Spectrum of Cribriform Proliferations of the Prostate

From Benign to Malignant

Thomas K. Lee, MD, PhD; Jae Y. Ro, MD, PhD

Context.—The presence of cribriform glands/ducts in the prostate can pose a diagnostic challenge. Cribriform glands/ducts include a spectrum of lesions, from benign to malignant, with vastly different clinical, prognostic, and treatment implications.

Objective.—To highlight the diagnostic features of several entities with a common theme of cribriform architecture. We emphasize the importance of distinguishing among benign entities such as cribriform changes and premalignant to malignant entities such as high-grade prostatic intraepithelial neoplasia (HGPIN) and invasive adenocarcinoma (acinar and ductal types). The diagnostic criteria, differential diagnosis, and clinical implications of these cribriform lesions are discussed.

Data Sources.—Literature review of pertinent publications in PubMed up to calendar year 2017. Photomicrographs obtained from cases at the University of California at Irvine and authors’ collections.

Prostatic adenocarcinoma is the most common new cancer diagnosis in men, and the number of deaths due to this disease is close to that of colorectal adenocarcinoma, approximately the second or third leading cause of death behind lung/bronchial cancers.1 Benign and malignant prostatic glands/ducts may share some common architectural patterns, particularly the cribriform pattern within glands and ducts. Although cribriform patterns are commonly seen in malignant processes, the differentiation between benign and malignant processes can often be subtle and difficult, with significant difference in clinical management and prognosis. Benign cribriform lesions in the prostate include cribriform hyperplasia and perhaps central zone glands that may appear proliferative with rare cribriform areas as well. Conversely, common premalignant and malignant cribriform lesions include high-grade prostatic intraepithelial neoplasia (HGPIN) and the cribriform pattern of invasive acinar adenocarcinoma (Gleason pattern 4), respectively, and less common entities, though still clinically important, are ductal adenocarcinoma and intraductal carcinoma of the prostate (IDC-P). Of significance, a recently described entity referred to as atypical intraductal cribriform proliferation (ACP) is also emerging as a low-grade variant of IDC-P and morphologically can mimic cribriform prostatic intraepithelial neoplasia (PIN) or cribriform invasive carcinoma. The current article focuses on the diagnostic criteria, differential diagnosis, and clinical implications of the above-mentioned entities (Figure 1).

Conclusions.—Although relatively uncommon compared with small acinar lesions (micropapillary carcinoma and small gland carcinoma mimickers), large cribriform lesions are increasingly recognized and have become clinically and pathologically important. The spectrum of cribriform lesions includes benign, premalignant, and malignant lesions, and differentiating them can often be subtle and difficult. Intraductal carcinoma of the prostate in particular is independently associated with worse prognosis, and its presence in isolation should prompt definitive treatment. Patients with atypical intraductal cribriform proliferation, intraductal carcinoma of the prostate, or even focal cribriform pattern of invasive adenocarcinoma in biopsies would not be ideal candidates for active surveillance because of the high risk of adverse pathologic findings associated with these entities.

(Arch Pathol Lab Med. 2018;142:938–946; doi: 10.5858/arpa.2018-0005-RA)
amylacea, a common feature in benign glands. The complex cribriform growth pattern seen in this benign process can mimic cribriform adenocarcinoma or HGPIN, and perhaps raise the possibility of ACP (discussed later).

Similarly, central zone glands located in the base of the prostate often show complex luminal tufting with mild nuclear pseudostratification and more eosinophilic cytoplasm compared with other benign glands. These central zone glands may occasionally display early cribriform architectural pattern (Figure 2, D), but, similar to benign cribriform hyperplasia, the cribriform central zone glands lack cytologic atypia or prominent nucleolus, and often show a very prominent basal cell layer. Central zone glands may show lipofuscin pigment, as seen in seminal vesicle epithelium.

These benign cribriform proliferations are readily recognized in radical prostatectomy or transurethral resection specimens, but are more challenging in needle core biopsies because of the lack of low-power architecture evaluation in biopsy material. However, the presence of often prominent basal cells and lack of cytologic/prominent nucleolus should be the prompt for a benign diagnosis.

