Macro- and microacinar proliferations of the prostate
(with emphasis on cancer mimics)

Rodolfo Montironi, MD (IT), FRCPath (UK), IFCAP (USA)

Polytechnic University of Marche Region (Ancona)
School of Medicine, Ancona, Italy
and
Arizona Cancer Center, Tucson, AZ, USA
Lesions with
1. small
2. large and cribriform
3. solid and nonglandular patterns
Further subdivided into
1. those of prostatic epithelial origin
2. those of nonprostatic epithelial origin

Door = Porta = Kapı
White coat = Camice = önlik
To eat = Mangiare = Yemek
Water = Acqua = Su
Book = Libro = Kitap
I = io = Ben
To drink = Bere = İçecek
To push = Spingere = İtmek
Lesions of *prostatic* epithelial origin

1. Atrophy

2. Adenosis (Atypical adenomatous hyperplasia, AAH))

3. Sclerosing adenosis

4. Radiation atypia in benign glands

5. Verumontanum mucosal gland hyperplasia
Small gland pattern

Lesions of \textit{prostatic} epithelial origin

\textbf{Atrophy}

1. Simple atrophy (cyst formation)
2. Post-atrophic hyperplasia
3. Partial atrophy

Proliferative atrophy and proliferative inflammatory atrophy (PIA) are \textit{optional designations}
Small gland pattern

Simple atrophy and postatrophic hyperplasia

1. *Lobular configuration*

2. *Basophilia* from the lack of cytoplasm, both apically and laterally compared to normal epithelium, such that the nuclei appear crowded and a nuclear outline of the glands is seen at low-power.

3. *Stroma altered by a pale fibrosis*, with periacinar collagen deposition, which can impart a sclerotic appearance.
Small gland pattern: Atrophy

- *Simple atrophy and postatrophic hyperplasia do not generally pose a diagnostic problem*
- IHC for *basal cell markers* shows uniform staining of the basal cells in simple atrophy and postatrophic hyperplasia, ruling out PCa
- *AMACR* is generally negative in simple atrophy and very uncommonly expressed in postatrophic hyperplasia
Small gland pattern: Partial atrophy

Differs from simple atrophy and postatrophic hyperplasia in several aspects:

• Although it generally retains a lobular architectural pattern of growth, it can show a more disorganized diffuse growth pattern.
Small gland pattern: Partial atrophy

- Focus of crowded glands with pale scant cytoplasm
  - The *attenuated cytoplasm is mostly apical* with most of the nuclei in the glands reaching the full height of the cells
  - The *lateral aspect of the cytoplasm is preserved* which results in nuclei that are more spaced and less crowded than simple atrophy or postatrophic hyperplasia
Small gland pattern

Atrophy

Simple atrophy

Post-atrophic hyperplasia

Partial atrophy

Montironi R et al, Histopathology 2011
Small gland pattern: Partial atrophy

Features seen within partial atrophy that create difficulty in its distinction from \textit{acinar (conventional) Pca}:  

1. Crowded and sometimes disorganized pattern of growth  
2. Relative high nuclear to cytoplasmic ratio with slightly enlarged nuclei  
3. Presence of visible yet small nucleoli  
4. Straight luminal borders in some glands  
5. Negativity of some of the glands for basal cell markers  
6. Positivity of some glands for AMACR
Small gland pattern: Partial atrophy

The disorganized pattern can give the focus a *pseudoinfiltrative appearance* in which the smaller glands of partial atrophy seem to be present between larger clearly benign glands.

1. It is usually focal and, most importantly, close inspection reveals that the smaller ‘suspicious’ glands are cytologically similar to the larger benign glands which they appear to infiltrate amongst.

2. The cytoplasm in partial atrophy is clear or pale in contrast to the typical amphophilic cytoplasm of PCa.
Small gland pattern: Partial atrophy

1. The high nuclear to cytoplasmic ratio seen in partial atrophy is the result of the lack of apical cytoplasm rather than marked nuclear enlargement which is seen in Pca

2. Nucleoli are usually absent to visible in partial atrophy and not as prominent as seen in PCa
Small gland pattern: Partial atrophy

Differs from *atrophic acinar PCa* in that atrophic cancers have one or more of the following features:

1. A more infiltrative appearance where the cancer glands infiltrate as isolated glands in between benign glands
2. Associated nonatrophic cancer
3. Prominent cytological atypia beyond what can be seen with benign atrophy
4. A focus of atrophic cancer should be supported by negative IHC stains for basal cell markers
Small gland pattern: Adenosis (AAH)

1. Proliferation of small acini
2. Prominent perinodular distribution of the abnormal glands (within or adjacent to typical hyperplastic nodules)
3. Some variation in size and shape
4. Individual glands are closely packed but separate and show no evidence of fusion
Small gland pattern: Adenosis

1. Pushing rather than infiltrating border but *may show a limited degree of infiltration*

2. Uncommonly, the small acini exhibit a more extensive, crowded, and nonlobular distribution, in a pattern termed *diffuse adenosis*
Small gland pattern: **Adenosis**

1. Lined by cuboidal to low columnar cells with moderate to abundant clear or lightly eosinophilic cytoplasm

2. The nuclei are round to oval and there is uniform fine chromatin

3. Nucleoli may be present but they are generally small. Uncommonly, enlarged nucleoli are identified in a subset of cells
Small gland pattern: Adenosis

1. May contain corpora amylacea and, in some instances, luminal eosinophilic crystalloids. Occasionally, basophilic luminal mucus may be seen.

