Intraductal lesions of the Prostate Gland and Their Clinical Significance

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Intraductal lesions of the prostate gland, defined as the presence of a layer of basal cells between an epithelial proliferation and the underlying stroma, are many and include benign, “premalignant,” or even possibly malignant lesions that are displaying intraductal / intraluminal and/or pagetoid spread. Because of such variability in clinical significance and their increased recognition, some of these lesions currently are under intense study due to a need to better define them and better understand their clinical significance. In particular is the issue of discriminating high grade prostatic intraepithelial neoplasia (HG-PIN or HGPIN) from intraductal carcinoma (IDC-P), as well as the benign and malignant mimics of these; some excellent reviews of this subject have been published recently, with details covered here (1-3, 50, 53).

HGPIN and IDC-P both are proliferations of prostate cells with the cytologic atypia of prostatic adenocarcinoma, but that are in intact glandular structures surrounded by at least a partial layer of basal cells (indicative of being “non-invasive”). Thus, at low power, involved glands are still rounded with smooth contours and do not have the infiltrative distribution of carcinoma glands, however they can be expanded by intra-glandular proliferation at the secretory cell layer, giving them a more basophilic appearance. The key differences are that IDC-P typically has a more complex architecture (either cribriform, solid or true papillary) and significantly increased cytologic atypia, and is more often associated higher grade carcinomas and poorer outcomes compared to HGPIN (1-3). This more complex architecture indicative of IDC-P is cribriform or solid growth patterns that can cause confusion with benign and malignant mimics, such as cribriform hyperplasia, proliferations of the verumontanum, seminal vesicle, HGPIN with cribriform or papillary architecture, prostatic adenocarcinomas of Gleason 4 and 5 patterns (especially ductal type adenocarcinoma), and even urothelial carcinoma in situ. It should also be mentioned here that any lesions with cytologic atypia and complex architecture (i.e. cribriform or solid growth) are starting to be recognized as the true “bad actors” in prostate cancer pathology, with more, larger and more complex malignant glands all increasing the risk of bad outcomes (4,5).

While the lecture will focus more on issues specific to IDC-P and HGPIN, this monograph will focus on the details related to all intraductal proliferations. Hence, the learning objectives are to:
1) Be made aware of benign intraductal lesions that can occur in the prostate gland in relation to:
   a. Possible therapy exposures.
   b. Potential to mimic premalignant lesions, carcinomas and carcinoma in situ.
2) Recognize HGPIN, its clinical significance, and its benign and malignant mimics.
3) Recognize IDC-P, its clinical significance, and its benign and malignant mimics.
4) Discuss outstanding issues related to the diagnosing HGPIN, IDC-P and carcinoma from each other.
**BENIGN INTRADUCTAL PROLIFERATIONS:**

A number of benign proliferations are commonly seen in the prostate gland, including cribriform hyperplasia (aka clear cell cribriform hyperplasia), basal cell hyperplasia, urothelial metaplasia/hyperplasia and squamous cell metaplasia/hyperplasia. All glands and ducts involved by these proliferations should have smooth and rounded contours, even if tightly crowded, without the irregularities or infiltrative appearance of carcinomas.

**Basal cell hyperplasia, Urothelial metaplasia/hyperplasia and Squamous metaplasia/hyperplasia:** All of these entities can be seen in the prostate gland at any time, however they are strongly suggestive of prior treatment exposure if they are prominent or extensive (whether in a biopsy or prostatectomy). Anti-androgen therapy exposure (ADT), such as combination flutamide and leuprolide (Lupron) that urologists might give to patients if there will be a delay in their treatment (and that they conveniently forget to tell the pathologists about), usually causes extensive atrophic changes in all prostate tissue; benign, HGPIN, malignant and stroma, along with an associated prominent patchy lymphocytic reaction. A subsequent proliferation of basal cells (basal cell hyperplasia), urothelial cell metaplasia/hyperplasia and/or squamous metaplasia/hyperplasia can develop as the gland recovers (6,7,8), although none of these may be present depending on the timing of the exposure. These entities almost never cause any diagnostic problems, however recognizing their association with ADT exposure is extremely important because it indicates that any residual prostate cancer might be extremely attenuated and atrophic, making it difficult or virtually impossible to identify and grade (7).

Basal cell hyperplasia is characterized by a proliferation of small round blue cells with small round nuclei with no pleomorphism, no mitotic activity, scant cytoplasm, and at most, small reactive nucleoli. There are no unique features to the urothelial or squamous epithelium; they mimic their counterparts at normal anatomic sites, although they can be present by themselves or be intermixed with each other and with basal cells. The squamous metaplasia can be more clear and glycogenated as well, depending on the type of drug exposure (estrogens are more likely to cause this, as well as an overall increase in squamatization). However, whenever one sees a substantial amount of urothelium in the prostate, one must always remember to consider a urothelial neoplasm, such as urothelial carcinoma in situ and rule out that possibility, which should be straightforward based on the presence of malignant cytologic atypia.

Radiation therapy, while typically associated with causing generalized prostate atrophy, can also cause similar changes as the gland recovers from treatment, although the cells can display significant radiation-induced atypia that can easily be confused with carcinoma if one is not experienced in recognizing such changes (9). Some generalizations that help are as follows: The more atypia, the more likely it is radiation atypia in benign glands, as when carcinoma comes back, it is clonal and has a more monotonous appearance compared to benign glands. Also, the crowding of the glands is another major tipoff of it being carcinoma, as even after radiation, benign glands and ducts retain their usual distribution patterns.