PREMALIGNANT AND MALIGNANT CRIBRIFORM LESIONS

High-Grade PIN

High-grade PIN is regarded as a nonobligatory precursor lesion to invasive adenocarcinoma.23 Historically, it was stratified into PIN 1 to PIN 3, where PIN 1 represented low-grade PIN.4 Low-grade PIN is no longer used as a diagnostic term, as it lacks reproducibility and clinical significance.5,6 It is well accepted that only HGPIN should be reported. In the older literature, the diagnosis of HGPIN alone carried a significant increased risk of identifying invasive adenocarcinoma on subsequent repeat biopsy (~50%–80%); however, a more recent study by Epstein and Herawi,2 evaluating the MEDLINE database and relevant studies addressing the significance of finding HGPIN on needle biopsies, demonstrated that the median risk of identifying invasive adenocarcinoma on subsequent repeat biopsies is only slightly above that for a prior benign diagnosis (median ~24% versus 19% for prior HGPIN versus benign, respectively). The lower risk in recent studies may be attributed to extended (saturation) prostate biopsies and the historical definition of HGPIN. The term HGPIN, introduced by Bostwick and Brawer,3 encompassed all intraductal neoplastic proliferations of the prostate, including what are considered aggressive lesions, such as intraductal carcinoma of the prostate (including ACP). After the introduction of extended biopsies, the incidence of missing carcinoma is significantly decreased, and therefore isolated HGPIN is recommended for follow-up instead of immediate repeat biopsy.

Androgen-regulated gene TMPRSS2 with ETS family member ERG gene is the most common gene alteration in prostatic adenocarcinoma (seen in up to 70%),7,8 and ERG expression by immunohistochemistry can be detected in prostatic neoplasias, including HGPIN (up to 20%).7,8 Recent studies9 suggest that cases with isolated ERG-positive HGPIN on biopsy have a higher incidence of identification of prostatic adenocarcinomas on repeat biopsies compared with ERG-negative HGPIN on initial biopsy. Expression of ERG in ACP and IDC-P has been reported to be significantly higher than in HGPIN, similar to reports for invasive adenocarcinoma ranging from 40% to 70% of cases (discussed further below).10–12 Of note, loss of the tumor suppressor gene PTEN is thought to be a late event in prostate cancer progression, with loss (partial or complete) reported in up to ~70% of prostate cancers.7,8 However, PTEN loss has not been reported in HGPIN, but is present in similar frequency in cases of ACP and IDC-P with associated invasive carcinoma.10–12

Histologically, HGPIN consists of normal-sized glands/ducts with tufting luminal epithelial growth (with rare cases...
of flat lumina), cytologic atypia with nuclear enlargement, mildly amphophilic cytoplasm, ovoid nuclear stratification, and prominent nucleoli. Identifying basal cells can be challenging, as HGPIN often has an attenuated, patchy basal cell layer and may not be seen in all sections of tissue. Rarely, HGPIN may proliferate in a loose cribriform pattern (Figure 3, A and B), though it should be cautiously diagnosed and other entities such as ACP need to be excluded, particularly if the glands/ducts are expansive with rigid and florid cribriform growth pattern. The utility of performing immunohistochemistry stains for basal cell markers is limited in distinguishing HGPIN from ACP or IDC-P, as all these entities have retained basal cells, and the distinction is best based on morphologic grounds; however, assessment of ERG expression and PTEN loss by immunostains may be of utility in certain difficult cases.

**Intraductal Carcinoma of the Prostate**

In the past, IDC-P loosely referred to the presence of malignant prostatic epithelial cells, as well as urothelial and squamous carcinoma cells, within preexisting ducts/acini in the prostate. Historically, Bostwick and Brawer\(^4\) introduced the term HGPIN and included cases under the updated definition of IDC-P as well. Kovi\(^5\) first described the pattern of growth of prostate cancer within preexisting ducts and glands. Subsequently, McNeal et al\(^14\) and McNeal and Yemoto\(^15\) showed that prostatic adenocarcinoma has the ability to invade and grow within surrounding benign ducts and acini in cribriform architecture, and this is often seen with carcinomas having higher Gleason score (GS) than those with noncribriform growth. The presence of HGPIN alone on biopsies does not warrant immediate rebiopsy or definitive therapy, but the presence of IDC-P should trigger at least an immediate biopsy to survey for unsampled high-grade prostatic adenocarcinoma or definitive therapy. The generally

![Figure 2. Benign cribriform lesions of the prostate. Clear cell cribriform hyperplasia (A and C) with cytokeratin 5/6 immunostain (B); central zone glands (D) (hematoxylin-eosin, original magnification ×200 [A, C, and D]; original magnification ×200 [B]).](image-url)
accepted diagnostic criteria used by Robinson and Epstein\textsuperscript{16} as well as Guo and Epstein\textsuperscript{17} include 3 major features: (1) dense solid/cribriform filling of glands, (2) loose cribriform/micropapillary growth with marked nuclear atypia 6 or more times normal, and/or (3) comedo-type necrosis. The presence of any of the features within round or branching medium to large glands/ducts showing preserved basal cells is diagnostic of IDC-P. Other helpful but not required minor

