber smooth contoured ducts surrounded by basal cells, and filled with a lumen spanning loose cribriform proliferation (**a**). IDC-P with intraglandular bridging (**b**), complex papillary pattern (ductal adenocarcinom type; **c**), complex micropapillary pattern, resembling serous-papillary ovarian cancer (**d**), and two cell type pattern (**e**). IDC-P with large hyperchromatic nuclei (six times larger than those in adjacent normal glandular cells; **f**). Gleason 4/5 pattern prostate cancer with intraductal spread (arrow heads) expressing the progesterone receptor (**g**) and the estrogen receptor α (**h**) on adjacent sections. Original magnifications: a (×50), b (×100), c (×50), d (×100), e (×100), f (×200), g (×50), h (×50).

conforming to diagnostic parameters (Table I) would be sufficient for IDP-P diagnosis. All intraductal lesions that appear more atypical either architecturally or cytologically than typical HGPIN, but do not meet the strict criteria for IDC-P (Table I) should be classified as borderline case between IDC-P and HGPIN.

It is noteworthy that IDC-P in the absence of infiltrating cancer is rare on biopsy [11,16]. On the other hand, the intraductal component of high grade PCa with complex papillary and cribriform growth pattern detected in prostate biopsy are frequently overlooked in the absence of immunohistochemical stains for basal cells.

Solid patterns of IDC-P may mimic intraductal spread of urothelial carcinoma of the prostate. Immunohistochemistry is very helpful in these cases. IDC-P expresses the androgen receptor (AR), frequently at high level, and is usually positive for PSA and PSAP. The expression of basal cell markers is limited to the basal cells of acini or ducts involved by IDC-P. Intraductal urothelial carcinoma lacks AR expression at high level, as well as PSA and PSAP, but is frequently positive for basal cell markers, such as 34βE12, p63, and CK 5/6.

Molecular Studies

Several studies have used molecular techniques, including polymerase chain reaction (PCR), comparative genomic hybridization (CGH) and fluorescence in-situ hybridization (FISH), to delineate molecular differences between HGPIN and IDC-P [5,19,20].

Using polymorphic microsatellite markers frequently lost in PCa, Dawkins et al. have reported loss of heterozygosity (LOH) being absent in Gleason grade 3 cancer, infrequent in HGPIN (9%) and Gleason grade 4 cancer (29%), but common in IDC-P (60%). The authors concluded that IDC-P is a distinct lesion from HGPIN and by contrast, represents a late event in PCa progression [5].

Another study analyzed IDC-P, HGPIN, and invasive PCa by PCR for LOH of the tumor suppressor genes TP53 and RB1, and by comparative genomic hybridization (CGH). At CGH analysis, IDC-P showed several chromosomal imbalances in contrast to HGPIN, where no changes were found. LOH of both TP53 and RB1 were frequently found in IDC-P (52%), followed by extracapsular tumor tissue (44%), invasive cancer (24%), PIN (19%), and benign prostatic tissue (17%) [19].These molecular data suggest that HGPIN and IDC-P are distinct intraductal lesions, where HGPIN is a precursor, and IDC-P an aggressive phenotype of PCa with intraductal spread.

Han et al. have used break-apart FISH assay to assess ETS gene aberrations, a specific and common molecular alteration involving PCa, in a cohort of 16 presumed cribriform HGPIN, and 45 cribriform IDC-P. ERG rearrangement was absent (0 of 16) in isolated cribriform HGPIN, and present in 75% (36 of 48) of cribriform IDC-P. All IDC-P showed concordance of ERG rearrangement status with adjacent invasive cancer [20]. This data further suggest that isolated cribriform HGPIN and IDC-P are biologically distinct lesions. Interestingly, there was no difference between intraductal cribriform lesions with or without marked nuclear atypia (nuclear size 6× normal or larger) and/or comedonecrosis regarding prevalence of ERG rearrangement. The authors concluded that the majority of intraductal cribriform lesions associated with invasive PCa most likely represent IDC-P and not cribriform HGPIN [20].

