**Cribriform Lesions of the Prostate**

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**Case**

- 75 y.o. male with persistently elevated PSA for 12 years  
- Multiple prostate biopsies: high grade PIN

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**ACCME/Disclosures**

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Dr. Ming Zhou declares she has no conflict(s) of interest to disclose.
Diagnosis

- High grade PIN
- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Intraductal carcinoma of the prostate

Workup of Cribriform Lesions of the Prostate
Cribriform Lesions of the Prostate Comprise A Wide Range of Lesions

- Central zone glands
- Clear cell cribriform hyperplasia
- Basal cell hyperplasia
- Cribriform PCa
- Ductal PCa
- Intraductal carcinoma

Central Zone Glands

- Seen in biopsies from the base
- No atypia
- May be mistaken for HGPIN; unlikely to be confused with PCa
- Pseud stratified nuclei; eosinophilic cytoplasm; prominent basal cells

Clear Cell Cribriform Hyperplasia

- Part of BPH; seen in transition zone/TURP
- Nodular collection of cribriform glands
- Clear/eosinophilic cytoplasm
- Prominent basal cells
- No atypia
- May be mistaken for HGPIN; unlikely to be confused with PCa

Diagnostic Approach to Prostate Cribriform Lesions in Prostate Biopsies

Cribriform Lesions in Prostate Biopsy

- Cytological Atypia in Secretory Cells (Nuclear Enlargement, Coarse chromatin, Prominent Nucleoli, Pleomorphism)

No

- Central zone glands
- Clear cell cribriform hyperplasia
- Basal cell hyperplasia
Basal Cell Hyperplasia
- Part of BPH; seen in transition zone/TURP
- Blue atrophic glands/nests
- Multiple layers of cells with scant cytoplasm

Diagnostic Approach to Prostate Cribriform Lesions in Prostate Biopsies

Cribriform Lesions in Prostate Biopsy

Cytological Atypia in Secretory Cells
(Nuclear Enlargement, Coarse chromatin, Prominent Nucleoli, Pleomorphism)

Yes
- Atypical Cribriform Lesion

No
- Basal cells

• Central zone glands
• Clear cell cribriform hyperplasia
• Basal cell hyperplasia

Cribriform PCa

Ductal PCa

Cribriform PCa
- All cribriform cancer glands are, regardless of size, shape and contour, pattern 4 (ISUP2014/WHO2016)

Ductal Adenocarcinoma of the Prostate
- Glands lined with pseudostratified columnar shaped nuclei
- Vast majority mixed with acinar PCa
- Graded as Gleason pattern 4 or pattern 5 with necrosis
- Any amount is considered to be significant and should be reported
**Diagnostic Approach to Prostate Cribriform Lesions in Prostate Biopsies**

- Cytological Atypia in Secretory Cells (Nuclear Enlargement, Coarse chromatin, Prominent Nucleoli, Pleomorphism)

  - Yes: Atypical Cribriform Lesion
  - No: Central zone glands, Clear cell cribriform hyperplasia, Basal cell hyperplasia

**Intraductal Carcinoma of the Prostate (IDC-P)**

**Current Concept**

- A distinct entity in 2016 WHO classification
- Atypical secretory cells that grow within and significantly expand prostatic ducts and acini
  - Retrograde spread of PCa cells into prostatic glands in majority
  - Precursor to PCa in rare cases

**2 Histological Hallmarks**

1. Expansile growth of atypical cells
   - Cribriform/solid architecture
2. Within native prostate glands
   - Basal cell layer at least partially preserved
Partially involves native benign glands

Intraductal Carcinoma of the Prostate

- Marked variation in nuclear size
- Pleomorphic nuclei >6X adjacent nuclei

Intraductal Carcinoma of the Prostate
Molecular Genetics

- Many genetic changes reported in IDC-P
- ERG gene fusion in 58-75% IDC-P; 100% concordance between IDC-P and adjacent PCa
- PTEN (cytoplasmic) loss in 84% IDC-P; 92% concordance between IDC-P and adjacent PCa
- IHC stains for ERG and PTEN may help distinguish IDC-P from its mimickers
Intraductal Carcinoma of the Prostate
(Clinical Significance)

- In radical prostatectomy, IDC-P is usually associated with high grade and volume PCa; indicates a worse prognosis
- IDC-P in needle biopsy is almost always associated with invasive PCa and may predict a worse pathologic findings in RP
- Isolated IDC-P without concomitant invasive cancer on needle biopsy is rare but generally warrants definitive treatment

Differential Diagnosis of Intraductal Carcinoma of the Prostate
/DDX for Atypical Cribriform/Solid Lesions

- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Cribriform high grade PIN
- Urothelial carcinoma involving the prostate
- Metastatic (colorectal) adenocarcinoma
High Grade Urothelial Carcinoma Involving Prostatic Acini

The Most Important Differential Diagnosis Is between IDC-P and Cribriform High Grade PIN