Figure 3. Noninvasive intraductal cribriform lesions of the prostate. High-grade prostatic intraepithelial neoplasia (A and B), extensive intraductal carcinoma of the prostate (C) with PIN-4 (triple cocktail: p63, high-molecular-weight cytokeratin, P504S/racemase) highlighting the presence of basal cells (D), and atypical intraductal cribriform proliferation (ACP) with associated invasive carcinoma (E) and PIN-4 highlighting basal cells in ACP (F) (hematoxylin-eosin, original magnifications ×200 [A, B, and E] and ×40 [C]; original magnifications ×40 [D] and ×200 [F]).
criteria have been described, such as the quantity of glands involved (>6), irregular branching glands, mitotic activity, and 2 distinct cell populations within the lumen (larger peripheral and smaller central cells). The overall incidence of identifying IDC-P with concomitant invasive adenocarcinoma on prostate biopsies or transurethral resection specimen is up to 20% in intermediate- to high-risk prostate cancer patients. In a recent prospective study evaluating more than 1100 consecutive prostate biopsies, the overall incidence of IDC-P was reported to be lower than 3%, and the presence of isolated IDC-P in needle core biopsies (without concomitant invasive cancer) has been reported to be between 0.06% and 0.3%. The rarity of finding isolated IDC-P on biopsies does not diminish its considerable clinical importance. Isolated IDC-P on biopsies is associated with adverse findings in radical prostatectomy specimens, including high GS and advanced stage, and with increased incidence of metastasis in patients undergoing nonsurgical treatment options.

Intraductal carcinoma of the prostate is generally accepted to be a late-stage progression of prostatic adenocarcinoma. The presence of IDC-P in radical prostatectomy specimens is often associated with adverse findings such as high GS, large tumor volume, advanced stage (pT3a/b), and/or lymph node metastasis, and was shown to be an independent adverse prognostic factor associated with biochemical recurrence and decrease in progression-free survival. The presence of IDC-P in prostate biopsies has also been found to be an independent prognostic factor in early biochemical recurrence in patients undergoing radiation therapy and a significant prognostic factor for disease-specific and overall survival in patients presenting with distant metastasis at initial diagnosis. Patients with only IDC-P in needle core biopsies have been found to have high GS (≥7) and advanced stage on radical prostatectomy specimens. Of note, there are some instances in which IDC-P in a radical prostatectomy specimen is present in isolation without concomitant invasive adenocarcinoma or associated with low-grade (Gleason 6) adenocarcinoma, suggesting that occasionally IDC-P may be an in situ carcinoma of the prostate that likely progressed from HGPIN to IDC-P. Miyai et al reported that not all IDC-P cases represent intraductal spread of preexisting invasive cancer and that a subset of IDC-P may be a precursor lesion, and they assigned this type as precursor-like IDC-P. However, because of its adverse prognostic implications, findings of IDC-P on biopsies should warrant definitive therapy, or at least an immediate rebiopsy. Several studies have shown molecular similarities between invasive adenocarcinoma and concomitant IDC-P. It is important to distinguish IDC-P from HGPIN on biopsies, as these are distinct entities with different clinical implications and management strategies. Lottan showed that loss of heterozygosity is seen more commonly in IDC-P (~60%, 12 of 20 cases) compared with HGPIN, Gleason pattern 3, or Gleason pattern 4 adenocarcinomas (~9% [1 of 11], 0% [0 of 13], and 29% [5 of 17], respectively) in radical prostatectomy specimens. Moreover, studies have shown that PTEN/ERG status concordance between IDC-P and invasive adenocarcinoma is higher than 95%, which is significantly less than is seen with HGPIN and invasive adenocarcinoma.

The presence of IDC-P (with or without associated invasive carcinoma) should be reported in all prostate specimens, biopsies, transurethral resections, and radical prostatectomies. It is important to note that the mere presence of IDC-P on biopsies should be followed with a comment stating its adverse prognostic implications. It is important to note that GS should not be assigned for IDC-P because it is not invasive adenocarcinoma, despite its clinical implications. It is recommended that tumor quantity assessment include IDC-P, particularly when in close association with invasive adenocarcinoma. Communication with clinicians is advised to convey the significance of IDC-P in patient management, and patients with IDC-P would not be ideal candidates for active surveillance.