The only other times that squamous epithelium is seen in the prostate is next to areas of infarct and focal injuries, such as prior TURP sites, repeated catheterizations, other focal ablative therapy sites, reactions to foreign material (stones, infectious agents), etc.

**Clear cell cribriform hyperplasia (CCH, cribriform hyperplasia (8, 10)):** Hyperplastic prostate glands of various morphologies are seen in the transition zone of virtually every prostate gland from older adult men, as this is a major component of Benign Prostatic Hyperplasia (BPH). This occasionally can be seen in central and peripheral zones as well, and can display various morphologies, typically with
papillary infoldings (luminal undulations) or cystic with a flat epithelial lining (attenuated or not), rarely with true papillary growth or cribriform formation, and these all lack the cytologic atypia diagnostic of the other malignant-associated lesions described below. Typical gland hyperplasia rarely causes any diagnostic problems. One exception may be with pseudohyperplastic carcinoma, although this carcinoma almost always is low grade with papillary infoldings that mimic gland hyperplasia, but that contains mild cytologic atypia (macronucleoli present, but they can sometimes be very difficult to visualize, and usually a striking uniformly basal location of the nuclei) and an infiltrative growth pattern with lack of a basal cell layer (11, 12). Another is with HGPIN as described below. In contrast to typical patterns of gland hyperplasia, cribriform hyperplasia, which many times is composed of cells with prominent clear cytoplasm (CCH), can cause diagnostic difficulties, especially if it is composed of expanded or stretched glands (expansile growth pattern) where it can very closely mimic forms of HGPIN, IDC-P or Gleason pattern 4 adenocarcinoma with cribriform growth patterns. Architecture of CCH can be analogous to these other entities, so discrimination is based on the lack of cytologic atypia in CCH (although sometimes the nuclei can appear enlarged and hyperchromatic), the lack of an infiltrative growth pattern, and the presence of basal cells that sometimes are very prominent (8, 10). CCH is reportedly seen in roughly 8% of untreated prostatectomies, and does not always have clear cytoplasm (8, 10). While not considered a hyperplasia, similar glands can be seen in the central zone (Central Zone Histology) of the prostate, and also frequently have a prominent basal cell layer. These can cause the same diagnostic difficulties as CCH and are discriminated from HGPIN, IDC-P or Gleason pattern 4 adenocarcinoma with cribriform growth patterns using the same criteria as those used for CCH and is rarely a problem, except that it can frequently be confused with HGPIN because the cells and cell nuclei can be enlarged and crowded, giving a low power impression of HGPIN on biopsy (13). However by requiring either significant cytologic atypia and/or prominent nucleoli for the diagnosis of HGPIN on biopsies from the prostate base, this confusion can be avoided.

**PREMALIGNANT AND POTENTIALLY MALIGNANT INTRADUCTAL LESIONS:**

Work in this area truly is a Bay-Area story, with Dr. John McNeal at Stanford University involved in the first reports of many of these entities; particularly prostatic intraepithelial neoplasia and its subsequent development as a diagnostic entity (PIN, although he originally called it intraductal dysplasia), as well as first description of intraductal carcinoma (IDC-P) and its association with more aggressive disease and coining this name for it (14). Ductal-type prostatic adenocarcinoma, which is a mimic of both HGPIN and IDC-P also was developed as a diagnostic entity here in the bay area by BW Young and MD Lagios in San Francisco (15), and Zaloudek, Williams and Kempson at Stanford (16).

**Prostatic intraepithelial neoplasia (PIN** (ref 17 for a contemporary review; ref. 51 for historical context review**))**:

This entity was first described by McNeal in the 1960s, further developed by Bostwick and McNeal together in the 1980s, as well as by many others (18 - 20). PIN is defined as “architecturally benign” prostatic ducts and acini that are lined by cytologically atypical acinar cells and have an intact basal cell layer. PIN originally had three different grades of increasing atypia; grades 1, 2 and 3. This later was condensed to low grade PIN (PIN grade 1) and High grade PIN (grades 2 and 3), with the distinction between them made by the presence of prominent macronucleoli in HGPIN (18 - 20). Although some pathologists also make the distinction based on the presence of significant nuclear pleomorphism, this
starts to encroach on the line used to distinguish IDC-P from HGPIN and care should be taken to prevent misclassification of these entities with significantly different clinical significance (52). I would suggest not using this criterion for the diagnosis of HGPIN if there is any hint of complex growth (either solid, cribriform or streaming of the cells through the lumen), but rather consider the diagnosis of IDC-P in such instances. The macronucleoli in HGPIN should be analogous to what you typically see in acinar type adenocarcinoma in your practice, or thinking of it another way, it should look like typical prostatic adenocarcinoma cells in ducts lined by an intact basal cell layer. Remember that epithelial cells (either basal or secretory cells) in reactive lesions can have small punctate nucleoli that are not large enough to qualify as macronucleoli; nucleolar size is heavily dependent on fixatives and tissue processing parameters, such that comparison to findings in other cells is the best method for determining relative nucleolar size.

Low grade PIN (LG-PIN):
LGPIN is composed of ducts with atypia that falls short of that used to diagnose HGPIN, and as such, it overlaps morphologically with central zone histology and reactive forms of atypia, such that it cannot be reliably diagnosed, and it does not appear to have any clinical significance (20, 21, 52). Therefore, LGPIN is no longer used as a diagnostic term in clinical practice, and has not been used significantly for at least 20 years.