2. Up to 18% of cases express AMACR.

3. Immunohistochemical staining demonstrates absence of basal cells in about one-half of all glands.
Small gland pattern: Adenosis

Common mimicker of PCa

The features shared in adenosis and prostate cancer are:

1. Crowded glands
2. Crystalloids
3. Medium-sized nucleoli
4. Scattered poorly formed glands and single cells
5. Minimal infiltration at periphery
6. AMACR immunoreactivity
<table>
<thead>
<tr>
<th>Adenosis</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular</td>
<td>Haphazard growth pattern</td>
</tr>
<tr>
<td>Small glands share features with admixed</td>
<td>Small glands differ from adjacent</td>
</tr>
<tr>
<td>larger glands</td>
<td>benign glands</td>
</tr>
<tr>
<td>Pale-clear cytoplasm</td>
<td>Amphophilic cytoplasm</td>
</tr>
<tr>
<td>Medium-sized nucleoli</td>
<td>Occasionally large nucleoli</td>
</tr>
<tr>
<td>Blue mucinous secretions rare</td>
<td>Blue mucinous secretions common</td>
</tr>
<tr>
<td>Basal cells present</td>
<td>Basal cells absent</td>
</tr>
<tr>
<td>Corpora amylacea common</td>
<td>Corpora amylacea rare</td>
</tr>
</tbody>
</table>
Small gland pattern: Adenosis

1. There is *lack of proof of a relationship between adenosis and PCa*

2. Adenosis should be considered as a *benign lesion* and patients followed conservatively

3. The term should *not be used as a ‘wastebasket’* for small glandular lesions that are difficult to classify or for suspicious atypical small gland proliferations
Small gland pattern: Sclerosing Adenosis (SA)

1. Benign, small, acinar proliferation in dense spindle cell stroma, with a distinct immunohistochemical profiles

2. Tiny microacini, cords, solid clusters, and single cells

3. Rarely seen in needle biopsy specimens, may simulate PCa and accounts for up to 10% of cases overdiagnosed as PCa
Small gland pattern: Sclerosing Adenosis

Multiple light microscopical and immunohistochemical features separate SA from PCa:

1. Intact basal cell layer
2. Unique immunophenotype of the basal cells, including abundant S-100 protein and smooth muscle actin (SMA) reactivity (i.e., myoepithelial metaplasia)
3. Cellular spindle cell stroma
4. Variably thickened basement membrane
5. Absence of significant cytological atypia
**Atypical sclerosing adenosis (ASA)**

- A series of five cases of the so-called atypical sclerosing adenosis was by Cheng L. and Bostwick DG
- The overall architecture is identical to that of SA
- Differs from it by the *presence of enlarged nuclei, prominent nucleoli*, and aneuploid DNA content in the majority of cases
- The term ASA does not imply that the lesion is premalignant
- Benign lesion that does not require treatment
- ASA may be mistaken for PCa, and should be distinguished from other mimics
- Architectural pattern: Small gland
- Pca mimicked: Gleason pattern ≤3

Lesions of nonprostatic epithelial origin

1. Nephrogenic adenoma
2. Mesonephric remnants
3. Ejaculatory duct epithelium and seminal vesicle
4. Mucinous metaplasia
5. Cowper’s (bulbourethral) glands
6. Colonic glands

Montironi R et al, Histopathology 2011
Small gland pattern: Nephrogenic adenoma

- Histologically, papillary structures, small tubules, or cystically dilated tubules lined by cuboidal, low columnar, or hobnail-shaped eosinophilic cells are seen.
- A lesion of presumed renal tubular origin; previous diagnostic and therapeutic procedures.
- Different locations within the urinary system, including the prostatic urethra where it might cause confusion with PCa and UC with small tubules.
NA vs. PCa

- Lesions predominantly composed of small tubules are those most likely to be confused with PCa
- Frequently negative for basal cell markers and not infrequently positive for AMACR, PSA, and/or PSAP
- **PAX2 and/or PAX8 immunostains can be used to arrive at the correct diagnosis**
NA vs. UC with small tubules

- The **tubules of urothelial carcinoma** are lined by attenuated urothelial cells in contrast to the varying admixture of cuboidal, columnar and occasionally flattened cells that line the tubules of NA.

