ARTHUR PURDY STOUT SOCIETY COMPANION MEETING: DIFFICULT NEW DIFFERENTIAL DIAGNOSES IN PROSTATE PATHOLOGY

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Most prostatic ductal adenocarcinomas of the prostate are characterized by cribriform and/or papillary architecture lined by columnar pseudostratified malignant epithelium. PIN-like ductal adenocarcinomas closely resembles high-grade prostatic intraepithelial neoplasia (HGPIN) composed of simple glands with predominantly flat or tufting architecture. Cytologically, tumors are characterized by tall columnar atypical cells, basally located nuclei, and amphophilic cytoplasm. The tumors lack marked pleomorphism, necrosis, solid areas, cribriform formation, or true papillary fronds. No basal cells are present on p63 and/or high molecular weight cytokeratin staining. PIN-like ductal adenocarcinoma differs from HGPIN by the presence of cystically dilated glands, occasionally more crowded 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 is accompanied by Gleason score 6 acinar carcinoma and behaves similar to Gleason score 6 acinar cancer. Recognition of this entity is critical to differentiate it from both HGPIN and conventional ductal adenocarcinoma.

High Grade PIN vs. Intraductal Carcinoma (IDC-P)

IDC-P is defined as malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells. Its distinction from HGPIN is that it has:

- Solid or dense cribriform pattern

or

- Loose cribriform or micropapillary pattern with either:
  - Marked nuclear atypia: nuclear size 6 x normal
  - Non-focal comedonecrosis

IDC-P on prostate biopsies is frequently associated with high-grade cancer and poor prognostic parameters at radical prostatectomy as well as potentially advanced disease following other therapies. These findings support prior studies that IDC-P represents an advanced stage of tumor progression with intraductal spread of tumor. Consideration should be given to treat patients with IDC-P on biopsy aggressively even in the absence of documented infiltrating cancer.
<table>
<thead>
<tr>
<th>Cribriform Acinar Adenocarcinoma</th>
<th>Cribriform IDC-P</th>
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<tbody>
<tr>
<td>Absence of contour or branching architecture of prostatic ducts</td>
<td>Contour or branching architectures of prostatic ducts</td>
</tr>
<tr>
<td>Irregular, infiltrating borders</td>
<td>Rounded, circumscribed borders</td>
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<tr>
<td>Absence of basal cells</td>
<td>Basal cells present</td>
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<table>
<thead>
<tr>
<th>Ductal Adenocarcinoma</th>
<th>IDC-P</th>
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<tbody>
<tr>
<td>Cribriform with large slit-like lumina</td>
<td>Cribriform with small rounded lumens</td>
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<td>Tall columnar cells</td>
<td>Cuboidal cells</td>
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<tr>
<td>Papillary fronds with fibrovascular cores</td>
<td>Micropapillary tufts lacking fibrovascular cores</td>
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<tr>
<td>Basal cells usually absent</td>
<td>Basal cells always present</td>
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Cribriform Gleason Pattern 3 Adenocarcinomas

vs.

Cribriform Gleason Pattern 4 Adenocarcinomas

With the exception of cases of cribriform acinar prostate cancer with comedonecrosis, which is Gleason pattern 5, all cribriform acinar prostate cancer should be graded as Gleason pattern 4 for the following reasons.

- Even in a highly selected set of images thought to be the best candidates for cribriform pattern 3, most experts interpret the cribriform patterns as pattern 4.

- Most of the cribriform foci thought to be candidates for cribriform pattern 3 (73%) are associated with more definitive pattern 4 elsewhere on the needle biopsy specimen.

- Conceptually, one would expect the change in grade from pattern 3 to pattern 4 to be reflected in a distinct architectural paradigm shift where cribriform as opposed to individual glands are formed, rather than merely a subjective continuum of differences in size, shape and contour of cribriform glands.

- The only reason why cribriform pattern 3 even exists is because of the original Gleason schematic diagram, although Gleason never specifically studied the prognostic difference between what he called cribriform Gleason pattern 3 compared to Gleason pattern 4, and many of Gleason’s cribriform Gleason pattern 3 cancers may not even have been infiltrating carcinomas due to the lack of availability of immunohistochemistry for basal cell markers.