High grade PIN (HG-PIN or HGPIN):
As stated above, HGPIN is best characterized as normal duct and acinar architecture that has an intact basal cell layer, but is lined by cytologically atypical acinar cells that usually mimic typical prostatic adenocarcinoma, although they can be more columnar and pseudostratified as well, more like a ductal-type adenocarcinoma that it sometimes mimics. HGPIN is most easily recognized at lower power where the glands appear darker than adjacent benign glands, and examination at high power shows the macronucleoli that discriminate it from benign. Sometimes, glands are only partly involved by the HGPIN, which can be a major help in recognizing its presence. Also in some cases, the atypia is greater towards the basement membrane with an apparent maturation of the cells towards the lumens. HGPIN also can grow in many architectural patterns, including conventional (with papillary infoldings analogous to normal benign prostate gland architecture and some ductal type adenocarcinomas), a flat pattern (no infoldings, similar to atrophic cystic glands or noncystic glands), a micropapillary pattern (intermediate between conventional and flat, with widely scattered more blunted infoldings) and a cribriform pattern (similar to CCH); other very rare patterns also have been reported (19, 51). There is no known clinical difference or significance between these different growth patterns, although performing such studies is difficult due to common mixing of the various types, and difficulty in collecting appropriate outcome measures. Anecdotally, I have a colleague that questions the existence of the cribriform pattern of HGPIN and raises the question as to whether it actually represents a form of IDC-P, however this has not been formally studied yet. Also, Epstein has published that he “no longer diagnosis cribriform HGPIN” on biopsy, but rather calls it an Atypical Cribriform Intraductal Proliferative lesion insufficient for the diagnosis of IDC-P (or in other words, AIP, as described below); see section on outstanding issues below (1). While the original significance of detecting only HGPIN on needle core biopsy was that of an increased risk of detecting prostatic adenocarcinoma on subsequent biopsy (original reports stating a roughly 30% to 50% likelihood), contemporary studies have shown that this risk actually is not statistically different than that of detecting carcinoma on follow-up after an initial set of totally benign biopsies; this currently stands somewhere between 10% and 30% for both benign and for HGPIN, depending on the study (1, 2,
This push to insignificance of HGPIN is due to a number of factors, including better biopsy technique, taking more biopsy cores, and performing targeted biopsies and saturation techniques; all ways to increase the likelihood of detecting any carcinoma that is present. This push towards insignificance might also be due in part to the increased recognition of IDC-P as separate from HGPIN, such that these more aggressive lesions may no longer be included in some of the more recent clinical outcome studies of HGPIN. Lastly, while its presence does suggest a slightly increased likelihood of carcinoma detection on follow-up biopsy, these are most likely low volume Gleason score 3+3=6 carcinomas (17). These facts, along with increased use of active surveillance management protocols that allow patients with carcinoma to keep their prostates, all actually no longer support the need to report HGPIN.

So why learn to recognize HGPIN if it has little or no clinical significance?

1. Because a number of both benign and malignant mimics of HGPIN exist, such that reporting HGPIN helps to prevent confusion between them and hopefully reduces the chance of misdiagnosis and misinterpretation.

2. In cases where HGPIN is present in multiple biopsies (more than half) without detection of carcinoma, the rate of detection of carcinoma on subsequent biopsy does again approach that of the historical 30 – 50%, although this is almost always turns out to be low grade cancers that allow patients to be on most active surveillance protocols (17).

3. Sometimes, there are some small infiltrative glands indicative of carcinoma and that lack basal cells, but are immediately adjacent to HGPIN and do not have a clearly infiltrative growth pattern (22). Because the basal cell layer sometimes is not complete around HGPIN, one cannot entirely exclude the possibility of such histology representing tangential sectioning of the adjacent HGPIN, and as such a definitive diagnosis of carcinoma should be avoided. Some have used the term “atypical glands adjacent to HGPIN “ (or PINATYP for short) to describe this situation (22), while others may just lump this into the group of lesions described as atypical small acinar proliferations (ASAP) which are foci of glands suspicious for carcinoma, but lacking definitive diagnostic features of carcinoma (23). In either case, both of these entities have roughly the same clinical significance of a 45% likelihood of detecting carcinoma on subsequent follow-up biopsy, and hence this situation should be reported.

4. From a basic science perspective, it is clear that HGPIN does have a relationship to the development of some, but not all prostatic adenocarcinomas. Therefore, its study could have impacts on our understanding of prostate cancer development, and improved screening, diagnostic and therapeutic approaches. The amount of HGPIN correlates with the amount of carcinoma and the number of carcinoma foci, molecular studies of HGPIN show the same abnormalities as those seen in carcinoma, and HGPIN also shows the ERG rearrangements of prostate cancer (17). The apparent “budding” of carcinoma off of HGPIN seen in PINATYP lesions also suggests that HGPIN is a precursor to some carcinomas. Arguments against HGPIN as a requisite precursor lesion of prostatic adenocarcinoma is that many carcinomas, particularly high grade carcinomas, lack the presence of any nearby HGPIN. Combining these observations suggests that there might be 2 mechanisms / pathways that lead to prostate cancer development; a HGPIN-dependent pathway that more likely has low grade carcinomas as a next step, and a HGPIN-independent pathway that yields high grade tumors; these issues continue to be under academic study.