**Atypical Intraductal Cribriform Proliferation**

Atypical intraductal cribriform proliferation (also referred to as atypical cribriform lesions in some reports) has encompassed any cribriform intraductal proliferations, including cribriform HGPIN and IDC-P. More recently, ACP is regarded as intraductal cribriform proliferations that show features more worrisome than usual HGPIN. More recently, Morais et al classified ACP (referred to as borderline intraductal proliferations in the report) on needle biopsies as having (1) loose cribriform lumen-spanning architecture beyond that of HGPIN, but lacking significant nuclear pleomorphism or necrosis to meet the criteria for IDC-P; (2) atypical nuclei with significant pleomorphism but insufficient for a diagnosis of IDC-P (<6 times larger than normal epithelial cells); and/or (3) dense cribriform or solid proliferation of atypical cells partially present in large ducts on the edge of core biopsy specimens. ACP should be considered analogous to atypical glands suspicious for microacinar prostate carcinoma; also termed atypical small acinar proliferations, in that although these are not considered defined entities, the mere presence of atypical glands suspicious for microacinar prostate carcinoma in needle biopsy increases the chances of identifying invasive carcinoma on subsequent biopsies. The authors showed that ACP alone on biopsies had a ~57% (12 of 21 cases) chance of carcinoma diagnosis on follow-up biopsies, and that a high proportion of these carcinomas were diagnosed as GS 7 or higher. Shah et al showed that in radical prostatectomy specimens, ACP was often seen in close association with GS 7 or higher compared with GS 6 carcinomas (~47% to <4%), and was present in cases with higher tumor volume. Moreover, ACP found in isolation away from invasive carcinoma was rare (~2%–3%), and isolated ACP may be considered a lower-risk counterpart to ACP seen in close association with invasive carcinoma.

Recent studies suggest that ACP is in the low-grade morphologic spectrum of IDC-P, with similar clinical and molecular features, where ACP is associated with interme-
mediate risk for invasive adenocarcinoma. Shah et al\textsuperscript{12} reported that ACP and IDC-P showed comparable frequencies of PTEN loss, 71% and 72%, respectively, in 106 prostate biopsy samples examined containing ACP and/or IDC-P. Hickman et al\textsuperscript{10} also showed that ACP and IDC-P had identical frequencies of PTEN loss in radical prostatectomy specimens at 66.7% each (n = 30 ACP and n = 24 IDC-P). Likewise, ERG expression was similar in both studies between ACP and IDC-P (56% versus 61%, Hickman et al\textsuperscript{10}, 41% versus 55%, Shah et al\textsuperscript{12}). There was further support for ACP and its relationship to invasive carcinoma in the same study by Shah et al\textsuperscript{12}; the proportion of PTEN loss and ERG expression in invasive carcinoma (69% and 52%, respectively) were similar to those in ACP (71% and 41%, respectively) and IDC-P (72% and 55%, respectively). In studies done in prostate biopsies, Morais et al\textsuperscript{11} showed a slightly lower frequency of PTEN loss in ACP compared with IDC-P (52% versus 76%, respectively), and ERG expression was also lower in ACP compared with IDC-P (27% versus 58%). Therefore, the presence of ACP only in biopsies would require an immediate rebiopsy to evaluate for the presence of clinically significant prostate cancer. The clinical, pathologic, and molecular similarities shared between ACP and IDC-P raise the question of whether the definition of IDC-P is too stringent, thus decreasing the diagnostic sensitivity of IDC-P as an entity, when perhaps ACP should be classified as low-grade IDC-P. Further studies are needed to define the precise terminology to be used in order to convey this important finding in pathology reports to our clinical colleagues.

**Invasive Acinar Adenocarcinoma (Cribriform Gleason Pattern 4)**

Historically, cribriform pattern of invasive adenocarcinoma was originally included in the Gleason pattern (GP) 3 category, but with increased evidence showing that cribriform patterns are associated with adverse outcomes (discussed in detail below), the 2005 International Society of Urological Pathology (ISUP) consensus conference recommended that all cribriform pattern be reclassified as GP 4.\textsuperscript{30,31} This included both small rounded cribriform glands and larger irregular cribriform glands; the former were thought to be less aggressive in the past, but this has been refuted by more recent studies. The cribriform pattern of adenocarcinoma with or without necrosis (GP 5 versus GP 4, respectively) may closely mimic both ACP and IDC-P,
or perhaps HGPIN, but these can be distinguished from cribriform adenocarcinoma by the lack of basal cell staining in cribriform adenocarcinomas (Figure 4, A and B).

