High-grade Prostatic Intraepithelial Neoplasialike Ductal Adenocarcinoma of the Prostate: A Clinicopathologic Study of 28 Cases

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Abstract: Most of the prostatic ductal adenocarcinomas of the prostate are characterized by cribriform and/or papillary architecture lined by columnar pseudostratified malignant epithelium. We report 28 cases of ductal adenocarcinomas on needle biopsy and transurethral resection of prostate closely resembling high-grade prostatic intraepithelial neoplasia (HGPIN) composed of simple glands with flat, tufting, or micropapillary architecture. The mean age of the patients was 68 years (range, 50 to 91 y). Prostate specific antigen serum level at diagnosis ranged from 1.2 to 12.1 ng/mL. Treatment included radical prostatectomy (n = 9), hormone therapy (n = 7), radiotherapy (n = 5), and cryotherapy (n = 1). Three patients had recent biopsies without information on treatment and 3 patients were lost to follow-up after diagnosis. The number of cores involved by tumor in each case ranged from 1 to 18, with more than 1 core involved in 13 cases. Flat was the most common pattern (42%), followed by tufted (41%), and micropapillary (17%) (some with more than 1 pattern). Fourteen cases revealed segments of dilated gland on the edge of the biopsies, suggesting a large gland component. In radical prostatectomies, tumor was primarily composed of small (25%), medium (17%), or cystically dilated (58%) cancer glands, with all cases demonstrating a mixture of different gland sizes. Cytologically, tumors were characterized by tall columnar atypical cells, basally located nuclei, and amphophilic cytoplasm. The tumors lacked marked pleomorphism, necrosis, solid areas, cribriform formation, or true papillary fronds. Immunohistochemically, α-methyl acyl coenzyme-A racemase staining was seen in 93% of cases, with the majority showing strong and diffuse staining. No basal cells were present on p63 and/or high molecular weight cytokeratin staining. In the radical prostatectomy specimens, tumor volumes ranged from a small focus (less than 0.01 cm^3) to 1.2 cm^3. Concurrent conventional acinar Gleason score 6 adenocarcinomas were seen in 6 of the 9 radical prostatectomy cases, in all cases as separate nodules from the PIN-like ductal adenocarcinomas. Only one of the PIN-like ductal adenocarcinomas at radical prostatectomy had extraprostatic extension, which was focal. PIN-like ductal adenocarcinoma differs from HGPIN by the presence of cystically dilated glands, a greater predominance of flat architecture, and less frequently prominent nucleoli. Verification often requires the immunohistochemical documentation of the absence of basal cells in numerous atypical glands. Although usual ductal adenocarcinoma is considered comparable to Gleason score 8, PIN-like ductal adenocarcinoma was accompanied by Gleason score 6 acinar carcinoma and behaved similar to Gleason score 6 acinar cancer. Recognition of this entity is critical to differentiate it from both HGPIN and conventional ductal adenocarcinoma.

Key Words: prostate cancer, high-grade intraepithelial neoplasia, ductal adenocarcinoma of the prostate

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Prostatic ductal adenocarcinoma is a subtype of prostatic adenocarcinoma that was originally described as arising from the large primary periurethral ducts of the transition zone around the region of the verumontanum. Subsequently, it was reported to also arise in smaller secondary ducts within the peripheral zone, where it is typically detected on needle biopsy. Its prevalence is estimated to be around 1% of prostatic tumors.[2,3,5,8] Prostatic duct adenocarcinomas are morphologically characterized by pseudostratified columnar epithelium, typically arranged in cribriform or papillary formations. They are commonly associated with conventional high-grade acinar adenocarcinoma of the prostate.[2]

High-grade prostatic intraepithelial neoplasia (HGPIN) has established immunohistochemical, genotypic, and morphologic similarities with prostatic adenocarcinoma and sometimes can pose diagnostic difficulties owing to its resemblance with invasive adenocarcinoma of the prostate.[3,5,7] Although most HGPIN are characterized by tufting epithelium, other morphologic appearances include flat, micropapillary, and cribriform. Although confusion between the micropapillary and especially cribriform patterns of HGPIN and ductal adenocarcinoma is well recognized, there has been only 1 study which has raised the issue of ductal adenocarcinomas closely resembling HGPIN with flat and tufted morphology.[10] We have termed this pattern as "PIN-like prostatic duct adenocarcinoma."

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METHODS

Twenty-eight cases of PIN-like ductal adenocarcinoma of the prostate were collected over 8 years from the consultation files of one of the authors from 1999 to 2007, with 24 cases over the last 3 years. The morphologic patterns, association with HGPIN and conventional acinar adenocarcinoma, and percentage of specimen involved were recorded.