A number of both benign and malignant mimics of HGPIN exist. Benign mimics include: Central zone histology (which lacks the macronucleoli of HGPIN),
Seminal vesicle epithelium (which does not have the macronucleoli of HGPIN, usually is pigmented and/or has degenerative nuclear atypia, and does not stain with typical immunohistochemical prostate markers (e.g. NKX3.1, P501s, PSA, PSAP all negative), but rather PAX-8 is positive in SV (one must always be careful not to interpret the pigment as a positive immunohistochemical reaction in seminal vesicles or other heavily pigmented tissues), CCH (which does not have the macronucleoli of HGPIN), Basal cell hyperplasia (this sometimes can have macronucleoli similar to HGPIN, but the cells are in the wrong anatomic location, at the basement membrane and having overlying normal secretory epithelium), Urothelial cell metaplasia (lacks macronucleoli and sometimes has nuclear grooves), and Verumontanum epithelium (very crowded glands, sometimes very columnar and/or papillary projections into lumens, but do not have macronucleoli and do not have cytologic atypia).

Malignant mimics of HGPIN include conventional prostatic adenocarcinoma, pseudohyperplastic carcinoma, cribriform patterns of prostatic adenocarcinoma (Gleason pattern 4), conventional ductal type prostatic adenocarcinoma (PDAC; Gleason pattern 4) and a relatively new entity called PIN-like adenocarcinoma (Gleason pattern 3, AKA PIN-like Ductal adenocarcinoma).

Lastly, HGPIN and IDC-P have overlapping features that can sometimes make it difficult to discriminate between them (see below).

HGPIN sometimes mimics conventional adenocarcinoma in that it can be lining small collections of small glands with straight luminal borders, although such glands will have basal cells, and should also lack the appearance of an infiltrative growth around benign glands. A low power view sometimes helps to recognize the lack of infiltration; this benign distribution of the glands in such cases can help one to recognize conventional patterns of HGPIN nearby.

PIN-Like Adenocarcinoma (24), also called PIN-like Ductal Adenocarcinoma is a relatively newly described entity that can very closely mimic HGPIN (hence the name), but is an infiltrative carcinoma and therefore lacks basal cells. Unlike conventional ductal type adenocarcinoma (PDAC), PIN-like ductal appears to behave in a low grade manner and should be included in with other Gleason pattern 3 carcinomas (usually ISUP Grade group 1 if pure or present with only other types of pattern 3). It is lined by low-grade appearing columnar cells and can have the papillary infoldings of conventional HGPIN, and hence the overlap. Also, the infiltrative nature of this carcinoma is sometimes extremely difficult to recognize, again mimicking HGPIN. Aids in recognition include overcrowding of the glands, irregular borders of the collections of these glands (infiltrative edges), lack of any partial involvement of the glands, more uniformity of the cells with a lack of maturation towards the lumens that can be seen in HGPIN. It also closely mimics pseudohyperplastic carcinoma to a degree where it can be difficult to tell these two low grade carcinomas apart (are the cells columnar enough to be PIN-like ductal or they cuboidal to a degree that they are pseudohyperplastic?), although there is no known clinical need to do so. PIN-like ductal also lacks both the more complex architecture and cytologic atypia of both conventional ductal type prostatic adenocarcinoma and IDC-P. If the growth pattern is complex to a degree that it would be classified as Gleason pattern 4, then it would be classified as ductal carcinoma if it lacked basal cells, and IDC-P if it had basal cells present.

Prostatic ductal carcinoma (PDAC): This entity was first described in the late 1960s and termed “endometrial carcinoma of the prostatic utricle,” thought to be arising from Mullerian Remnants of embryologic development, however subsequent work performed in the bay area showed this actually to be a prostatic adenocarcinoma that had histology that mimicked endometrial carcinoma (15, 16). Because of this different histomorphology, and that these lesions are usually seen more centrally and/or around the urethra, they were termed ductal adenocarcinoma to discriminate them from conventional
small acinar adenocarcinoma of the prostate, although they can be seen anywhere in the prostate and are more commonly associated with conventional adenocarcinoma rather than being purely of ductal morphology (25, 26). To reduce potential confusion, it must be remembered that PDAC is a type of carcinoma based on cytologic findings and is not based on microanatomic location, while IDC-P is based on the requirement that it be located within prostatic ducts and acini, and is not strictly defined by cytology alone (1-3). Depending on series, practice and diagnostic criteria, the incidence of PDAC is somewhere between 1-5% of all prostate cancers detected. Again, they are characterized by complex cribriform and papillary (both true papillary with fibrovascular cores and pseudopapillary without them) growth patterns that separate these from PIN-like carcinomas. They are lined by either simple columnar or pseudostratified/stratified columnar cells with atypia that can range from very mild (this can make them difficult to discriminate from HGPIN and PIN-like carcinoma; use the presence of complex growth patterns to recognize them) to extremely atypical to a degree that they might appear similar to an intestinal-type (e.g. colorectal) adenocarcinoma or urothelial carcinoma (WATCH OUT). These tumors are usually very large and infiltrative, making them easy to recognize as carcinoma, however if small, they can be confused with HGPIN if they have low grade cytology, or IDC-P if they have high grade cytology. The discriminating difference is the presence of basal cells in IDC-P and HGPIN, and lacking in PDAC. However, most GU pathologists allow rare basal cells to be present around tumors with this morphology, but this can confound discrimination from IDC-P (how many basal cells is too many? And clinically, does it matter? See below). While this issue can be debated, I and my urologists take the more practical approach and consider IDC-P to be an aggressive lesion as well, in which case discrimination from invasive carcinoma (whether conventional or PDAC) on biopsy becomes less of an issue; as long as some invasive carcinoma is present somewhere, these patients need to be treated rather than put on active surveillance! Outcome data supports this practice (see below).