The GS system was redefined and updated by the ISUP consensus conference in 2005, with subsequent introduction of a novel prognostic group system developed by the Johns Hopkins group at ISUP in 2014, led by Jonathan Epstein, MD. As mentioned above, some of the significant changes to the pattern-based Gleason system included assignment of all cribriform glands (without necrosis) and glomeruloid glands as GP4, leading to inclusion of 4 patterns in GP 4: cribriform glands, poorly formed glands, fused glands, and glomeruloid glands. This change led to an apparent increase in the diagnosis of GS 7 (3 + 4 or 4 + 3), with a concomitant decrease in the prevalence of GS 6, in both needle core biopsies and radical prostatectomy specimens. Currently, GS 7 (3 + 4) is the most commonly diagnosed prostatic adenocarcinoma. Furthermore, the ISUP 2014 consensus conference also included the addition of a novel prognostic group grading system developed by the Johns Hopkins group using “grade group” designation into a 5-tier grading system: grade groups 1 (≤GS 6), 2 (GS 7, 3 + 4), 3 (GS 7, 4 + 3), 4 (any GS 8), and 5 (≥GS 9). The new grade group system has been validated in a large study including more than 20,000 radical prostatectomy cases, and it is recommended for use in conjunction with the updated GS. Of importance in the new grade group system is the separation of GS 7 into grade groups 2 and 3 to reflect the overwhelming evidence that there is a significant difference in prognosis between cases with GP 4 lower and higher than 50% (3 + 4 versus 4 + 3). Moreover, it is recommended that the percentage of GP 4 be included in the reporting, as recent studies showed a linear stratification of prostate-specific antigen biochemical recurrence associated with GP 4.

With the increase in the diagnosis of GP 4 and its inclusion of 4 different morphologic patterns, several recent studies examined the prognostic significance of these 4 individual GP 4 patterns. In 2011, Iczkowski et al demonstrated that the presence of cribriform pattern was an independent risk factor significantly associated with biochemical failure after radical prostatectomy in 155 patients studied, and the risk was similar to that for tumors with infiltrating GP 5 in a subset of patients. Subclassification of GS 7 adenocarcinoma by morphologic variant of GP 4 was suggested recently. Dong et al examined 241 consecutive radical prostatectomy specimens with GP 4 and demonstrated that ~13% (22 of 165) of patients with cribriform pattern developed metastasis compared with ~2.5% (2 of 76) of patients without cribriform pattern. Furthermore, the presence of cribriform pattern was shown to be an independent predictor of developing postradical prostatectomy metastasis and biochemical failure (hazard ratio, 5.62; \( P = .02 \); and hazard ratio, 1.97; \( P = .01 \), respectively). Choy et al examined 585 radical prostatectomy specimens with GS 6 and GS 7 (grade groups 1 and 2) and reported a significant difference in 5-year biochemical recurrence-free survival for GS 7 cases with the presence of cribriform architecture compared with those without cribriform architecture (68% versus 85%, respectively, \( P < .01 \)), showing that the presence of cribriform architecture is an independent risk factor for worse outcome among GS 7 cancers. Similarly, a nested case-control study (52 cases and 109 controls) by Kweldam et al demonstrated that the presence of cribriform pattern in radical prostatectomy was an independent adverse predictor for both distant metastasis-free survival and disease-specific survival (hazard ratios, 8.0 and 5.4, respectively, \( P \leq .001 \)). A separate study by Kweldam et al demonstrated that the presence of cribriform patterns and/or intraductal carcinomas on GS 3 + 4 biopsies is an independent factor for biochemical recurrence after radical prostatectomy, and that there is a higher frequency of cribriform/intraductal patterns with increasing percentage of GP4 in GS 3 + in biopsies. Keefe et al reported that the presence of cribriform architecture identified on prostate biopsies in patients with GS 7 (3 + 4) was associated with significant risk for non–organ-confined disease and upgrading to GS higher than GS 7 (3 + 4) on radical prostatectomy in 104 patients studied, and suggested that the presence of cribriform pattern on biopsy may be a contraindication for active surveillance.

Overall, among the 4 patterns of GP 4 assigned under the 2005/2011 ISUP, the cribriform pattern of invasive carcinoma is associated with worse outcomes in several studies, including increased risk for metastatic disease, biochemical failure, and disease-specific mortality in postradical prostatectomy patients, as well as increased risk for upstaging and upgrading after biopsy on radical prostatectomy specimens. It is also suggested by some that perhaps the presence of cribriform pattern should be mentioned in pathology reports in both biopsy and prostatectomy specimens, and that patients with cribriform pattern 4 would not be ideal candidates for active surveillance.