Immunohistochemical studies were performed either on the available paraffin blocks and/or submitted by contributors in 19 and 22 of the 28 cases, respectively. Immunohistochemistry was performed at our institution using antibodies against p63 and high molecular weight cytokeratin (HMWCK) (all predilutes, Ventana, Tucson, AZ), and α-methyl acyl coenzyme-A racemase (AMACR) (1:100, Zeta Corporation, Sierra Madre, CA). In addition, a predilute PIN-4 Cocktail (P504S + HMW CK + p63) from Biocare Medical (Concord, CA) was used in some cases. Positive results consisted of dark brown nuclear (p63) and cytoplasmic (34betaE12) staining of basal cells and red cytoplasmic granular staining (AMACR) of secretory epithelial cells. Appropriate positive and negative controls were included. Only staining that was moderate or strong was considered positive.

Clinical follow-up was possible in all but 3 cases with an additional 3 recent cases having only short follow-up.

RESULTS

Clinical

The mean age of the patients was 68 years (range, 50 to 91 y). All but 1 case was diagnosed on needle biopsies, with the 1 other case seen on transurethral resection. On 15 available cases, prostate specific antigen serum levels at diagnosis ranged from 1.2 to 12.1 ng/mL (mean 5.9). The clinicopathologic data are summarized in Table 1.

Histology

The numbers of cores involved by PIN-like ductal adenocarcinoma in each case ranged from 1 to 18, with more than 1 core involved in 13 (46%) of the cases. The average length of the positive cores involved by PIN-like ductal adenocarcinoma was 39% (range, 5% to 90%). In cases with a small percentage of the length of the core

TABLE 1. Clinicopathologic Features

Study No.	Age	No. Cores Involved/ Total No. Cores	Percent Overall Involvement	Treatment	Findings at RP	Pathologic Stage	Follow-up (mo)
1	54	3/6	5	RP	PLDCA and 3+3 = 6	T2	NED (25)
2	66	1/4	40				LFU
3	70	1/5	20	BT			NED (26)
4	54	3/5	70	RP	PLDCA and 3+3 = 6	T3a	NED (8)
5	70	5/6	50	HT			NED (32)
6	61	1/1	45				LFU
7	68	2/3	60	HT			NED (17)
8	83	2/3	30	HT			NED (2)
9	68	4/6	60	XRT			NED (2)
10	77	2/3	40	HT			NED (8)
11	74	1/3	25	CT			NED (4)
12	69	8/10	40				LFU
13	63	1/2	10	RP	PLDCA and 3+3 = 6	T2	NED (5)
14	73	8/9	30	HT			NED (8)
15	91	1/2	90	BT			NED (9)
16	63	2/5	10	BT			NED (6)
17	85	1/1	70	HT			NED (5)
18	75	9/13	80	XRT			NED (8)
19	77	5/8	50	HT			NED (3)
20	50	4/10	30	RP	PLDCA and 3+3 = 6	T2	NED (4)
21	65	2/4	25	RP	PLDCA and 3+3 = 6	T2	NED (2)
22	71	18/24	20	RP	PLDCA and 3+3 = 6	T2	NED (3)
23	51	2/4	5	RP	PLDCA	T2	NED (3)
24	70	4/5	50	RP	PLDCA	T2	NED (5)
25	59	1/4	20				Recent
26	63	11/13	90	RP	PLDCA	T2	Recent
27	77	TURP	20				Recent
28	65	3/8	10				Recent

BT indicates brachytherapy; CT, cryotherapy; HT, hormone therapy; LFU, lost to follow-up; NED, no evidence of disease; PLDCA, PIN-like ductal adenocarcinoma; RP, radical prostatectomy; TURP, transurethral resection; XRT, external beam radiotherapy.

involved by tumor, a larger number of malignant glands were required to reach the diagnosis.

Analogous to the architectural patterns seen in HGPIN, PIN-like ductal adenocarcinoma displayed flat (Figs. 1, 2), tufted (Fig. 3), and micropapillary (Fig. 4) patterns. The majority of cases (85%) showed a combination of 2 or more patterns, with flat and tufted the most common association. Overall, flat (42%) and tufted (41%) were the most frequent, followed by micropapillary (17%) (some with more than 1 pattern). PIN-like ductal adenocarcinoma glands were generally round with great variation in size. Dilated glands were too large to visualize their entire circumference on biopsy and only segments of the gland were seen on the edge of the core (Fig. 5). These dilated glands were seen on 14 needle biopsies. Smaller glands had a striking resemblance to HGPIN. The only difference was that in some areas, the small glands were more crowded and the cells appear to overlap in a greater degree than HGPIN (Figs. 1A, 2A). In addition, the majority of the cases of PIN-like ductal adenocarcinoma showed less prominent nucleoli than HGPIN. In only 4 cases (14%), there were rare malignant glands with prominent nucleoli typical of HGPIN. The epithelium showed the morphology of prostatic ductal adenocarcinoma with tall columnar cells, basally located nuclei, and amphophilic cytoplasm (Figs. 2, 6). The tumors lacked marked pleomorphism, solid areas, dense cribriform formation, or necrosis. Mitoses were rare to absent. Two cases showed prominent Paneth-cell – like neuroendocrine change (Fig. 3).