Also PDAC is considered an aggressive form of prostatic adenocarcinoma and should be assigned a Gleason grade (pattern) of 4, unless necrosis is present, and then it should be assigned grade 5. Because these grade assignments correlate with outcome whether the tumor is PDAC or not, one could argue that its recognition and reporting is unnecessary, however if the amount of this tumor is small, e.g. would yield an overall Gleason score of 3+4=7, the urologist might still consider active surveillance for such patients if it is not clearly reported as having ductal features, so in such cases it should be clearly indicated that PDAC is present so that one can better consider either rebiopsy to better determine tumor extent or just go directly with a more aggressive approach to therapy.

Besides many of the entities described here, other potential mimics of PDAC include tumors of the prostatic urethra and urinary bladder; including urothelial carcinomas with glandular differentiation and intestinal type adenocarcinomas, however tumor heterogeneity, locations and extent of involvement usually help discriminate between these possibilities. If tumor type is still unclear, immunohistochemistry for prostate (NKX3.1, PSA, PSAP, P501s), urothelial (GATA-3, uroplakin, P63, high molecular weight Keratins, CK7) and intestinal (CK20, CDX-2, villin, MUC2, STAT-6) can be helpful, although I sometimes see GATA-3 positivity in prostate.

Intraductal carcinoma (IDC-P):
Despite the presence of basal cells around IDC-P, it is considered an indicator of aggressive disease that requires therapeutic intervention (see clinical significance below). This entity was first identified by Kovi et al in 1985 and defined by McNeal and Yemoto in the 1990s (14), yet there has always been some debate as to whether this represents intraductal growth of a more aggressive form of HGPIN (akin to a high grade in situ lesion) or retrograde invasion of the duct system by a carcinoma (like a form of pagetoid spread; last month I had a case where IDC-P was filling the lumens of the seminal vesicle,
which adds support to this theory), or whether both mechanisms are possible (1, 27). This has led some
to classify the latter as “regular IDC-P” when it is present near associated invasive carcinoma, and
“precursor IDC-P” when there is no invasive carcinoma identified, suggestive of a de novo
intraepithelial lesion; however “apparent” precursor IDC-P could be due to additional intraductal spread
and colonization from other unsampled areas and/or due to undetected invasive carcinoma. Additional
confusion exists because of inconsistent labeling of these lesions, including some labeled as or included
in studies as HGPIN (and thus may have contributed to the previously reported clinical significance of
HGPIN), or as carcinoma in situ / prostatic carcinoma in situ, gland dysplasia, etc, however IDC-P is
now accepted as a distinct entity in the current WHO 2016 Classification of Tumors (28), with defined
diagnostic criteria. These criteria, developed by Guo and Epstein, take into account both architecture
and cytology (1, 29). It defines IDC-P as intraductal growth of malignant cells with at least either
architectural abnormalities (either solid growth or cribriform growth with more than 70% of the gland
lumen filled with tumor cells) or a micropapillary growth pattern requiring either marked nuclear
pleomorphism (nucleus more than 6x normal size) and/or comedonecrosis (29). However it should be
noted that other definitions and diagnostic criteria have also been published to describe these lesions (2,
30, 31). So in more general terms, IDC-P is characterized by much larger and more pleomorphic tumor
cells than typically seen in HGPIN, including more complex architecture (solid and cribriform growth
patterns), occasional comedonecrosis, and an apparent streaming of the highly atypical cells through the
duct lumens. Other features include enlarged / stretched / expanded ducts and glands that can have
irregular branching contours (2, 31). Some cases of IDC-P are composed of more columnar cells and
mimic ductal type adenocarcinoma (PDAC), although others would suggest that this just represents
intraductal spread of PDAC, but cases where no PDAC is present still occur, supporting that these
lesions are IDC-P. Also, IDC-P has a basal cell layer surrounding them which PDAC should not, (or
PDAC has an extremely attenuated one, but where would you draw the line? Or do you even need to
draw the line? See significance below).
Incidence of IDC-P on biopsy is seen in roughly 2.8% of cases when evaluating all comers, however
only 0.3% of all comers have IDC-P without any carcinoma present, but only 10% of these cases (0.03%
of all cases) had no carcinoma on subsequent radical prostatectomy (1, 2, 32).

Clinical significance: Despite the presence of basal cells, and in stark contrast to HGPIN, numerous
outcome studies (both historical and contemporary) have identified IDC-P as an indicator of more
aggressive disease and prognostic of poorer outcomes. Some recent examples are as follows:
In large clinical trials evaluating radiation therapy outcomes in intermediate and high risk patients, the
presence of IDC-P was an independent predictor (including independent of Gleason grade) of earlier
biochemical recurrence and metastatic failure (33). Although the effect was less in patients that received
long-term ADT, the ADT was given for 3 years starting at enrollment, but outcomes were measured
from enrollment date, creating a severe bias in the ADT arm (i.e. they got treatment for an additional 3
years), and suggesting that IDC-P may be even more significant in this more heavily treated group.
IDC-P has been found in prostatectomies to be an independent risk factor for biochemical recurrence
and reduced cancer-specific survival, even independent of grade (34).
In patients with only IDC-P at biopsy, 90% of those treated with prostatectomy had invasive carcinoma
with a median Gleason score of 8, along with the majority being at least stage pT3 (35).
In a larger study of cases with IDC-P and Gleason score 3+3=6 carcinoma as the highest grade on
biopsy, 7% were diagnosed with metastatic disease prior to any additional therapy, and only 20% of
those getting RP had 3+3=6 in their prostatectomy (36).
In a very large cohort study, evaluating 1176 biopsies, 33 cases were found to have IDC-P, with 90% having carcinoma present, of which all were grade group 2 or higher and 33% were grade group 5, and findings at prostatectomy were worse than predicted by nomograms (Partin Tables), further indicating the significance of IDC-P over conventional pathologic parameters (32).

