Pathology of the Urachus

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Updates in Epithelial Neoplasms of the Urachus

1. New classification scheme.
2. Modified criteria for pathologic diagnosis.
3. Potential use and limitations of immunohistochemistry.
5. Newly identified genomic alterations.

Epithelial Neoplasms of the Urachus

- Adenomas
  - Villous adenoma
  - Mucinous cystadenoma

- Adenocarcinomas
  - Non-cystic adenocarcinomas
    - Enteric (intestinal) adenocarcinoma
    - Mucinous (colloid) adenocarcinoma
    - Signet ring cell adenocarcinoma
    - Adenocarcinoma, NOS
    - Mixed adenocarcinoma
  - Cystic adenocarcinomas
    - Mucinous cystic neoplasm of LMP
    - Mucinous cystadenocarcinoma

- Non-glandular neoplasms
  - Urothelial neoplasms
  - Squamous cell neoplasms
  - Neuroendocrine neoplasms
  - Mixed type neoplasms

- Mixed carcinomas

WHO Classification of Tumours of the Urinary System and Male Genital Organs
Edited by Holger Moch, Peter A. Humphrey, Thomas M. Ulbright, Victor E. Reuter
1. Villous Adenoma

- Histologically identical to its GI counterpart.
- ~50 cases reported along the urinary tract; only a subset documented to be truly urachal.
- 23 - 94 yo (mean mid-60s’) with no gender predilection.
- Presents mostly with hematuria and irritative symptoms, and only rarely with mucusuria.
- ~35% with concomitant adenoCA.
  - Should sample generously.
- Pure villous adenoma has excellent prognosis.
  - Those associated with adenoCA may recur or metastasize.
Villous Adenoma
• Comprises ~10% of adenoCA involving the bladder.
• Peak in the 50’s - younger than in bladder CA.
• M:F = 1.4-1.7:1
• Presents with hematuria (2/3), umbilical/pelvic pain, mass, weight loss, and mucusuria (4-17%).
• Serum CEA antigen and CA 125 may be elevated.
# Urachal Adenocarcinoma

## Criteria for diagnosis\(^1\):

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Location of tumor in bladder dome and/or <strong>anterior wall</strong>.*</td>
</tr>
<tr>
<td>2</td>
<td>Epicenter of carcinoma in the bladder wall.</td>
</tr>
<tr>
<td>3</td>
<td>Absence of <strong>widespread</strong> cystitis cystica and/or cystitis glandularis beyond the dome or anterior wall.</td>
</tr>
<tr>
<td>4</td>
<td>Absence of a known primary elsewhere.</td>
</tr>
</tbody>
</table>

* The presence of urachal remnant in association with the tumour is supportive of the diagnosis, but its absence does not preclude a urachal origin.

- Criteria may rule out advanced stage tumors and applicable only for resection specimens.
- “Sharp demarcation between tumor and surface” removed.

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Mucinous (Colloid) Adenocarcinoma
Urachal Adenocarcinoma – Histology

Mucinous (50%) ≈Mucinous CA
- Ovary
- Appendix
- Pancreas
- Others

Enteric (24%) ≈Colorectal AdenoCA

NOS (9%)

Signet ring cell (7%) ≈SRC CA
- Gastric
- Colorectal
- Breast
- Lung
- Others

* 10% are mixed and 4-8% are admixed with minor nonglandular CA
Immunohistochemistry

CDX2 commonly expressed in Enteric and Non-enteric subtypes

- Enteric +
- Mucinous +
- NOS +
- Signet ring cell +
Urachal Adenocarcinoma
Immunohistochemistry

- CK20+
- CK7+(~60%) and nuclear β-catenin rare/focal + (6%):
  - Value vs. colonic adenoCA (CK7-, diffuse nuclear β-catenin+).

- Pitfalls in IHC:
  - P501S (prostein) and PSMA may have immunoreactivity.
  - GI tract (signet ring CA) markers claudin-18 and REGIV are +.

Loss or mutation of \textit{APC} gene --- \(\beta\)-catenin accumulates in cytoplasm and translocate to nucleus.
Staging of Urachal Adenocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>No invasion beyond the urachal mucosa</td>
</tr>
<tr>
<td>II</td>
<td>Invasion confined to the urachus</td>
</tr>
<tr>
<td>III</td>
<td>Local extension into:</td>
</tr>
<tr>
<td>IIIA</td>
<td>Bladder</td>
</tr>
<tr>
<td>IIIB</td>
<td>Abdominal wall</td>
</tr>
<tr>
<td>IIIC</td>
<td>Peritoneum</td>
</tr>
<tr>
<td>IIID</td>
<td>Viscera other than the bladder</td>
</tr>
<tr>
<td>IV</td>
<td>Metastasis to:</td>
</tr>
<tr>
<td>IVA</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant sites</td>
</tr>
</tbody>
</table>

- Tendency for tumors to be classified as “higher stage” (0-17% stage I or II).