Association with conventional acinar Gleason score 6 adenocarcinoma on the concurrent needle biopsy was observed in 5 cases (17%). HGPIN was found in 8(28%) cases with variability in the location of HGPIN, some

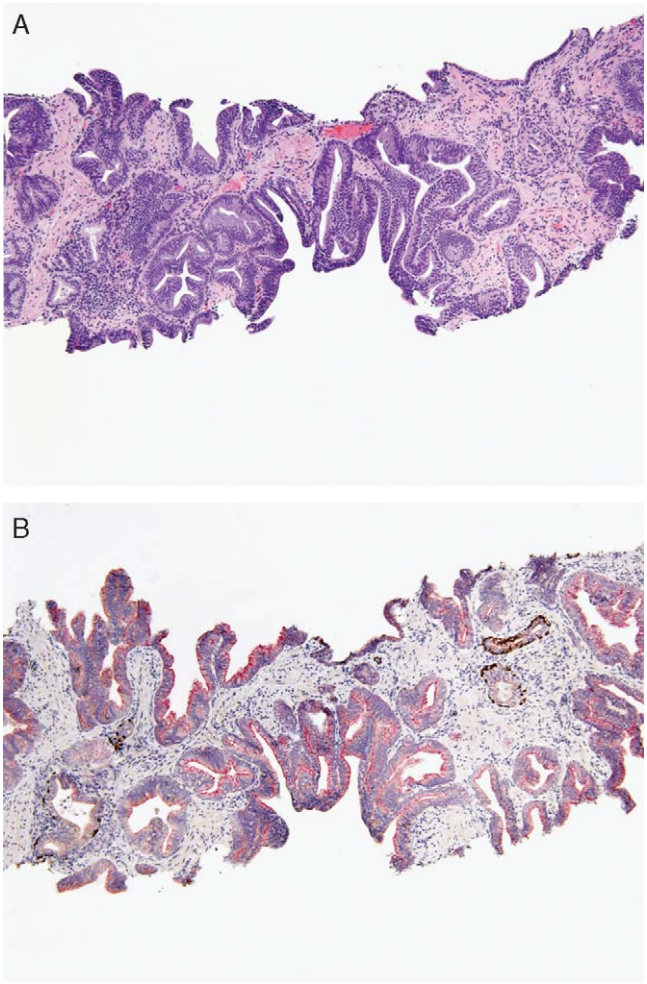

FIGURE 1. A, Low-power view of PIN-like ductal adenocarcinoma on needle biopsy showing crowded glands lined by columnar epithelium with a flat and tufting pattern. B, Triple antibody cocktail with intense AMACR positivity in PIN-like ductal adenocarcinoma and absence of basal cells (p63 and HMWCK).

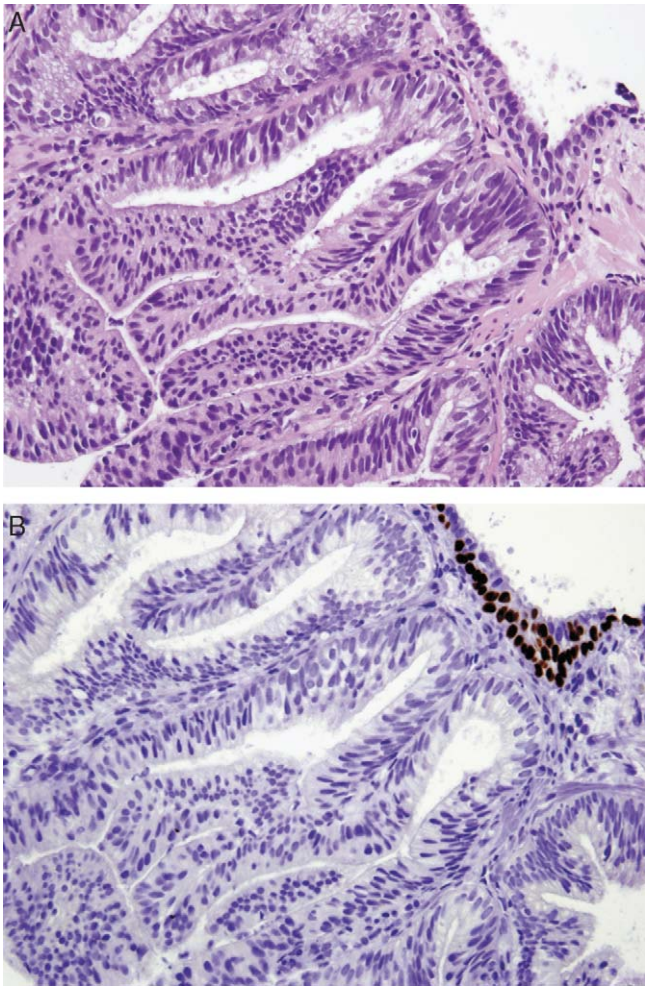

FIGURE 2. A, High-power view of PIN-like ductal adenocarcinoma with typical cytology of ductal adenocarcinoma. Glands are lined by pseudostratified columnar epithelium with mild-moderate nuclear atypia and amphophilic cytoplasm. Although the glands are similar in size to those seen in HGPIN, the glands are more crowded than HGPIN. B, p63 immunohistochemical study showing absence of basal cells in PIN-like ductal adenocarcinoma glands.