Prostatic Ductal Adenocarcinoma

In the authors’ experience, there is significant confusion among clinicians and nonurologic pathologists alike between the terms prostatic ductal adenocarcinoma (PDCa) and IDC-P. Many seem to equate these 2 entities and perhaps use them interchangeably. It is important to stress that PDCa is an aggressive form of invasive adenocarcinoma (analogous to GS 8 or above acinar adenocarcinoma), often seen in association with conventional acinar adenocarcinoma and rarely (<1%) in its pure form. It was previously referred to as endometrioid adenocarcinoma because of its morphologic resemblance to endometrial adenocarcinoma and its possible Müllerian origin. It can be centrally located within large central ducts or in the peripheral ducts. The distinguishing features of PDCa include tall pseudostratified columnar epithelium with abundant cytoplasm, in contrast to the low cuboidal morphology seen in cribriform acinar adenocarcinomas and IDC-P. Nuclear atypia and prominence of nucleioli are also present in PDCa. The most common architectural patterns are papillary and/or cribriform (often slitlike rather than rigid form of cribriform and frequently associated with necrosis), with the presence of true fibrovascular cores in papillary pattern, which are not seen in IDC-P (Figure 4, C and D). Other morphologic features have been described previously, such as foamy gland, micropapillary, and mucinous variants of PDCa.

The cribriform pattern of PDCa is likely to mimic IDC-P, but the cytomorphic feature of tall columnar pseudostratified epithelium in PDCa should be easily recognized. Intraductal carcinoma of the prostate often has rounded or slightly branching borders, whereas PDCa has irregular contours and shows large, complex growth patterns. The use of immunohistochemical stains for basal cells is also helpful, but caution should be used in interpreting them, as PDCa may have rare attenuated basal cells, or, when prominent basal cells are seen, they may represent...
intraductal spread of PDCa. In addition, PTEN loss and ERG expression have been reported in PDCa, but at a lower frequency, 18% and 11%, respectively, significantly lower than seen in IDC-P. Distinction between PDCa and IDC-P should be made in reporting because PDCa is assigned a GS (regarded as GP 4 or GP 5 if necrosis present) and IDC-P is not. Of note, a lower-grade PDCa was recently described and termed PIN–like ductal adenocarcinoma; it was composed of pure individual glands (no cribriform architecture) with similar tall columnar cells as in PDCa, but without significant nuclear atypia. Its behavior is analogous to that of GS 6 acinar adenocarcinoma, and it should be distinguished from its aggressive ductal adenocarcinoma counterpart.