In patients diagnosed with metastatic prostate cancer at initial presentation, IDC-P and Gleason pattern 5 on the diagnostic biopsies of the prostate gland were the only independent predictors of cancer-specific survival and overall survival, again suggesting possible ADT resistance (37).

In a study of detailed evaluation of comedonecrosis, it was found that in 95% of examples it was present in the IDC-P while only 36% of examples were present in the invasive carcinoma, strongly suggesting that when you identify comedonecrosis, it more likely represents IDC-P rather than Gleason pattern 5 carcinoma (38). While I can only speculate, I do know that Gleason did not have immunohistochemistry for basal cells, and tumors with comedonecrosis ended up having the worst prognosis when he developed his grading scheme, further suggesting the aggressive nature of IDC-P (39, 40).

Many of these outcomes are worse than expected for grade group 4 and 5 carcinomas and suggest that IDC-P, despite having basal cells around it, is likely an indicator of more aggressive disease. While reasons for this might not be known, the concept of a tumor being able to grow within gland lumens “outside of the body” suggest that these tumors may have added survival capabilities. In addition, numerous molecular studies have been performed that show IDC-P has molecular abnormalities and characteristics similar to the most aggressive prostatic adenocarcinomas (41-44). For these reasons, it seems most prudent to suggest treatment for IDC-P even if no invasive carcinoma is identified on biopsy, as it has been shown that almost all do have carcinoma present, and more likely is high grade than not (1-3, 32, 35, 36).

Significant debate has occurred over whether IDC-P should be considered and reported as Gleason pattern 4 (or 5 if necrosis is present) when grading carcinomas in pathology reports for prostate biopsies. While the “party line” is that this should not be performed (1-3, 28, 31, 53), the data seems to indicate that including the IDC-P into the report is not unreasonable, and therefore I actually do it. This is only an issue when the Gleason score otherwise would be 3+3=6 (grade group 1) or 3+4=7 (grade group 2); whatever amount of IDC-P is present in higher grade groups will not alter their Gleason scores or their grade grouping, as they already are high. As the presence of IDC-P is so strongly associated with higher grade tumors, the probability of having cases where this will have an effect is extremely low. For example in a study performed at Johns Hopkins, only 73 such cases were identified in a search of the files over 13 years (36). Even in cases where 3+3=6 is the only carcinoma found at biopsy, only 20% of these will have 3+3=6 at prostatectomy and 80% will not, which yields a much greater biopsy-to-prostatectomy discordance rate than one would get if the IDC-P was included in the grade (45)!!! Such a comparison supports including IDC-P in the grade assignment. Also, doing so could prevent potential error of the urologist putting a patient on active surveillance due to the 3+3=6 diagnosis, and the subsequent poor outcomes (36)!!!

Reporting: In any case, IDC-P should be recognized and reported whenever it is identified (1-3, 28). However, while one could argue that it does not need to be reported in cases that already have high grade carcinoma present (grade groups 3, 4 and 5), outcome studies quoted above suggest that IDC-P DOES add additional prognostic information beyond the Gleason score even in such high grade cases, further supporting that it should be reported in any and all cases where it is recognized (32-37).

Mimics of IDC-P: Essentially all of the entities with cribriform or solid growth patterns discussed to this point are in the differential for the diagnosis of IDC-P. In particular are HGPIN, PDAC, and other cribriform lesions such as CCH. In addition, one must always consider urothelial carcinoma in situ, especially if the lesion has solid growth and/or highly pleomorphic tumor cells. While one might
consider Urothelial CIS in the prostate a rare occurrence, studies have shown it to be present in almost half of prostates resected in cystoprostatectomies for bladder cancer (46). If examination does not exclude this possibility, addition of immunohistochemical stains to discriminate urothelial carcinoma from a prostatic lesion should be performed as previously described (see the end of PDAC section).

Outstanding Issues and Considerations:
As there are proliferative lesions with features intermediate to those of HGPIN and IDC-P, the main key outstanding issue is: Where does one draw the line between HGPIN and IDC-P?
As discussed, HGPIN typically is characterized by glands without architectural abnormalities, but that are lined by cells with the morphology of conventional prostatic adenocarcinoma, and the lesion now is recognized as having little or no clinical significance, while typical IDC-P has abnormal intraductal architecture and cytologic atypia, and been shown in some outcome studies to be a powerful independent risk factor for more aggressive disease and bad outcomes (32-37). Despite these incredible contrasts in outcome when comparing typical examples of these entities, there are lesions with features that are intermediate between these typical extremes and cause diagnostic dilemmas when no carcinoma is identified. The terms Atypical cribriform Intraductal Proliferation or Atypical Intraductal Proliferation (AIP) have been proposed for such lesions, as it is unclear which category they really belong in, and is similar to the use of the term atypical small acinar proliferation (ASAP) when findings for the diagnosis of carcinoma from benign are indeterminate. Lesions fall into this category the following ways: 1) They lack the architecture diagnostic of IDC-P, but are lined by highly atypical cells similar to those expected in IDC-P, 2) Looser cribriform lesions that do not fulfill or reach the diagnostic threshold of IDC-P and lack the typical cytologic atypia of IDC-P and 3) Suspicious lesions that are on the edge of a biopsy that cannot be completely visualized. In a study using these criteria, roughly 50% of cases had either carcinoma or IDC-P diagnosed on follow-up biopsy, however all of the biopsies with carcinoma were Gleason score 7 or higher, which is a much higher rate of higher grade carcinoma than one expects on follow-up biopsy after HGPIN (17) and even ASAP (47)!!! A more recent study found essentially the same findings, with a 66% positive follow-up rate with all carcinomas grade group 2 or higher (48). Therefore the data are more supportive of immediate repeat biopsy after AIP than they are for ASAP!!!

