Variants of Urothelial Carcinoma

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Subtyping Urothelial Carcinoma: Why?

- Pathologists: Recognition as Urothelial
- Urologists/Oncologists: Prognosis and Therapy
Urothelial Carcinoma: Selected Variants

- Squamous/Glandular diff
- Plasmacytoid
- "Deceptively bland"
- Small cell
- Micropapillary
- Sarcomatoid

Alternative Differentiation in Urothelial Carcinoma

Urothelial Carcinoma with Alternative Differentiation
Urothelial Carcinoma with Alternative Differentiation

- Recognition as Urothelial
  - Conventional urothelial component
    - CIS
    - Non-invasive papillary
    - Invasive
  - Prior history of urothelial carcinoma

Differential Diagnosis: Urothelial Carcinoma with Alternative Differentiation

- Squamous
  - Primary vesical SCCA
    - Cervical carcinoma
- Glandular
  - Primary vesical adenocarcinoma
  - Bowel primary
  - Urachal

Diagnostic Comment is Critical!

Urinary bladder, TURBT - Invasive carcinoma with glandular differentiation, involving muscularis propria

Comment: Carcinomas with glandular (enteric) features may have identical histologic, immunophenotypic, and molecular features regardless of their anatomic site of origin. The possibility of direct extension (or metastasis) from another anatomic site of origin (especially colorectal) must be excluded clinically/radiographically before this neoplasm is accepted as primary to the urinary bladder (i.e. either urothelial carcinoma with glandular differentiation or primary adenocarcinoma).
HR-HPV E6/E7 mRNA In Situ Hybridization Validation Against PCR, DNA In Situ Hybridization, and p16 Immunohistochemistry in 162 Samples of Cervical, Vulvar, Anal, and Head and Neck Neoplasia

Anne M. Mills, MD, Dave C. Dirks, MS, Melinda B. Pratlee, PhD, Stacey E. Mills, MD, and Mark H. Stucker, MD

Abstract: Immunohistochemical expression of oncogenic types of HPV and p16 is necessary for human papillomavirus (HPV)-related neoplasms. An HPV E6/E7 mRNA in situ hybridization (ISH) assay was developed at the Molecular Diagnostics Laboratory, Department of Pathology, University of Illinois College of Medicine. The assay is a sensitive and specific method for diagnosis and monitoring of HPV-related neoplasms. The ISH assay was performed on paraffin-embedded tissue sections from formalin-fixed human papillomavirus (HPV)-positive and HPV-negative cases. The results demonstrated the efficacy of the ISH assay for detecting HPV-related neoplasms.

Key Words: HPV, human papillomavirus, in situ hybridization, DNA, p16, immunohistochemistry, and a previously validated HPV DNA ISH assay for HPV-related squamous and basal and HPV-negative cases.

Performance: The ISH assay was compared to HPV DNA ISH and p16 immunohistochemistry, and showed excellent correlation with HPV DNA ISH and p16 immunohistochemistry.

Figure: Plasmacytoid Carcinoma

Plasmacytoid Carcinoma

Visualization: The visualization software allows interactive exploration of the histological features, enabling a detailed examination of the tissue architecture and cellular morphology. The software also facilitates the measurement of cellular and tissue parameters, providing valuable insights into the biological processes occurring within the tissue sample.
Plasmacytoid Carcinoma

- Recognition
  - Inflammatory cells
  - Gastric and breast cancer
- Prognosis
  - Poor response to chemotherapy
  - Unusual patterns of disease failure
Plasmacytoid Carcinoma

Plasmacytoid Carcinoma

Plasmacytoid Carcinoma

Plasmacytoid Carcinoma

Cytookeratin AE1/3
Rhabdoid Plasmacytoid Plasmacytoid Carcinoma: Presence of Signet Ring-Like Cells Plasmacytoid Carcinoma: Signet-ring Adenocarcinoma
In a previous study, a series of mucinous adenocarcinomas was reported which consisted principally of signet-ring tumor cells and only a few glandular structures, either without cystic spaces filled with mucin or with only a few of these present. All were diffusely infiltrating carcinomas and often produced widespread metastases. In many instances these tumors were either not recognized clinically or diagnosed so late in the course of the disease that radical surgery could not be performed. Because of their microscopic appearance and their very malignant course, and to distinguish them from uncomplicated mucinous carcinomas, they were grouped and classified as signet-ring cell carcinomas.
Plasmacytoid Carcinoma: Presence of Signet Ring-Like Cells

PAS stains do NOT help!
WHO 2016 Criteria

- Plasmacytoid Carcinoma
  - No extracellular mucin
  - Similar to "diffuse type" gastric CA or lobular breast CA

- Mucinous AdenoCA with Signet-Ring Cells
  - Extracellular mucin
  - Similar to mucinous adenocarcinoma of colon

"Most cases reported in the literature as signet ring cell adenocarcinoma of the bladder, specifically those not associated with extracellular mucin, would now be classified as plasmacytoid carcinoma"

Saphir O. Am J Pathol 1955; 31:223-31

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Peritoneal spread common
- Bowel serosa and mesentery
- Ovary
- Peritoneal carcinomatosis
- Malignant effusions (pleural)

Plasmacytoid Carcinoma: Peritoneal Spread

Plasmacytoid Carcinoma in Peri-Ureteral Tissue
Plasmacytoid Carcinoma in Peri-Prostatic Tissue

Plasmacytoid Carcinoma in Lymph Node

Cytokeratin AE1/3

BRIEF COMMUNICATIONS

Frequent somatic CDH1 loss-of-function mutations in plasmacytoid variant bladder cancer.

