APPLICATION OF IMMUNOHISTOCHEMISTRY TO CHALLENGING UROLOGIC PATHOLOGY CASES

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Disclosures

- I have nothing to disclose

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Outline

- The prostate/bladder interface
- Advanced prostate cancer
- Another urothelial mimic

Bladder
Prostate
Urethra
Urinary bladder TUR from 70-year-old man
Diagnosis

- Urothelial carcinoma, with invasion of lamina propria and muscularis propria

IHC panel

<table>
<thead>
<tr>
<th>Urothelial markers</th>
<th>Prostate markers</th>
<th>Benign urothelium</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>p63</td>
<td>PSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMWK (34BE12, CK903)</td>
<td>PSAP</td>
<td></td>
<td></td>
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<tr>
<td>GATA-3</td>
<td>P501S</td>
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<tr>
<td>Uroplakin</td>
<td>(NKX3.1)</td>
<td></td>
<td></td>
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<tr>
<td>Thrombomodulin</td>
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</tbody>
</table>

High molecular weight keratin

Benign urothelium  Tumor

GATA-3

PSAP

Benign urothelium  Tumor

P501S
Diagnosis

- Poorly differentiated carcinoma
  - Comment: Most consistent with prostatic adenocarcinoma

Points of emphasis

- History is essential as prostate cancer, especially post treatment, can exhibit a variety of morphologic appearances
- Staining for prostate-specific markers such as PSA, PSAP, and P501S can be decreased or absent in poorly differentiated prostate cancer

Typical use case

High sensitivity antibody (90% positive across all prostatic adenocarcinomas)

TUR from 67-year-old man
Diagnosis

- High-grade urothelial carcinoma with squamous differentiation, invasive into muscularis propria

New information after signout

- First, clinician immediately called – no papillary tumor seen at cystoscopy, seemed to be mass pushing into bladder
- Second, the tumor was sent for UCSF500 sequencing...
UCSF500 Results for this Patient

<table>
<thead>
<tr>
<th>Gene</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN2A/B</td>
<td>Deletion</td>
</tr>
<tr>
<td>TMPRSS2/ERG</td>
<td>Fusion</td>
</tr>
<tr>
<td>FOXA1</td>
<td>Frameshift</td>
</tr>
</tbody>
</table>

Diagnosis

- Prostatic carcinoma with extensive squamous differentiation

Prostate cancer with squamous features

- Parwani et al. AJSP 2004;28:651.
- Often post-treatment
- Can show pure squamous morphology or mixed adenosquamous morphology
- “Whereas the adenocarcinoma component is typically high grade, the squamous component has a wide range of differentiation.”
- Squamous component usually negative for PSA and PSAP and positive for HMWK
Points of emphasis

- Clinical history is essential
- Clinical impression can be helpful
- In cases with aberrant differentiation, IHC patterns can be dramatically altered

Prostate biopsy from 69-year-old man
Benign prostate Tumor

CK7

Benign prostate Tumor

CK20

Benign prostate Tumor

p63
GATA-3
uroplakin II
PSAP

Diagnosis

- High-grade urothelial carcinoma
Points of emphasis

- The clinical presentation of prostatic adenocarcinoma and urothelial carcinoma can overlap

TURP from 67-year-old man
Diagnosis

- Ductal adenocarcinoma of the prostate, Gleason score 4+5=9
Subsequent course

- Patient received definitive therapy for prostate cancer (external beam radiation plus hormone therapy)
- Bladder biopsies showed high-grade papillary urothelial carcinoma

Clinical follow-up

- Patient subsequently underwent cystoprostatectomy, which showed urothelial carcinoma involving the bladder, prostate, and multiple regional lymph nodes

Diagnosis

- Urothelial carcinoma in situ colonizing prostatic ducts, with focal invasion into prostatic stroma
Points of emphasis