## Staging of Urachal Adenocarcinoma

<table>
<thead>
<tr>
<th>Ashley et al, 2006 (Mayo System)</th>
<th>Pinthus et al, 2006 (Ontario System)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  Confined to the urachus and/or bladder</td>
<td>T1  Confined to the submucosa</td>
</tr>
<tr>
<td>II Extension beyond the muscular layer of the</td>
<td>T2  Confined to the muscular wall of the bladder</td>
</tr>
<tr>
<td>urachus and/or the bladder</td>
<td></td>
</tr>
<tr>
<td>III Infiltration to the regional lymph nodes</td>
<td>T3  Extension into the periurachal or vesical soft</td>
</tr>
<tr>
<td>IV Infiltration to nonregional lymph nodes or</td>
<td>T4  Invasion to adjacent organs, including abdominal</td>
</tr>
<tr>
<td>other distant sites</td>
<td>wall</td>
</tr>
</tbody>
</table>

- Migration to lower stages (13-43% as I and 29-46% as II in Mayo stage).
- Studies regarding the staging systems suggest utility ---- but are influenced by grouping the higher and lower stages.

Urachal Adenocarcinoma

Prognosis

• 5-year survival ~45% to 50%.

• Independent predictors of outcome:
  • Spread outside of bladder, adjacent organs, abdominal wall, and metastasis, and presence of residual disease.

• Metastatic sites:
  • Lungs (22%), bone (22%), liver (16%), lymph nodes (11%), peritoneum (11%).

• Management:
  • Cystectomy with urachal resection and umbilectomy.
  • Chemotherapy with cisplastin &/or 5-FU containing therapy.
Urachal Adenocarcinoma
Newly Identified Molecular Alterations

• MAP-kinase activation
  • KRAS (26%), BRAF (9%), NRAS (5%), NF1 (19%) mutations.
    • KRAS mutation in mucinous type urachal adenoCA.
    • ?KRAS mutation against EGFR tyrosine kinase inhibitors.

• Wnt/β-catenin pathway activation
  • APC (25%), RNF43 (14%) mutations.
    • APC truncating mutations frequent in colonic adenoCA

• Chromosome 12p amplification (3/7 cases)
  • Resembles in testicular germ cell tumor.

• 35 yo M with metastatic urachal CA to lungs.
• EGFR amplification and KRAS wild-type.
• Treated with cetuximab (anti-EGFR monoclonal antibody).
  • 25% decreased tumor burden in 8 mos.

EGFR amplification

1. Eur Urol 2016 (Epub ahead of print)
3. Urachal Mucinous Cystic Tumors

Cystadenoma
Included 31 Mucinous Cystic Tumors:

- Compared to noncystic adenocarcinoma:
  - No age (24 - 80 years, mean 47) or gender differences.
  - No significant difference in size (0.8 - 8cm).
    - Grossly with cystic lumina, mostly unilocular and with copious mucin.
  - Presented mostly as incidental (32%) or mass (32%) lesions.
  - Identical IHC with CDX2+, CK7+/-, CK20+, and β-catenin-.

Spectrum of Urachal Mucinous Cystic Tumors

Criteria analogous to ovarian mucinous neoplasms:

- **Cystadenoma**: areas of proliferation, papillae formation and low grade atypia.
- **MCNLMP**: significant stratification and unequivocal malignant cytologic features, often with stroma-poor papillae and a cribriform pattern.
- **Invasive CA**:
Mucinous Cystic Neoplasm of Low Malignant Potential (71%)

Courtesy, Steven Smith M.D.
Urachal Mucinous Cystic Tumors (MCTs)

1. Better progression-free survival for non-invasive MCT.

![Graph showing survival rates]

2. There is risk for pseudomyxoma peritonei similar to appendiceal and ovarian MCTs.
   - Carcinomatosis or spread from rupture of non-invasive MCTs.

4. Urachal Non-Glandular Neoplasms

**Urachal Urothelial Carcinoma**

- 59 yo M with supravesical mass and unremarkable bladder lumina.
• Only 45 cases reported:
  • Urothelial (25), squamous (14) or neuroendocrine (6) carcinomas.
  • Pure or predominantly nonglandular histologies.
    • Diagnostic criteria different from urachal AdenoCA.

• Poor prognosis:
  • Urothelial carcinoma – 38% DOD in 15 months.
  • Squamous cell carcinoma – 50% DOD in 9 months.
  • Neuroendocrine carcinoma – 80% DOD in 30 months.

Thank you!
### TABLE 5. Proposed Criteria for Pathologic Diagnosis of Urachal Nonglandular Carcinoma*

Diagnosis requires 1-3 and any 1 of 4-6

1. Located at dome, anterior wall, or midline supravesical area to umbilicus
2. Epicenter away from bladder surface
3. No primary tumor elsewhere, except urothelial carcinoma in the GU tract
4. Closely related to urachal remnant
5. Tumor does not involve an intact bladder mucosa
6. Cystic/cavitary with intraluminal urothelial papillae or with reverse invasive front†

*Modified from Paner et al.†
†Sharply demarcated growth opposing the surface around mucosal involvement.