- **CK 20, high-molecular-weight cytokeratin and p63**: positive in more than half of urothelial carcinomas.
<table>
<thead>
<tr>
<th>Features</th>
<th>UC with small tubules</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admixed nested, tubular, cystic, polypoid, papillary</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Oedematous and inflammatory background</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell lining</td>
<td>Attenuated</td>
<td>Mixture</td>
</tr>
<tr>
<td>Prominent BM</td>
<td>no</td>
<td>Yes</td>
</tr>
<tr>
<td>Invasion of the <em>muscularis propria</em></td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>IHC</td>
<td>Distinctive for UC</td>
<td>Distinctive for NA</td>
</tr>
</tbody>
</table>
**Atypical nephrogenic metaplasia**

- 18 cases described by Cheng et al

- *Nuclear enlargement, nuclear hyperchromasia, and enlarged nucleoli*

- Two patients had recurrent nephrogenic metaplasia, and the remainder were alive without recurrence or urothelial carcinoma

- No direct evidence that links atypical nephrogenic metaplasia to cancer

- Awareness of the spectrum of cytological changes is critical to prevent overdiagnosis of cancer
- Architectural pattern: Small gland
- Pca mimicked: Gleason pattern $\leq 3$

Lesions of *nonprostatic* epithelial origin

- Mucinous metaplasia
- Cowper’s (bulbourethral) glands
- Colonic glands
# Expected immunoreactivity in benign mimickers of prostate carcinoma of nonprostatic epithelial origin

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>PSA/PAP*</th>
<th>Basal Cell–Associated Markers</th>
<th>AMACR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejaculatory duct/Seminal vesicle</td>
<td>-/+</td>
<td>+ (basal cells)</td>
<td>-</td>
</tr>
<tr>
<td>Cowper’s gland</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Mesonephric remnants</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Nephrogenic adenoma</td>
<td>-/+</td>
<td>-/+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Architectural pattern: Large and cribriform glands

1. Basal cell hyperplasia
2. Clear cell cribriform hyperplasia
3. Medium- to large-sized hyperplastic glands
4. Reactive epithelial atypia

Types of prostate carcinoma mimicked

1. Cribriform Gleason patterns 3, 4, and 5
2. Ductal adenocarcinoma
3. Pseudohyperplastic

Montironi R et al, Histopathology 2011
Basal cell proliferations of the prostate

1. Ordinary (or usual) BCH
2. BCH with prominent nucleoli (or atypical BCH)
3. Basal cell carcinoma (adenoid cystic carcinoma)
BCH (with prominent nucleoli) vs. HGPIN

1. The nuclei in BCH tend to be round whereas, at times, the cells form small solid basal cell nests. In contrast, the cells in HGPIN tend to be more pseudostratified and columnar and do not occlude the glandular lumina.

2. Within areas of BCH, atypical looking basal cells can be seen underling the overlying benign appearing secretory cells. HGPIN has full-thickness cytological atypia with the nuclei oriented perpendicular to the basement membrane.
Ordinary (or usual) BCH

BCH with prominent nucleoli
**BCH vs. HGPIN**

- In BCH, IHC shows multilayered staining of the basal cells, whereas an interrupted immuno-reactive basal cell layer is seen in HGPIN.
- AMACR is negative in florid BCH and positive in HGPIN and Pca.
- Glutathione-S-transferase pi is positive in florid BCH and negative in PCa.
BCH with prominent nucleoli (or atypical BCH)
Central zone epithelium
**BCH (with a glandular architecture or when florid) vs. PCa**

- **BCH can be distinguished from PCa by its very basal cell appearance**
  1. The glands in BCH appear basophilic at low power due to multilayering of basal cells which have scant cytoplasm
  2. Gland-forming PCa of the prostate almost always has more abundant cytoplasm resulting in a more eosinophilic appearance to the glands

- **Utilization of IHC with basal cell specific antibodies (34betaE12 or p63) can differentiate between these two lesions**
Expected immunoreactivity in glandular lesions of prostatic epithelial origin

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Basal Cell–Associated Markers</th>
<th>AMACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign glands including atrophy, postatrophic hyperplasia, etc</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Adenosis</td>
<td>+/- (patchy)</td>
<td>-/+</td>
</tr>
<tr>
<td>Basal cell hyperplasia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Prostatic adenocarcinoma, PIN-like
BCH vs. basal cell carcinoma

Characteristics of basal cell carcinoma that can help in the differential diagnostic distinction from basal cell hyperplasia

1. Extensive infiltration between normal prostate glands
2. Extension out of the prostate
3. Perineural invasion
4. Necrosis
5. IHC studies for Ki67 and BCL2 may also be of value:
   • the proliferative index in basal cell hyperplasia is low (<5%)
   • BCL2 is not overexpressed
Clear cell cribiform hyperplasia

• At low-power a nodular appearance and intervening cellular stroma
• Cribriform glands have clear cytoplasm and uniform round lumina
• The cells comprising the central cribiform areas are cuboidal to low columnar secretory-type cells with uniform round nuclei and clear cytoplasm
• They lack nuclear atypia and nucleolar enlargement
• Basal cells are prominently displayed around the periphery
CCCH mimics

CCCH enters the differential diagnosis of Gleason grade 4 cribriform Pca

The distinction of clear cell cribriform hyperplasia from cribriform carcinoma is based on

1. the ‘low power’ nodularity
2. cellular stroma
3. presence of basal cells, and
4. lack of significant cytological atypia
Take home message

• The diagnosis of PCa and its mimickers should not be based on one feature only (i.e., nucleoli or lack of basal cell markers)

• but rather on a case's constellation of architectural, cytological, and ancillary features