Reports of using immunohistochemistry to reduce the diagnosis of AIP have been attempted and show that PTEN loss does not appear to occur in HGPIN and hence may help to push some of these borderline cases over to the IDC-P category; such studies have also shown that the probability of diagnosing carcinoma on repeat biopsy goes up for PTEN-negative lesions, compared to that of AIP alone (47). While I do use PTEN frequently for AIP, I have found that it only rarely pushes me over to a diagnosis of IDC-P, while if PTEN is present, I definitely stay with the diagnosis of AIP, but my experience is very limited.

There are a number of other factors that could be examined to further clarify issues related to IDC-P, including additional outcome studies in relation to subclassifications of morphology. In particular, do different patterns of IDC-P confer different risks? Does partial basal cell loss in these lesions have any meaning? Are there any additional features or tools that could reduce the diagnosis of AIP? Does the presence of IDC-P confer any radiation resistance or sensitivity? Can molecular characteristics unique to IDC-P be identified, and can they be exploited for either therapy or diagnosis? There are numerous others.

Practical Considerations and Summary:
What are some of the tips to recognizing and reporting lesions with these findings? Close inspection shows that there are a number of key themes running through this list of entities that one should keep in mind to help in recognizing these entities and discriminate between them to help improve diagnostic accuracy, as well as understand their relationship to prognosis and patient outcomes. These include:

1. That all noninvasive “intraductal” lesions have smooth contours of the involved glands, and whether crowded or not, they do not show an infiltrative growth pattern that would be indicative of invasive carcinoma. They also have at least some basal cells lining their ducts and acini that will not be present in a carcinoma. However it must be remembered that carcinomas can sometimes also have smooth contours to the individual glands, but careful inspection shows infiltrative nature of such tumors.

2. Any lesion with severe cytologic atypia and/or comedonecrosis needs to be reported, as these are indications of an aggressive lesion, whether intraductal or not. For example, it appears that any lesion with cytologic atypia of carcinoma AND a complex growth pattern (whether invasive or not) portends the worse prognosis, with increasing size correlating with worse behavior (4, 5).

3. Any lesion with complex architectural growth pattern and obvious cytologic atypia cannot be missed and must be reported, whether it is clearly infiltrative (PDAC) or not (IDC-P) (4, 5).

4. Conversely, any low grade lesion without complex growth and without cytologic atypia is likely of little clinical significance, however one never wants to miss a diagnosis of carcinoma, even if it is Gleason score 3+3=6 (at least at the time of this writing). I am alluding to the concept that is starting to develop that lesions without complex growth patterns (i.e. without cribriform, papillary, solid, expansile or necrosis), may not actually be carcinomas, but rather might represent either the precursor lesion of carcinoma, or indicate a field effect of increased risk of developing carcinoma. Such a theory would explain why pure Gleason score 3+3=6 carcinomas are almost never seen beyond the prostate gland, and are never seen to metastasize (49).

More practical considerations for handling these findings in needle biopsies (these are just the way that I practice and are presented here for your consideration):

a. If carcinoma is present, always report it and grade it per the modified Gleason grading system (ISUP 2014 amendments) and assign appropriate grade group if you wish. If it has columnar features, you should at least suggest that it could be a ductal type adenocarcinoma (PDAC); if the columnar cells only have mild cytologic atypia without complex growth pattern, I just suggest that some may consider it to be ductal carcinoma without calling it outright, however if they have high grade atypia, I will diagnose it as ductal type carcinoma.

Once carcinoma is present, these other situations below are no longer of any clinical significance EXCEPT FOR THE NEED TO RECOGNIZE IDC-P AND AIP!!!

b. If HGPIN is the only finding (no carcinoma), data suggest that you do not need to report it; many urologists will now just ignore it. However, I do report it if it is obvious and/or present on multiple cores, and it has been shown that the more cores involved by HGPIN, the more likely to diagnose carcinoma on a repeat biopsy (17).