- There is poor reproducibility amongst experts differentiating cribriform pattern 3 vs. pattern 4 due to:

  1) Disagreement as to what are the key diagnostic features in a given case (ie. irregular distribution of lumina & variable slit-like lumina favor pattern 4 vs. small glands & regular contour favor pattern 3.
2) Disagreement as to assessment of given criteria: regular vs. irregular distribution of lumina

p63 Positive Prostate Adenocarcinoma

vs.

Basal Cell Carcinoma

Rarely, prostate cancer can aberrantly express diffuse p63 staining in a nonbasal cell distribution leading to the erroneous diagnosis of atrophy or basal cell carcinoma. Over 90% show a distinctive morphology composed predominantly of glands, nests, and cords with atrophic cytoplasm, hyperchromatic nuclei, and visible nucleoli. The diagnosis of prostate cancer is based on the morphology and confirmed by the absence of high molecular weight cytokeratin staining and positivity for alpha-methylacyl-CoA racemase (AMACR) in the atypical glands.

Basal cell carcinoma usually differs from p63 positive cancer in its architectural patterns. Patterns unique to basal cell carcinoma include: 1) adenoid cystic pattern; 2) large solid basaloid nests with comedonecrosis; 3) nests surrounded by a rim of collagen where the there is a dual cell population of cells consisting of inner cells with eosinophilic cytoplasm and outer basaloid cells with scant cytoplasm; and 4) irregular sized and shaped basaloid nests often with a desmoplastic stromal response. There is one pattern of basal cell carcinoma that consists of individual small glands with multilayering that resembles basal cell hyperplasia and p63 positive prostate cancer. The lack of high molecular weight cytokeratin positivity (HMWCK) and positivity for PSA and AMACR rules out this pattern of basal cell carcinoma.

There are several other situations where there is immunohistochemical labeling of prostate cancer with basal cell markers. Prostate cancer may show scattered cells positive for basal cell markers. The positivity is not in a basal cell distribution and represent aberrant staining of cancer cells. This phenomenon is more typically seen with HMWCK as compared to p63. More rarely, one can see adenocarcinoma of the prostate with focal retention of its basal cell layer. Only cases that are the most unequivocal prostate cancer based on architecture and cytology should be diagnosed in the face of basal cell staining.


Partial Atrophy

vs.

Prostate Cancer

Partial atrophy is the most common mimicker of prostate cancer. Partial atrophy may still retain the lobular pattern of post-atrophic hyperplasia, or have more of a disorganized diffuse appearance. Partial atrophy lacks the basophilic appearance of fully developed atrophy as the nuclei are more spaced apart. The presence of crowded glands with pale cytoplasm may lead to an overdiagnosis of low-grade adenocarcinoma. At higher power, however, the glands have benign features characterized by undulating luminal surfaces with papillary infolding. Most carcinomas have more straight, even luminal borders. In addition, the glands are partially atrophic with nuclei in areas reaching the full height of the cytoplasm. The nuclear features in partial atrophy tend to be relatively benign without prominent nucleoli, although nuclei may appear slightly enlarged with small nucleoli. One should hesitate diagnosing cancer when the nuclei occupy almost the full cell height and the cytoplasm has the same appearance as surrounding more obvious benign glands. Partial atrophy typically has a patchy basal cell layer and may express racemase and in small foci on needle biopsy no basal cells may be present, mimicking the staining pattern seen with prostate cancer.


Gastrointestinal Stromal Tumors (GIST)

vs.

Other Prostatic Stromal Tumors

Gastrointestinal stromal tumors (GISTs) are typically not included in the differential diagnosis of spindle cell tumors seen on prostate needle biopsy. However, their recognition is critical due to their unique clinical management. Rectal or extraintestinal GIST can result in a clinical impression of a prostatic lesion. One should consider CD117 (c-kit) in the immunohistochemical panel to exclude GIST before diagnosing a solitary fibrous tumor, leiomyosarcoma, or specialized prostatic stromal tumor on prostate needle biopsy.