- Urothelial carcinoma can spread through the prostatic ducts and simulate high-grade prostatic adenocarcinoma
- An extended IHC panel may be warranted, as staining can be patchy
- The treatment options for urothelial and prostate carcinoma are very different

Prostate triple stain (HMWK, p63, AMACR)

Cystoprostatectomy from 67-year-old man

P501S
Points of emphasis
- Beware the prostate/bladder interface
- IHC can be useful
- IHC can also be misleading, particularly in the setting of aberrant differentiation (e.g. squamous)

Outline
- The prostate/bladder interface
- Advanced prostate cancer
- Another urothelial mimic

Prostate TUR from 50-year-old man

GATA-3  P501S  NKX3.1
Liver biopsy from same patient

TTF-1  Synaptophysin  Chromogranin

NKX3.1
Diagnosis

- Prostate: Prostatic adenocarcinoma, Gleason score 4+5=9
- Liver: Metastatic small cell lung carcinoma

Subsequent findings

- Clinician noted the absence of a lung mass and requested additional pathology review
Diagnosis

- **Prostate**
  - Prostatic adenocarcinoma, Gleason score 4+5=9
  - Small focus of tumor highly suspicious for small cell neuroendocrine carcinoma

- **Liver**
  - Metastatic small cell neuroendocrine carcinoma
    - Prostatic origin most likely
    - Cannot formally exclude another site of origin

Points of emphasis

- Prostatic small cell carcinoma is rare (~1% of cases), but incidence is much higher in treated patients with advanced disease
- It may be a small component of the tumor
- Clinically aggressive tumor with poor prognosis
- Most cases are negative for PSA, PSAP, and NKX3.1
- More than half are positive for TTF-1
UCSF500 Results for this Patient

chromogranin    synaptophysin    TTF-1
TURP from 67-year-old man

Diagnosis

- Prostatic adenocarcinoma
  - PSA staining was very strong, urothelial markers were weak to absent
Diagnosis

- Prostatic adenocarcinoma with mismatch repair deficiency

**MMR-deficient prostate cancer**

- 7/60 (12%) advanced prostate cancers are hypermutated, with MMR gene mutations and MSI
  - Usually due to complex MSH2 and MSH6 mutations

**MSH2/MSH6 loss – UCSF500**
**Checkpoint inhibitors**

Tumor cell

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<table>
<thead>
<tr>
<th>MHC</th>
<th>TCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>PD-1</td>
</tr>
</tbody>
</table>
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T cell

**Points of emphasis**

- Advanced prostate cancer can develop an MMR-deficient, microsatellite unstable phenotype
- These tumors are likely to show improved response to immunotherapy
- IHC can identify many of these tumors, but unclear when to use (reportedly no characteristic morphologic pattern)

**Outline**

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**Disease control rate with MMR deficiency: ~90%**

**Disease control rate with wild-type MMR: ~10%**

**Putative mechanism: more neoantigens = improved immunotherapy response**
Diagnosis

- High-grade urothelial carcinoma with micropapillary features and invasion of muscularis propria

Subsequent findings

- UCSF urologist mentioned that the original urologist who performed the TUR felt that the mass was not typical for urothelial carcinoma
- We requested block for additional work-up
Diagnosis
- Bladder paraganglioma

Clinical follow-up
- Neoadjuvant chemotherapy and cystoprostatectomy canceled
- Repeat TURBT negative for residual tumor
- Patient chose surveillance over partial cystectomy
- Resolution of episodic attacks (palpitations, sweating, headaches, heat intolerance)

Bladder paraganglioma
- Very rare tumor (<0.05% of bladder tumors)
- ~10% show malignant behavior
- A well-recognized mimic of urothelial carcinoma (Zhou et al. AJSP 2004;28:94)
  - Muscularis propria involvement
  - Nuclear atypia
  - Cautery artifact

Points of emphasis
- Clinical history can be essential
- Beware cautery artifact
- Don't forget the rare diagnoses
- GATA-3 can be helpful but stains a lot of entities, including paraganglioma