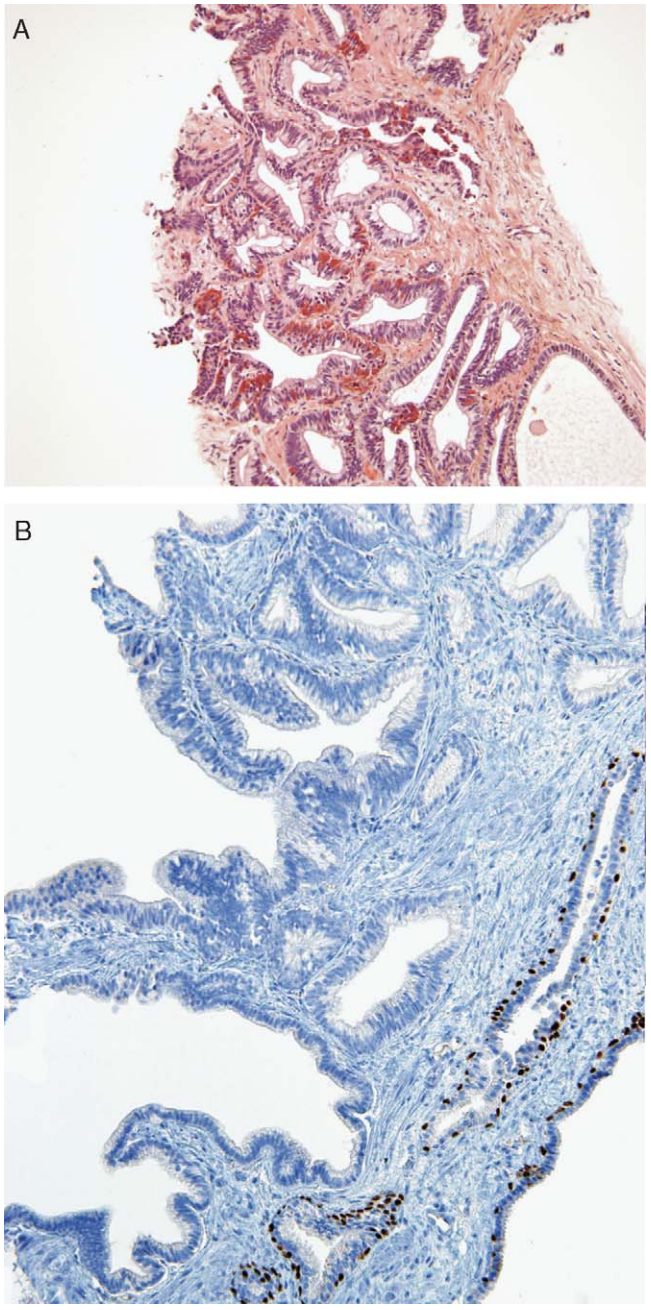

FIGURE 3. A, PIN-like ductal adenocarcinoma with prominent paneth-cell – like neuroendocrine differentiation. B, p63 immunohistochemical study showing absence of basal cells in PIN-like ductal adenocarcinoma glands.

showing proximity and others away from PIN-like ductal adenocarcinoma.

Immunohistochemistry

In 27 (96%) cases, outside or in-house immunohistochemically stained slides were available for review. These cases consisted of 8 cases with HMWCK (34βE12,) only, 3 cases with p63 only, and 16 cases stained with the 3-antibody cocktail [HMWCK (34βE12), AMACR, and p63].