There is some evidence to suggest that IDC-P may be regulated by estrogens and their receptors. Mosquera et al. [21] have identified five morphological features of PCa associated with TMPRSS2-ERG gene fusion, including blue-tinged mucin, cribriform growth pattern, macronucleoli, signet-ring cell features, and IDC-P. In a subsequent study, the same group of authors has identified an 87 gene expression signature for TMPRSS2-ERG tumors that was associated with estrogen receptor (ER) signaling pathways. TMPRSS2-ERG expression was found to be increased by ERα agonist (estradiol) and decreased by ERβ agonists [22]. In fact, IDC-P and related Gleason pattern 4/5 PCa may express ERα and the estrogen inducible progesterone receptor (PR; Fig. 1g,h), indicating that these tumors are regulated by estrogens and could be targeted accordingly [23].

Histogenetic Aspects

McNeal et al. have provided evidence that both Gleason pattern 4/5 and IDC-P may derive directly from HGPIN [2,24,25]. Similar results have been reported recently in the Lo-MYC and Hi-MYC transgenic mouse model [26]. The authors document a direct linage between HGPIN and intraductal cribriform lesions that progress to microinvasive cancer. These intraductal cribriform lesions resembling IDC-P represent an intermediate step in progression from mouse HGPIN to invasive carcinoma, and are triggered by MYC overexpression [26]. As IDC-P is frequently associated with Gleason pattern 4/5, and not with Gleason pattern 3 cancers (using the 2005 modified Gleason grading), it might be argued that PCa originating from the IDC-P lineage behave distinctly more aggressive over time as compared to those which do not have an IDC-P origin. This is in line with previous studies showing that several chromosomal anomalies including MYC gene amplification (8q24) are almost identical in so called ''cribriform HGPIN,'' cribriform carcinoma, and Gleason primary pattern 4/5 tumors [27]. Alternatively, one cannot exclude that in some cases, IDC-P derives from Gleason pattern 4/5 tumors that spread back into pre-existing ducts using these natural passages as low-resistance highways of rapid growth [8].

Clinical Implications

The diagnosis of HGPIN in prostate biopsies does not dictate therapeutic decisions, and has no prognostic implications in terms of PSA recurrence after prostatectomy [14,15]. By contrast, the presence of IDC-P

in prostate biopsies is frequently associated with high-grade cancer and poor prognostic parameters at radical prostatectomy [2–12]. In a study of 130 radical prostatectomies, McNeal et al. have found a strong association of IDC-P with high Gleason score, large tumor volume, positive surgical margins, and extensive perineural invasion, all of which contributed to an increased risk of progression following prostatectomy. IDC-P was an independently significant variable in the prediction of pathological stage, tumor volume, and treatment failure [2]

Recent clinical studies indicate that intraductal spread predicts poor response to neoadjuvant chemotherapy, androgen deprivation therapy (ADT), and external beam radiation [28–30]. To identify morphologic features of preoperatively treated PCa that predict outcome, Efstathiou et al. [28] have performed a detailed morphologic evaluation of specimens obtained from 115 patients with high-risk PCa who had preoperative androgen ablation, alone or in combination with chemotherapy. Multivariate analysis on prostatectomy specimens identified the presence of cribriform pattern or intraductal spread (IDC-P) as a stronger predictor of early (<4 year) biochemical relapse than pathologic stage, tumor volume, PSA level at diagnosis, and biopsy Gleason score [28].

O'Brien et al. [29] have assessed the clinical significance of post-chemotherapy tumor histopathology in 50 high-risk prostate cancers treated with pre-prostatectomy docetaxel and mitoxantrone. In univariate analyses, IDC-P ($P = 0.001$) and cribriform pattern of PCa ($P = 0.014$) were associated with shorter relapse-free survival (RFS). In multivariate analyses, baseline PSA ($P = 0.004$), lymph node metastases ($P < 0.001$), and cribriform histology ($P = 0.007$) were associated with shorter RFS. In multivariable logistic regression analysis, only IDC-P ($P = 0.007$) predicted lymph node metastases. This indicates that IDC-P and cribriform growth pattern of PCa predict post-chemotherapy outcome [29].

A recent study has assessed the prognostic significance of IDC-P in biopsies and transurethral resections prior to external beam radiotherapy with or without ADT. In a series of 118 intermediate, and 132 high risk PCa patients, IDC-P was identified as an independent prognosticator of early biochemical relapse (<36 months) and metastatic failure after radiotherapy [30]. IDC-P could be identified in about 20% of the biopsies of the patients with intermediate and high risk prostate cancer and is therefore not a rare finding [30].