I almost never report HGPIN if the biopsy is from the base, as central zone histology is so similar to HGPIN; I require prominent macronucleoli for this diagnosis at this site. I do not report or suggest HGPIN if there is any possibility that it is some form of reactive atypia. I almost never report HGPIN based on cytologic atypia without macronucleoli, but I do seriously consider IDC-P or AIP in those situations, and I definitely will call it one of these if complex architecture is present. I also do not call something HGPIN if it has any complex architecture, such as solid, cribriform or papillary growth.

c. What do you do if you only have IDC-P without any invasive carcinoma? I clearly report it, I suggest at least an immediate follow-up biopsy at a bare minimum, I indicate that definitive treatment is
acceptable, and I refer the urologist to the literature (33, 35, 36). Data suggests that there is undetected carcinoma present, AND that it likely is high grade as well, so one is completely justified in treating IDC-P even if there is no carcinoma on the biopsies. If you do not feel comfortable with this, then do ask the urologist to get an immediate repeat biopsy. Patients with IDC-P should not be put on an active surveillance protocol at this time (36).

d. If I do not have any carcinoma, and the findings are intermediate between HGPIN and IDC-P, I diagnose it as AIP, and I handle this just like IDC-P, except that I do not suggest definitive treatment (47, 48).

e. Do you grade IDC-P? While the recommendations are not to grade IDC-P (28), if I do have invasive carcinoma present, for grading I just count the IDC-P as if it were part of the carcinoma for grading purposes. If you ignore the presence of basal cells in IDC-P (i.e. you were considering it to be cancer), it would graded as either Gleason pattern 4 (if cribriform) or grade 5 (if solid and/or containing comedonecrosis). Again, this is not a universally accepted practice, however the outcome data does support this practice!!!

f. Do you ever use Immunohistochemistry for discriminating IDC-P from HGPIN or AIP? I actually do this fairly liberally, however I strongly admit that having the PTEN intact when I think something is IDC-P, and PTEN missing when I think something is HGPIN is very humbling. Clearly these diagnoses should be based on the histologic findings and I find myself diagnosing almost all of these as AIP, but I will suggest in which direction I am favoring based on the outcome of these stains. Although if PTEN is absent, I will sometimes diagnosis as IDC-P; findings in studies of AIP indicate that this more likely is an aggressive lesion, so I feel more comfortable pushing towards IDC-P in these situations (47, 48).

g. Do you routinely perform IHC for basal cells when there is a question of whether something is intraductal or not? Yes and no! If it is high grade and irregular, I may just diagnose as carcinoma, I definitely will not do if there are areas of obvious carcinoma present. If there are no obvious areas of carcinoma, then I might do it for high grade lesions (when I think something is either IDC-P or ductal carcinoma), however per item c. above, IDC-P is also known as an aggressive lesion, so you really cannot go wrong either way. For example, if you diagnose as carcinoma, but actually is IDC-P, you will almost certainly never know, as carcinoma almost certainly will show up on repeat biopsy or prostatectomy. If you diagnose as IDC-P and it actually is carcinoma, then again you likely will not know since these are so closely related.

For low grade lesions, I will diagnose as HGPIN unless it has features that make me think that it could be PIN-like or pseudohyperplastic carcinoma Glands are too crowded and show infiltrative growth pattern), then I will do IHC stains to rule out these mimics.

h. When you have small glands suspicious for carcinoma next to HGPIN, what do you do? It depends on many factors. If it is a first time biopsy, I likely will just diagnose as PINATYP (specifically: “Atypical glands adjacent to high grade prostatic intraepithelial neoplasia; sc. Because of proximity to HGPIN, tangential sectioning of the HGPIN cannot be entirely excluded, precluding definitive diagnosis of carcinoma, consider repeat biopsy”) and then just move on. This finding predicts a 46% probability of finding carcinoma on a follow-up biopsy. I do this because immunohistochemistry and level sections likely will not be helpful. If the patient is back for a second or third round of biopsies, I try to do anything to stop the urologist from treating the patient like a pin cushion. If I find all benign tissue on these follow-up biopsies, I will then report any atrophy and/or acute inflammation that I see. It is amazing how many times that all of these biopsies from these patients are full of acute and chronic inflammation and generalized atrophy (we should write this up); all features that can explain the serum PSA rise that the urologist uses to trigger the biopsy. If they have HGPIN or PINATYP on the repeats, I will level these and do IHC stains if necessary to see if I can get to a diagnosis of carcinoma, however
these patients likely will then go on to active surveillance at our institution (so maybe I do not need to chase so hard?).

i. If you have focal basal cell staining of an intraductal lesion, what do you do? If it has the cytology of HGPIN, I ignore it and just report as HGPIN and mention focal basal cell loss (the diagnosis based on H&E findings, and the presence of any basal cells in a low grade lesion should be considered a benign lesion or HGPIN), unless it has the budding of PINATYP, then I report it as that (see h. above). If it is IDC-P vs. invasive carcinoma with rare basal cells, then you might think that you have a big problem. I report these as IDC-P suspicious for high grade carcinoma, and then describe that at a bare minimum immediate rebiopsy is needed, but that definitive therapy is also acceptable (see c. above). The biggest difficulty here actually is whether it is IDC-P or PDAC. If the cells are columnar, there are at least some areas without any basal cells and that appear to have infiltrative growth pattern, then I likely will call PDAC, although this can be very difficult depending on the amount of basal cells present.

j. In analogous manner, if you are on the fence between AIP and IDC-P, or HGPIN and AIP, what do you do? See item f. above.

References:


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49. Ross HM, Kryvenko ON, Cowan JE, Simko JP, et al., "Do adenocarcinomas of the prostate with Gleason score (GS) ≤6 have the potential to metastasize to lymph nodes?," AJSP 36(9): 1346-52 (2012). PMID: 22531173


Figure 1: Gleason’s Grading Schematic. Patterns below the heavy dashed line that is drawn to encroach into the Gleason pattern 3 area are considered Gleason pattern 4 using the recommendations of the ISUP 2014 Consensus Conference Recommendations (*). The similar situation is depicted using a finely dashed line for clarifications between Gleason patterns 4 and 5.