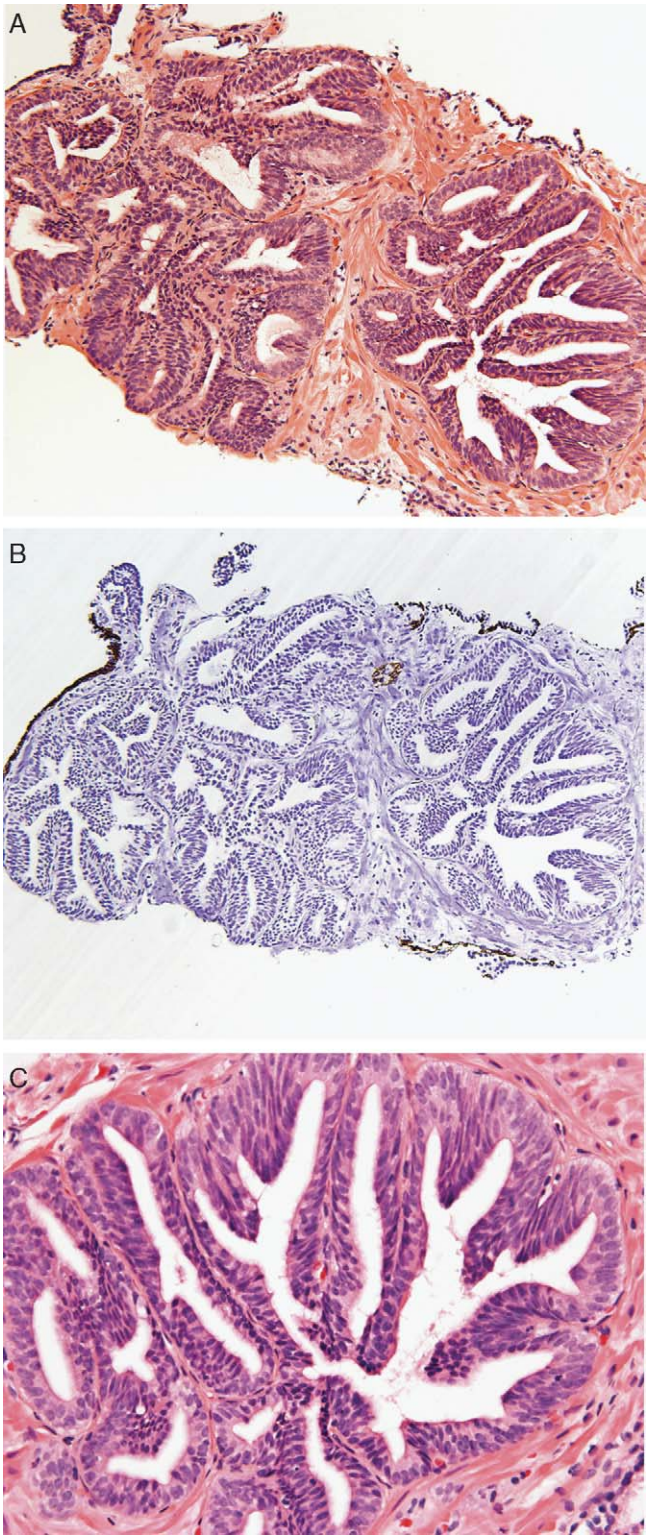

FIGURE 4. A, Tufted and micropapillary patterns of PIN-like ductal adenocarcinoma. B, HMWCK/p63 cocktail immunohistochemical study showing absence of basal cells. C, High power of PIN-like ductal adenocarcinoma gland with micropapillary formation.

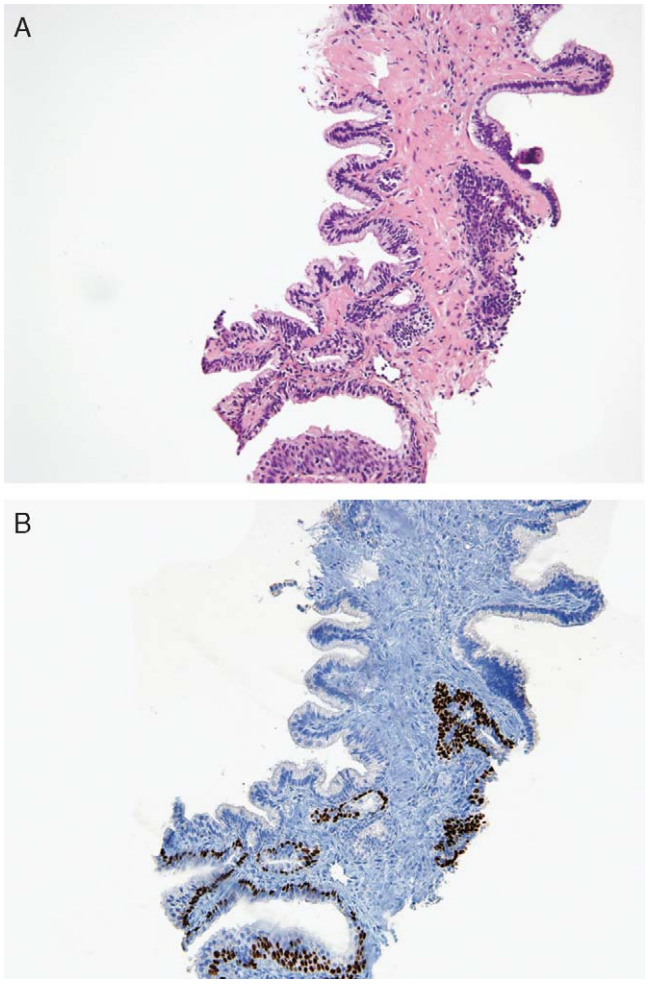

FIGURE 5. A, On both sides of the needle core, strips of malignant epithelium suggest the presence of cystically dilated glands. B, p63 immunohistochemical study showing absence of basal cells in the atypical dilated glands. Numerous identical negative glands were seen in this case.