<table>
<thead>
<tr>
<th></th>
<th>HGPIN, cribriform type</th>
<th>IDC-P</th>
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<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Putative precursor lesion to PCa</td>
<td>Intraductal spread of advanced stage PCa</td>
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<tr>
<td><strong>Clinical Significance in Prostate Biopsy</strong></td>
<td>Cancer risk associated with the diagnosis of HGPIN in prostate biopsy: ~ 20%</td>
<td>Almost always associated with high grade/volume PCa</td>
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<tr>
<td><strong>Patient Management</strong></td>
<td>HGPIN diagnosed in prostate biopsy does not mandate a repeat biopsy within 1st year when HGPIN is focal</td>
<td>Intermediate repeat biopsy</td>
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</table>
Atypical cribriform lesion with basal cells intermixed with or within 3 mm from the border of PCa
- ERG gene fusion: 75%
- ERG fusion status concordant between IDC-P and adjacent PCa in 100% cases

- IDA-P and cribriform HGPIN are genetically distinct
- ERG gene status identical between IDC-P and PCa

IDC-P: resulting from intraductal spread of PCa

# cases | IDC-P | Cribriform HGPIN | P value
--- | --- | --- | ---
43 | 23.8 | 2.4 | N.A.
1 | 0.34-0.19 | 6.32-0.13 | 0.406
1 | 5.3-0.8 | 2.0-6.9 | N.A.
1 | 1.5-1.3 | 0.42-0.15 | N.A.
1 | 0.6-0.5 | 0.2-1.8 | N.A.
| 1.8 (0.3%) | 17 (58.9%) | 0.197
| 18 (76.1%) | 19 (75.0%) | N.A.
| 36 (83.7%) | 1 (4.3%) | N.A.
| 11 (78.6%) | 1 (4.3%) | N.A.
| 15 (54.5%) | 14 (48.3%) | 0.724
| 22 (51.2%) | 9 (29.0%) | 0.35
| 2 (27.9%) | 9 (29.0%) | N.A.

Diagnostic Criteria for IDC-P
(Guo CC and Epstein JI, Mod Pathol. 2006)

- Large glands with growth of atypical cells that span the entire lumen and preserved basal cells
- Solid architecture
- Dense cribriform
- Non-focal comedonecrosis (>1 gland)
- Marked atypical nuclei >6X adjacent benign nuclei

IDC-P
Intraductal Carcinoma of the Prostate

Significance of IDC-P in Prostate Biopsy


- IDC-P in prostate biopsies should be reported even when it is associated with an extensive and high-grade PCa, as it may provide additional prognostic value
Significance of Finding Intraductal Carcinoma of the Prostate without Concomitant Invasive Carcinoma on Prostate Needle Biopsy

(Guo & Epstein, Mod Pathol 2006; Robinson & Epstein, J Urol, 2010)

- 83 men with biopsies showing only IDC-P
- 21/23 radical prostatectomies (RP)
  - Stage
    - T3a: 12 (42.9%), T3b: 3 (14.3%), T2: 12 (42.9%)
  - Gleason score
    - Mean 7.9 (7-10)
    - 37%: primary or secondary pattern 5; 11% had tertiary pattern 5
- Follow up
  - Available in 66 (79.5%) for 1-58 months
  - 4 (6%) had bone mets (including one with RP)
  - 4 (6%) had PSA recurrence (including 3 with RP)

- At RP, men with biopsies showing only IDC-P typically have high grade (GS >7) and advanced stage (pT3) PCa
- Men with IDC-P as the sole finding in PBx should be treated with definitive therapy

Diagnostic Criteria for IDC-P

(Guo CC and Epstein JL, Mod Pathol. 2006)

Large glands with growth of atypical cells that span the entire lumen and preserved basal cells

- Solid architecture  
  or  
- Dense cribriform  
  or  
- Non-focal comedonecrosis (>1 gland)  
  or  
- Marked atypical nuclei >6x adjacent benign nuclei

Clinical Significance of Borderline Lesions between High Grade Prostatic Intraepithelial Neoplasm (HGPIN) and Intraductal Carcinoma of the Prostate (IDC-P) on Needle Biopsy


- 60 prostate biopsies with borderline intraductal proliferation falling short of IDC
  - Repeat biopsy in 35, RP in 1
    - Invasive PCa in 15
    - Definitive IDC-P in 3
  - Invasive Pca
    - GS 6-10% (8/15); GS 7-33% (5/15); GS8-13% (2/15)
- Borderline lesions between HGPIN and IDC-P are associated with a substantial increased risk (50%) of PCa/IDC on subsequent biopsy; immediate repeat biopsy should be recommended
Working up and Reporting Atypical Cribriform Lesions in Prostate Biopsy

**IDC vs PCa vs HGPIN in Prostate Biopsy**

**Associated with PCa**
- Overall GS would be changed
- **IHC**
  - Report
  - Note the adverse prognostic significance

**Without PCa**
- Overall GS would not be changed
- **IHC**
  - No IHC
  - Do not report

**Atypical intraductal proliferation**
- **IHC**
  - Diagnose IDC and document its poor prognostic significance in the report
  - Advise immediate rebiopsy or recommend definitive therapy
- **Recommend immediate repeat biopsy**

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**Working up the Cribriform Lesions of the Prostate**

- Prostate cribriform lesions comprise a wide range of lesions from normal to premalignant to highly aggressive
- Look for nuclear atypia and basal cells
- It is critical to distinguish IDC-P from cribriform high grade PIN
- Any atypical cribriform lesion not diagnostic of IDC should be worked up by repeat biopsy

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**Questions?**