CONCLUSIONS

Although relatively uncommon compared with small acinar lesions (microacinar carcinoma and small gland carcinoma mimickers), large cribriform gland lesions are increasingly recognized and have become clinically and pathologically important. The current article illustrates the vast diversity in cribriform proliferations in prostatic glands/ducts with important diagnostic/treatment implications. Benign lesions such as cribriform hyperplasia in the setting of benign prostatic hyperplasia or central zone glands with cribriform architecture may pose a diagnostic challenge in limited sampling, and perhaps warrant additional ancillary immunohistochemistry or urologic pathology consultation to avoid overdiagnosing these as more worrisome lesions with unnecessary medical management. Other cribriform lesions described include the premalignant HGPIN, where one should exclude other morphologically similar lesions with increased risk of adverse pathologic outcome, such as ACP and IDC-P. The latter 2 lesions are likely the same entity, with ACP being a low-grade variant of IDC-P, as they share similar molecular features and often are associated with invasive adenocarcinoma. Intraductal carcinoma of the prostate may be misdiagnosed as cribriform acinar adenocarcinoma and assigned a GS, where in fact IDC-P is regarded as a late presentation of high-grade invasive carcinoma growing within preexisting glands/ducts, and not an invasive adenocarcinoma in and of itself. Moreover, it has been suggested that use of low-cost immunohistochemical stains for PTEN and ERG may help differentiate cribriform HGPIN from ACP and IDC-P in limited samples, but the utility of basal cell markers is limited, as all these lesions by definition retain some basal cells. Recognition of the spectrum of cribriform glandular proliferations in the prostate is important, as treatment and prognostic implications among them are vastly different.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7–30.
2. Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. J Urol. 2006;175(3, pt 1):820–834.
3. Bostwick DG, Brawer MK. Prostatic intra-epithelial neoplasia and early invasion in prostate cancer. Cancer. 1987;59(4):788–794.
4. McNeal JE, Bostwick DG. Intraductal dysplasia: a premalignant lesion of the prostate. Hum Pathol. 1986;17(1):64–71.
5. Allam CK, Bostwick DG, Hayes JA, et al. Interobserver variability in the diagnosis of high-grade prostatic intraepithelial neoplasia and adenocarcinoma. Mod Pathol. 1996;9(7):742–751.
6. Epstein JI, Grignon DJ, Humphrey PA, et al. Interobserver reproducibility in the diagnosis of prostatic intraepithelial neoplasia. Am J Surg Pathol. 1995;19(8):873–886.
7. Lotan TL, Gumuskaya B, Rahimi H, et al. Cytoplasmic PTEN protein loss distinguishes intraductal carcinoma of the prostate from high-grade prostatic intraepithelial neoplasia. Mod Pathol. 2013;26(4):587–603.
8. Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science. 2005;310(5764):644–648.
9. Shah RB, Li J, Dhanani N, Mendrinos S. ERG overexpression and multifocality predict prostate cancer in subsequent biopsy for patients with high-grade prostatic intraepithelial neoplasia. Urol Oncol. 2016;34(3):120 e121–e122.
10. Hickman RA, Yu H, Li JH, et al. Atypical intraductal cribriform proliferations of the prostate exhibit similar molecular and clinicopathologic characteristics as intraductal carcinoma of the prostate. Am J Surg Pathol. 2017;41(4):550–556.
11. Morais CL, Han JS, Gordetsky D, et al. Utility of PTEN and ERG immunostaining for distinguishing high-grade PIN from intraductal carcinoma of the prostate on needle biopsy. Am J Surg Pathol. 2013;39(2):169–178.
12. Shah RB, Yoon J, Liu G, Tian W. Atypical intraductal proliferation and intraductal carcinoma of the prostate: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma. Histopathology. 2017;71(5):693–702.
13. Kovi J. Microscopic differential diagnosis of small acinar adenocarcinoma of prostate. Pathol Ann. 1985;20(1):157–196.
14. McNeal JE, Redwine EA, Freiha FS, Starney TA. Cribriform adenocarcinoma of the prostate. Cancer. 1986;58(8):1714–1719.
15. McNeal JE, Yenokian CE. Carcinoma within prostatic ducts and acini: morphologic and clinical correlations. Am J Surg Pathol. 1996;20(7):802–814.
16. Robinson BD, Epstein JI. Intraductal carcinoma of the prostate without invasion: a discrepancy between needle biopsy: emphasis on radical prostatectomy findings. J Urol. 2010;184(4):1328–1333.
17. Guo CC, Epstein JI. Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. Mod Pathol. 2006;19(12):1526–1531.
18. Cohen RJ, McNeal JE, Baillie TJ. Patterns of differentiation and proliferation in intraductal carcinomas of the prostate: significance for cancer progression. Prostate. 2000;43(1):11–19.
19. Zhou M. Intraductal carcinoma of the prostate: the whole story. Pathology. 2011;43(6):533–539.
20. Van der Kwast T, Al Daoud N, Collette L, et al. Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. Eur J Cancer. 2012;48(9):1318–1325.
21. Wath L, Li J, Magi-Galluzzi C, Zhou M, et al. Clinicopathologic characteristics of intraductal carcinoma detected in prostate biopsies: a prospective cohort study. Histopathology. 2013;63(4):574–579.
22. Kryvenko ON, Gupta NS, Vranic N, et al. Gleason score 7 adenocarcinoma of the prostate with lymph node metastases: analysis of 184 radical prostatectomy specimens. Arch Pathol Lab Med. 2013;137(5):610–617.
23. Cohen RJ, Chan WC, Edgar SG, et al. Prediction of pathological stage and clinical outcome in prostate cancer: an improved pre-operative model incorporating biopsy-determined intraductal carcinoma. Br J Urol. 1998;81(3):413–418.
24. Dawkins HJ, Sellner LN, Turbett GR, et al. Distinction between intraductal carcinoma of the prostate (IDC-P), high-grade dysplasia (PIN), and invasive prostatic adenocarcinoma, using molecular markers of cancer progression. Prostate. 2000;44(4):263–270.
25. Shah RB, Magi-Galluzzi C, Han B, Zhou M. Atypical cribriform lesions of the prostate: a clinicopathological and molecular study with a proposal to expand the 2014 International Society of Urological Pathology (ISUP) grading system.
26. Kato M, Tsuzuki T, Kimura K, et al. The presence of intraductal carcinoma of the prostate: the whole story. Pathology. 2011;43(6):533–539.
27. Cohen RJ, Chan WC, Edgar SG, et al. Prediction of pathological stage and clinical outcome in prostate cancer: an improved pre-operative model incorporating biopsy-determined intraductal carcinoma. Br J Urol. 1998;81(3):413–418.
28. Miyai K, Divatia MK, Shen SS, Miles BJ, Ayala AG, Ro JY. Clinicopathological analysis of intraductal proliferative lesions of prostate: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40(2):470–477.
29. Kato M, Tsuzuki T, Kimura K, et al. The presence of intraductal carcinoma of the prostate in needle biopsy is a significant prognostic factor for prostate cancer patients with distant metastasis at initial presentation. Mod Pathol. 2016;29(2):166–173.
30. Shah RB, Yoon J, Liu G, Tian W. Atypical cribriform lesions of the prostate: relationship to prostatic carcinoma and implication for diagnosis in prostate biopsies. Am J Surg Pathol. 2010;34(4):470–477.
31. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40(2):244–252.
32. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: a comparative study with consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol. 2017;41(4):E1–E7.
32. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol*. 2016;69(3):428–435.