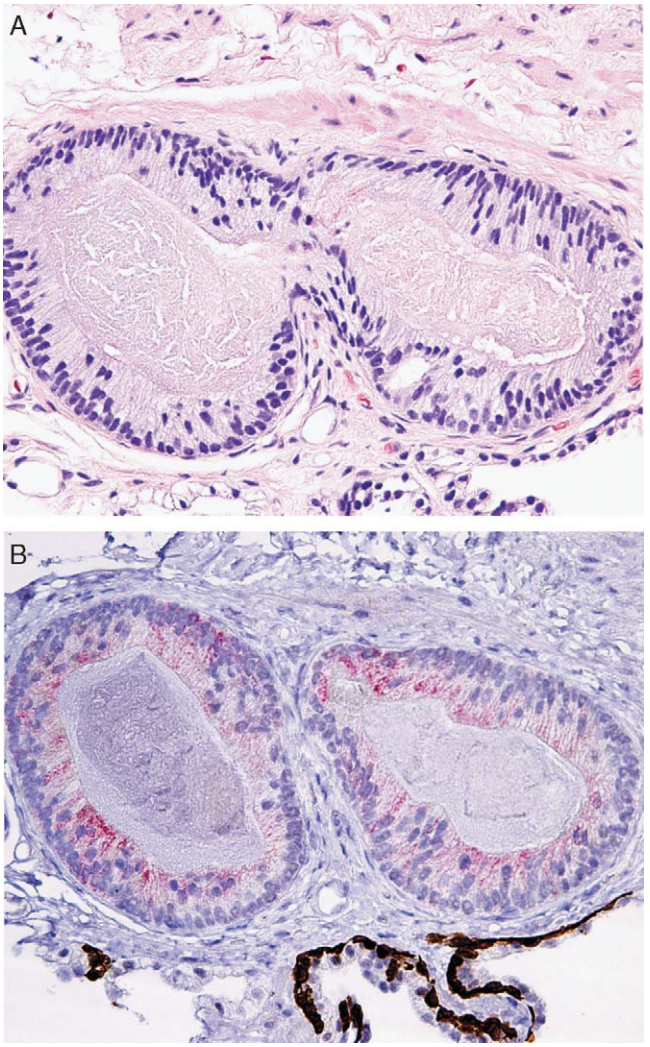

FIGURE 6. A, High power of PIN-like ductal adenocarcinoma resembling flat HGPIN. B, Antibody cocktail stained slide showing AMACR positivity in PIN-like ductal adenocarcinoma glands and absence of basal cells. This gland was surrounded by numerous other similar glands without basal cells.

The only case without immunohistochemistry was diagnosed based on the presence of well-established micropapillae and presence of numerous glands lined by atypical columnar cells which resembled HGPIN, but were more crowded and involved 80% of 1 core. All cases with available immunohistochemical slides were uniformly negative for basal cell markers (p63 and/or HMWCK). AMACR was positive in 14 (93%) of the cases with available immunohistochemical slides with strong and diffuse staining in 12, focal in 2, and negative in 1 case.

Findings at Radical Prostatectomy

Nine (32%) patients underwent radical prostatectomy and had specimens available for review. The pathologic stages of the specimens were pT2 (organ-confined) in 8 cases and pT3a (extraprostatic extension) in 1 case. Seminal vesicle involvement was not seen in any of the cases. All cases had conspicuous PIN-like ductal adenocarcinoma on the radical specimen with the exception of a sole case with only 1 small focus of PIN-like ductal adenocarcinoma. Association with conventional acinar adenocarcinoma was seen in 6 prostatectomies; in all these cases, the grade was Gleason score $3+3=6$. In all available cases, PIN-like ductal adenocarcinoma and conventional acinar adenocarcinoma were anatomically distinct tumor foci. The majority of the PIN-like ductal adenocarcinoma showed architectural features similar to the biopsy with a mixture of small glands resembling HGPIN (Fig. 7) in addition to medium (Fig. 8) and large glands (Fig. 9). Overall, the majority of the PIN-like ductal adenocarcinoma glands in the radical prostatectomy specimens were of small, medium, and large glands in 25%, 17%, and 58% of the cases, respectively. No case had lymph node metastasis. Extraprostatic extension of tumor was documented in 1 radical

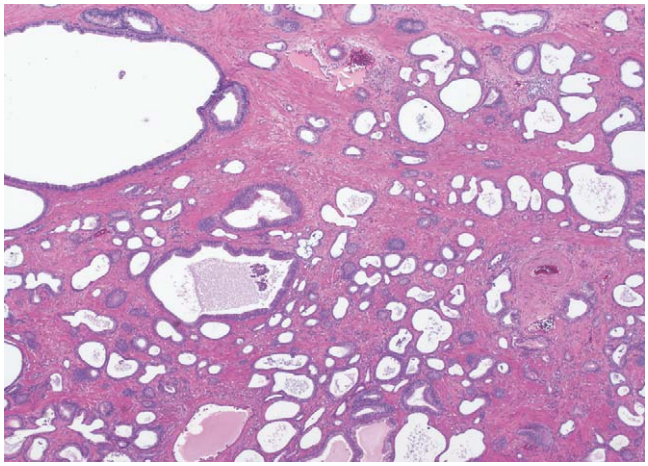

FIGURE 7. Radical prostatectomy with PIN-like ductal adenocarcinoma show significant gland size variation from small to medium to large glands.