DISCUSSION

HGPIN is accepted by most of urologists and pathologists as a facultative precursor of PCa. Nevertheless, the current definition of HGPIN also includes unusual HGPIN variants with signet-ring, and small cell neuroendocrine features [15,18]. The mean survival of patients with signet-ring and small cell neuroendocrine carcinoma is 28 and 9–17 months, respectively [31]. Classifying intraductal spread of these very aggressive tumor entities under the category of HGPIN is problematic, because these tumors are most unlikely facultative precursors, but lethal subtypes of PCa. In the same way, IDC-P does not meet the criteria of a facultative precursor, but is an aggressive phenotype of PCa, and cannot be merged with HGPIN under the same diagnostic category. Given the prognostic impact of IDC-P, a Gleason grade should be assigned for each IDC-P and incorporated in the Gleason score both in biopsies and in prostatectomy specimens. In general, the various growth patterns of IDC-P and fall into the Gleason pattern 4/5 categories based on the 2005 modified Gleason grading (Table II).

The incidence of IDC-P in prostatectomy specimens depends on tumor volume. In the series of McNeal, IDC-P was observed in 10% of cases with tumor volume less than 2 ccm, 28% in tumors between 2 and 4 ccm, and 47% in tumors larger than 4 ccm [2]. In prostatectomy specimens, IDC-P is virtually always associated with invasive cancer, which makes the diagnosis of intraductal spread and its separation from HGPIN much easier than in cases of isolated IDC-P in prostate biopsy. Given its prognostic significance, the amount or percent of IDC-P should be reported. A new postoperative nomogram incorporates IDC-P as a variable, and may enhance prediction [32].

Reporting IDC-P on prostate biopsies both as a rare isolated finding and as a more common finding in combination with prostatic adenocarcinoma is of paramount importance, because its diagnosis has, in apparent contrast to HGPIN, profound prognostic implications, and may influence therapeutic decisions. IDC-P on prostate biopsies is frequently associated with high-grade cancer and poor prognostic parameters at

TABLE II. Growth Pattern of Intraductal Cancer of the Prostate (IDC-P) and Their Correlation With Primary Gleason Grades (GG) Based on the 2005 Modified Gleason Grading

IDC-P Pattern	GG
Solid	5
Cribriform	4
Cribriform with CN	5
Complex papillary	4
Complex papillary with CN	5
Intraluminal bridging	4

CN, comedonecrosis.

radical prostatectomy as well as advanced disease following other therapies [2–12]. In a recent study enrolling 250 patients with intermediate and high risk PCa, the presence of IDC-P in prostate biopsies was identified as an independent prognosticator of early biochemical relapse (<36 months) and metastatic failure after radiotherapy [30]. This indicates that IDC-P is a significant risk factor for radiation therapy failure. In the presence of IDC-P on prostate biopsies, radical prostatectomy combined with extended lymphadenectomy may be more effective in improving survival than radiotherapy.

IDC-P in the absence of infiltrating cancer is rare on biopsy. In a series of 83 men in whom biopsy showed only IDC-P, Robinson and Epstein [11] have reported the pathological outcome with extraprostatic extension in 51% of cases and an average Gleason score of 7.9 at radical prostatectomy. While the presence of HGPIN in prostate biopsies has no prognostic implications at the time of prostatectomy, and does not dictate therapeutic decisions, definitive therapy is recommended in men with IDC-P on needle biopsy even in the absence of infiltrating cancer. In borderline case between IDC-P and HGPIN that do not meet the strict criteria for IDC-Pa on needle biopsy immediate repeat biopsy is recommended [7,8,11,12].

Another feature of IDC-P refers to the TMPRSS2-ERG gene fusion, which is regulated by estrogens and their receptors [22]. Pharmacological inhibition of TMPRSS2-ERG gene fusion IDC-P using drugs that antagonize ERα and PR activity may have a promise as new therapeutic strategy for this aggressive subtype of PCa [22,23]. However, this issue warrants further evaluation in clinical studies.

CONCLUSION

Current histopathological, molecular, and clinical characteristics identify IDC-P as an aggressive phenotype of PCa, and clearly separate this entity from HGPIN which is a facultative precursor of PCa. The most prevalent growth patterns of IDC-P fall into the Gleason pattern 4/5 categories. The diagnosis of IDC-P on prostate biopsy predicts high-grade cancer and poor prognostic parameters at radical prostatectomy, and poor response to neoadjuvant ADT, CT and external beam radiation. Reporting IDC-P in prostate biopsy and prostatectomy specimens has a major impact in terms of diagnosis, prognosis, and therapy of prostate cancer.

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