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Dr. L. Priya Kunju declares she has no conflict(s) of interest to disclose.

Case History

47 year old man

- Presented with gross hematuria
- Mass in urinary bladder on cystoscopy
- TURBT: showed a papillary urothelial carcinoma invasive into lamina propria (T1)
- Proceeded to cystectomy
- Slide from cystectomy specimen with tumor
Differential Diagnosis

Invasive Micropapillary carcinoma

Urinary bladder primary
(micropapillary urothelial carcinoma/micropapillary UC)

Or

Metastasis from another site

- Same morphology is seen in metastatic sites
- Carcinomas of lung, breast, ovary, GI tract, salivary glands can mimic micropapillary UC and pose a diagnostic challenge in small biopsies
- Metastatic micropapillary serous carcinoma of ovary is an important consideration in biopsies from abdominal LN, mesentery or peritoneum in female patients
- Micropapillary UC enters into DD in carcinoma of unknown primary in appropriate clinical setting
**GATA-3**

- Zinc finger transcription factor expressed in urothelium, mammary epithelium, distal renal tubules, T-lymphocytes
- Expressed in majority of conventional urothelial and breast carcinomas
- **Majority (57-100%) of micropapillary urothelial carcinomas express GATA-3**
- Positive GATA-3 expression is a useful indicator of urinary tract origin, if breast carcinoma is not in the differential diagnosis

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**Diagnosis**

**Invasive Micropapillary UC**

- Male patient with epicenter of tumor in urinary bladder
- TURBT: exophytic papillary UC component with invasive micropapillary UC extending into lamina propria
- CIS in cystectomy
- Strong, diffuse GATA3 expression

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**Micropapillary UC**

- Rare tumors; **<6% of all UCs**
- Prominent preponderance in men

| Micropapillary UC | M:F 5:1-10:1, Conventional UC (NOS) | M:F 3:1 |
Micropapillary UC

Non-invasive

- Slender, elongated, filiform projections or micropapillae lacking prominent fibrovascular cores
- Budding micropap fronds
- Glandular features and micropapillary fronds

Invasive

- Associated with Pap UC

- Associated with CIS

CIS with micropap projections lacking fibrovascular cores
Invasive Micropapillary UC: Morphology

- Small tumor nests with prominent stromal retraction spaces (lacunae), back to back lacunar spaces
- High-grade nuclei with pleomorphism
- Multiple nests within same lacunar space
- No host response/stromal reaction
- “Reverse” or inverted cellular polarity
- Peripherally placed nuclei
- Intracytoplasmic vacuolization
- Epithelial ring forms
- Frequent angiolymphatic invasion
- Psammoma bodies extremely rare

Amin Mod Pathol 1994; Sangoi et al. AJSP 2010
How good are we at diagnosing micropapillary UC?

Sangoi et al (AJSP 2010): 60 images, 30 cases (10 classic invasive micropap UC and 20 non-classic)

• Moderate agreement ($k: 0.54$) for 30 cases among 14 GU pathologists.
• 10 “classic” cases: relatively uniform (93% agreement)
• 20 cases with extensive retraction & varying sized tumor nests: variable agreement
• Verdict: Good in classic cases; not so good in challenging/non-classic cases

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**Micropapillary UC Immunohistochemistry**

<table>
<thead>
<tr>
<th>IHC</th>
<th>Staining pattern</th>
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</thead>
<tbody>
<tr>
<td>GATA 3</td>
<td>Usually positive (&gt;90%)</td>
</tr>
<tr>
<td>Uroplakin</td>
<td>Usually positive (&gt;90%)</td>
</tr>
<tr>
<td>CK 7</td>
<td>Usually positive (&gt;95%)</td>
</tr>
<tr>
<td>CK 20</td>
<td>Variably positive (55%)</td>
</tr>
<tr>
<td>p63</td>
<td>Variably positive (25-30%)</td>
</tr>
<tr>
<td>HMWCK/34βE12</td>
<td>Variably Positive (15%)</td>
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</table>
Invasive micropapillary carcinoma
IHC panel For Primary

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Uroplakin</th>
<th>ER</th>
<th>WT-1</th>
<th>Pax-8</th>
<th>Mammaglobin</th>
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<tr>
<td>Bladder</td>
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<tr>
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<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Adapted Lotan et al AJSP 2009

Micropapillary UC Prognosis

- Invasive micropapillary UC is an aggressive variant
- Frequently under staged clinically
- Majority present with muscle invasive disease, lymphovascular invasion frequent; high rate of LN metastasis
- Any amount of micropapillary differentiation may be considered significant. Prognosis worsens with increase of this component
- While invasive micropapillary UC is an aggressive disease, non-invasive micropapillary UC is not always associated with a worse outcome

Reporting Recommendations

- Invasive micropapillary UC can be an associated with conventional invasive UC, admixed with other divergent variants of UC or present as an exclusive pattern
- Report type (micropapillary w/wo other variants) & amount [% of invasive micropapillary UC]
- “Invasive HG urothelial carcinoma with extensive micropapillary features extending into muscularis propria; invasive micropapillary component accounts for 60% of the carcinoma”
- Flat CIS is reported, if present.
- Recommend a repeat TUR if muscularis propria is not included in TURBT
Micropapillary UC Treatment

- Intravesical BCG (bacille Calmette-Guerin) therapy is not effective in non-muscle invasive micropapillary UC
- Chemotherapy has questionable efficacy
- Some experts have proposed early radical cystectomy for the treatment of this variant
- Subset of cT1 patients managed conservatively had similar outcome compared to patients undergoing early radical cystectomy*

*Spaliviero et al J Urol 2014

Micropapillary UC Prognosis

- Recent studies have shown that patients with micropapillary UC present at higher stage than conventional urothelial carcinoma, however the survival outcomes following radical cystectomy were similar to that of conventional urothelial carcinoma when matched for stage and other prognostic clinicopathologic features


HER2 (ERBB2) & Micropapillary UC

- Genomic alterations in ERBB2 (HER2) gene are significantly enriched in micropapillary UC
- Mutations in extracellular domain of ERBB2 (38-40%)
- ERBB2 (HER2) amplification by FISH (15-42%)
- HER2 protein over-expression by IHC (50-68%)
- Patients with ERBB2 amplification appear to have worse cancer specific survival than those who do not
- Prognostic value of HER2 IHC over-expression is inconsistent especially if not associated with HER2 amplification by FISH
- Therapies to target HER2 such as trastuzumab and lapatinib are under investigation
Take-away

- Micropapillary UC can have an invasive and non-invasive growth pattern.
- Invasive micropapillary UC typically shows small tumor nests surrounded by prominent retraction space (lacuna), back to back lacunae, multiple tumor nests within same lacunar space, and elongated nests (micropapillae), reverse polarity with peripheral nuclei.
- Invasive micropapillary UC is aggressive and frequently associated with muscle invasive disease and lymphovascular invasion.
- Pathology Reports should include amount (percentage) of invasive micropapillary carcinoma; Repeat TUR is recommended if the biopsy lacks muscularis propria.

THANK YOU