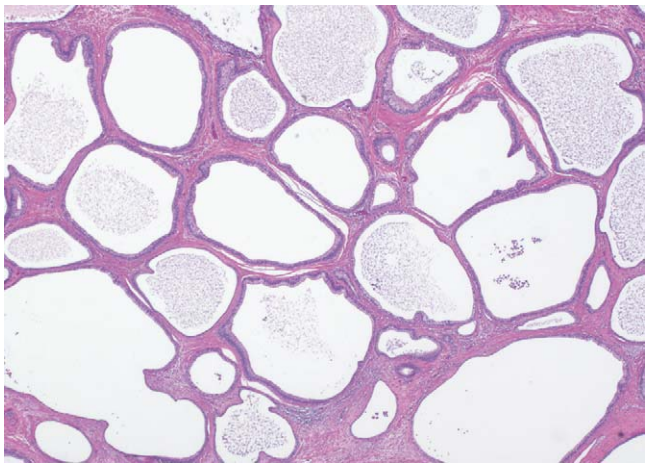

FIGURE 9. Radical prostatectomy with cystically dilated glands.

prostatectomy specimen and in this case cystically dilated glands of PIN-like ductal adenocarcinoma were responsible for focal extraprostatic extension (Fig. 10). In the radical prostatectomy specimens, tumor volumes ranged from a small focus (less than 0.01 cm^3) to 1.5 cm^3, with the mean 0.51 cm^3.

Follow-up

The median follow-up was 5 months (mean, 10.8; range, 1 to 32 mo). Treatment included radical prostatectomy (n = 9), brachytherapy (n = 4), hormonal therapy (n = 7), cryotherapy (n = 1), and external beam radiation (n = 1). Three patients were lost to follow-up after diagnosis, and in 3 cases the recent diagnosis precluded therapeutic and prognostic information. In none of the patients has there been evidence of biochemical progression, local recurrence, or metastatic disease.

DISCUSSION

PIN-like ductal adenocarcinoma is an unusual subset of prostatic adenocarcinoma that strikingly resembles HGPIN and has only been recently recognized. Hameed and Humphrey[10] reported 8 cases of what was called stratified epithelium in prostatic adenocarcinoma and was the first to highlight that this lesion mimics HGPIN. Their inclusion criterion was the presence of glands with stratified epithelium in the absence of cribriform formation. Although it was recognized that some of the cases resembled conventional prostatic ductal adenocarcinoma, they did not designate them as such. They chose to grade their cases as conventional acinar adenocarcinoma with assigned Gleason scores of 3+3 = 6 in 6 cases and 3+4 = 7 in the other 2 cases. Reviewing 150 in-house consecutive cases, they estimated the incidence of PIN-like ductal adenocarcinoma was

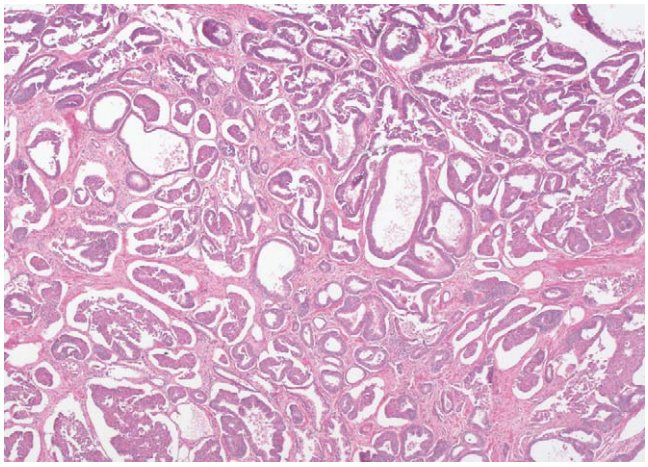

FIGURE 8. Radical prostatectomy with predominance of crowded medium-sized glands of PIN-like ductal adenocarcinoma.

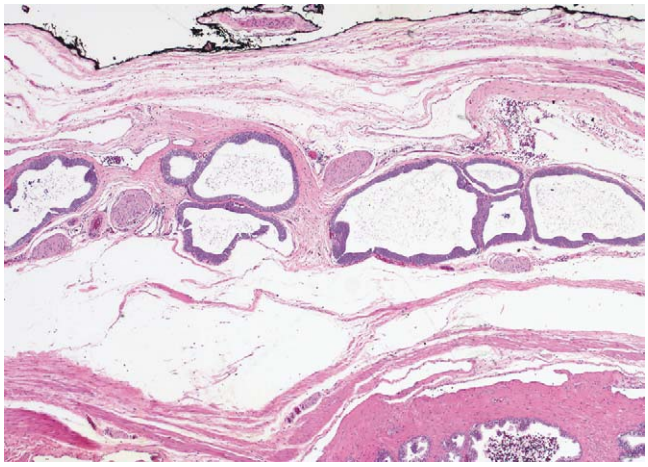

FIGURE 10. Radical prostatectomy with focal extraprostatic extension by cystically dilated glands of PIN-like ductal adenocarcinoma.