33. Billis A, Guimarães MS, Freitas LL, Meirelles L, Magna LA, Ferreira U. The impact of the 2005 International Society of Urological Pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. *J Urol*. 2008;180(2):548–552; discussion 552–553.

34. Danneman D, Drevin L, Robinson D, Stattin P, Egevad L. Gleason inflation 1998–2011: a registry study of 97,168 men. *BJU Int*. 2015;115(2):248–255.

35. Helpp B, Egevad L. The significance of modified Gleason grading of prostatic carcinoma in biopsy and radical prostatectomy specimens. *Virchows Arch*. 2006;449(6):622–627.

36. Iczkowski KA, Torkko KC, Kotnis GR, et al. Digital quantification of five high-grade prostate cancer patterns, including the cribriform pattern, and their association with adverse outcome. *Am J Clin Pathol*. 2011;136(1):98–107.

37. Dong F, Yang P, Wang C, et al. Architectural heterogeneity and cribriform pattern predict adverse clinical outcome for Gleason grade 4 prostatic adenocarcinoma. *Am J Surg Pathol*. 2013;37(12):1855–1861.

38. Choy B, Pearce SM, Anderson BB, et al. Prognostic significance of percentage and architectural types of contemporary Gleason pattern 4 prostate cancer in radical prostatectomy. *Am J Surg Pathol*. 2016;40(10):1400–1406.

39. Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH, van Leenders GJ. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod Pathol*. 2015;28(10):1400–1406.

40. Kweldam CF, Kummerlin IP, Nieboer D, et al. Presence of invasive cribriform or intraductal growth at biopsy outperforms percentage grade 4 in predicting outcome of Gleason score 3+4=7 prostate cancer. *Mod Pathol*. 2017;30(8):1126–1132.

41. Keeffe DT, Schieda N, El Hallani S, et al. Cribriform morphology predicts upstaging after radical prostatectomy in patients with Gleason score 3 + 4 = 7 prostate cancer at transrectal ultrasound (TRUS)-guided needle biopsy. *Virchows Arch*. 2015;467(4):437–442.

42. Epstein JI, Woodruff JM. Adenocarcinoma of the prostate with endometrioid features: a light microscopic and immunohistochemical study of ten cases. *Cancer*. 1986;57(1):111–119.

43. Ro JV, Ayala AG, Wishnow KI, Ordonez NG. Prostatic duct adenocarcinoma with endometrioid features: immunohistochemical and electron microscopic study. *Semin Diagn Pathol*. 1988;5(3):301–311.

44. Samarutunga H, Duffy D, Yaxley J, Delahunt B. Any proportion of ductal adenocarcinoma in radical prostatectomy specimens predicts extraprostatic extension. *Hum Pathol*. 2010;41(2):281–285.

45. Seipel AH, Delahunt B, Samarutunga H, Egevad L. Ductal adenocarcinoma of the prostate: histogenesis, biology and clinicopathological features. *Pathology*. 2016;48(5):398–405.

46. Seipel AH, Wildlund F, Wildlund NP, Egevad L. Histopathological features of ductal adenocarcinoma of the prostate in 1,051 radical prostatectomy specimens. *Virchows Arch*. 2013;462(4):429–436.

47. Lee TK, Miller JS, Epstein JI. Rare histological patterns of prostatic ductal adenocarcinoma. *Pathology*. 2010;42(4):319–324.

48. Morales CL, Herawi M, Toubaji A, et al. PTEN loss and ERG protein expression are infrequent in prostatic ductal adenocarcinomas and concurrent acinar carcinomas. *Prostate*. 2015;75(14):1610–1619.

49. Tavora F, Epstein JI. High-grade prostatic intraepithelial neoplasialike ductal adenocarcinoma of the prostate: a clinicopathologic study of 28 cases. *Am J Surg Pathol*. 2008;32(7):1060–1067.