1.3%. To the best of our knowledge, the only other report on this lesion is found in an abstract by Amin et al.[1]

In our study, we have interpreted these lesions as variants of prostatic ductal adenocarcinoma on the basis of their similar cytologic characteristics. The hallmark of ductal adenocarcinoma is the presence of pseudostratified columnar epithelium in contrast to the simple cuboidal epithelium of acinar prostatic carcinoma. Although classic ductal adenocarcinoma consists of cribriform and papillary formation, it is recognized that other architectural patterns exist and that cytology and not the architecture defines this variant of prostate cancer.

Most studies consider ductal morphology as a more aggressive morphologic phenotype with comparable behavior to Gleason score 8 acinar adenocarcinoma.[4,9,12] In a prior study from our institution on 58 prostate needle biopsy cases with ductal adenocarcinoma, 20 tumors were treated by radical prostatectomy. Extraprostatic spread of tumor was seen in 63%, positive margins in 20%, and seminal vesicle invasion in 10% of cases.[4] In contrast, in the current study of 10 patients with PIN-like ductal adenocarcinoma on needle biopsy who underwent radical prostatectomy, only 1 patient had tumor with focal extraprostatic extension. In addition, 1 of the patients who did not undergo radical prostatectomy had evidence of extraprostatic extension on the needle biopsy. Although the possibility exists that our prostatectomy specimens represent a selection bias with more aggressive tumors being treated by other modalities, the same selection bias was in affect with our prior study. Also even with the selection bias inherent in a surgical series, one would have expected more adverse findings in 10 radical prostatectomy specimens carried out for Gleason score 8 acinar adenocarcinoma.

The current study, therefore, raises the issue of how to grade PIN-like ductal adenocarcinoma. The recommendation for grading usual prostatic ductal adenocarcinoma is to denote that they are comparable to Gleason score $4+4=8$ acinar adenocarcinoma.[6] Our preliminary findings suggest that PIN-like ductal adenocarcinoma is less aggressive with behavior more akin to Gleason score 6 acinar adenocarcinoma. If one ignored the ductal cytology in these cases, the presence of single glands without necrosis or cribriform pattern would be analogous on the basis of architecture to Gleason score 6 acinar adenocarcinoma. In addition, of the associated conventional acinar adenocarcinomas seen in 6 prostatectomies within our series, all were Gleason pattern 3. This contrasts with typical ductal adenocarcinoma, where the accompanying acinar carcinoma, when present, is usually Gleason pattern 4. Until larger studies with long term follow-up are performed, we believe that it is reasonable not to assign a grade but to state in a comment that these tumors seem to be less aggressive than typical ductal adenocarcinoma and at this time may be best considered as Gleason score 6 for purposes of treatment and predicted prognosis.

As its name indicates, PIN-like ductal adenocarcinoma on needle biopsy must be primarily distinguished from HGPIN. PIN-like ductal adenocarcinoma is distinct from HGPIN by the higher prevalence of flat epithelium, more crowded glands, and often large dilated glands. Although somewhat counterintuitive, PIN-like ductal adenocarcinomas may have less cytologic atypia than HGPIN. Whereas HGPIN by definition requires the presence of prominent nucleoli, PIN-like ductal adenocarcinoma often had tall-pseudostratified epithelium in the absence of visible nucleoli. If one were to misdiagnose these lesions as PIN, they would have to be considered low-grade PIN, yet the extensive nature of the process would be distinctly against the diagnosis of low-grade PIN. In addition to qualitative differences between HGPIN and PIN-like ductal adenocarcinoma, quantitative factors must also be taken into consideration. Extensive involvement of 1 or many needle cores is often necessary for the diagnosis. Focal HGPIN may be indistinguishable from PIN-like ductal adenocarcinoma both on the hematoxylin and eosin-stained slides and with immunohistochemistry, because scattered glands of HGPIN may not have a basal cell layer with HMWCK and/or p63 staining. Even in the cases where a small percentage of the biopsy was occupied by tumor, multiple glands were required to make a diagnosis of PIN-like ductal adenocarcinoma. Whereas an immunohistochemically documented absence of basal cells is often essential to establish the diagnosis of PIN-like ductal adenocarcinoma, AMACR overexpression seen in 93% of our cases is not helpful. The strong and diffuse staining seen in the majority of PIN-like ductal adenocarcinomas cannot be used to distinguish this lesion from its major mimicker, HGPIN, which is also often positive for AMACR. The rate of AMACR seen in our study was higher than reported by Hameed et al, where only 50% of the cases showed AMACR positivity, and is also high compared with conventional prostatic ductal adenocarcinoma.[10,11]

Given that current recommendations for follow-up for HGPIN do not necessarily require immediate rebiopsy, it is all the more crucial that pathologists be aware of this distinct subtype of prostatic ductal adenocarcinoma and distinguish it from HGPIN. In addition, distinguishing this pattern of ductal adenocarcinoma from the more typical papillary and cribriform patterns is crucial, as PIN-like ductal adenocarcinoma seems to behave less aggressively than conventional ductal adenocarcinoma.

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