Plasmacytoid bladder cancer is an aggressive histologically variant with a high rate of metastases and mortality. Using whole-exome and targeted sequencing, we identified a somatic mutation in the CDH1 gene in 44% of plasmacytoid carcinomas and in 2% of non-bladder cancer control. Further analyses of the expression of the paired box gene expressed in normal and neoplastic epithelium (PAX6) and the CDH1 was significantly decreased in CDH1-mutated bladder cancer compared to control.

CDH1-mutated bladder cancer cells exhibit cell membrane

Plasmacytoid tumor tumor consist of malignant epithelial cells with a characteristic immunophenotypic and dysregulated growth with visceral tissue invasiveness. These tumors have also been associated with different regions of the genitourinary tract, often involving the prostatic ducts, prostate parenchyma, and aberrant growth, consistent with which frequently

nature genetics
Plasmacytoid Carcinoma

- Differential Diagnosis
  - Metastatic carcinomas to bladder?
    - Lobular breast
    - Diffuse type gastric
    - Hematopoietic

Urothelial Carcinoma with Plasmacytoid Features

GATA-3

Lobular breast CA: GATA-3

GATA-3 Positive
- Urothelial CA
- Breast CA
- T-lymphocyte subset
- Salivary gland CA
- Paraganglioma
- Parathyroid
- Subset of squamous cell CA
- Prostatic basal cells (patchy)
- GYN tract urothelial neoplasia
Gastric Carcinoma Met to Bladder

Urinary bladder

Stomach

Immunohistochemical Differential

<table>
<thead>
<tr>
<th>Type</th>
<th>GATA3</th>
<th>S100p</th>
<th>CK7</th>
<th>CK20</th>
<th>ER</th>
<th>PR</th>
<th>CD138</th>
<th>P63</th>
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<tbody>
<tr>
<td>Urothelial</td>
<td>73</td>
<td>64</td>
<td>99</td>
<td>73</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>Gastric</td>
<td>10</td>
<td>50</td>
<td>60</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>30</td>
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<tr>
<td>Breast</td>
<td>100</td>
<td>50</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>60</td>
<td>100</td>
<td>0</td>
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</tbody>
</table>

Immunohistochemical Differentiation of Plasmacytoid Urothelial Carcinoma From Secondary Carcinoma Involvement of the Bladder
Deceptively Bland Carcinoma

Invasive urothelial carcinomas....

“Deceptively benign” 
and 
“Under-diagnosed”
**Invasive urothelial carcinomas....**

“Deceptively bland” and “Under-diagnosed”

1) Nested Carcinoma  
2) Tubular Carcinoma  
3) Microcystic Carcinoma  
4) Large nested
Invasive Urothelial Carcinoma: Nested Variant Cytology

Invasive urothelial carcinoma, nested variant

Invasive Urothelial Carcinoma: Microcystic Variant
Non-Invasive Endophytic Urothelial Carcinoma

“Deceptively Bland” Carcinomas

• Prognosis
  – Stage-for-stage behaves as aggressively as a high-grade carcinoma
  – I don’t recommend a “low-grade” designation

Nested Variant with Lymph Node Met
“Deceptively Bland” Carcinomas

- Differential Diagnosis
  - Nephrogenic adenoma
  - von Brunn nests
  - Inverted/Endophytic Urothelial Neoplasia
Small Cell Carcinoma

- In our hospital, small cell carcinoma is the most frequently under-diagnosed, clinically significant bladder tumor upon re-review of outside slides
- Requires different chemotherapy regimen
Large Cell Neuroendocrine Carcinoma

Small Cell Carcinoma

• Differential Diagnosis
  – Rhabdomyosarcoma (alveolar)
  – Lymphoma
Rhabdomyosarcoma vs. Small Cell Carcinoma

Desmin

Synaptophysin

Myogenin

Micropapillary Carcinoma

“Slender, delicate filiform processes or tight papillary clusters reminiscent of papillary serous carcinoma of the ovary”
Lymph Node Metastasis

Therapeutic Significance: 1994-2005

• On TURBT
  IF:  pT1 (no invasion of muscularis propria)
  AND: ……micropapillary morphology
  THEN: suggest re-staging biopsies

J Urol 2006; 175: 881-885
Micropapillary Carcinoma: Cystectomy for pTa and pT1 Disease?

- Pathologic assessment
  - Extent of micropapillary component?
  - Definition of non-invasive micropapillary?
  - Definition of invasive micropapillary?


Where does the land stop and the water start?

When does typical urothelial carcinoma become micropapillary?
**Recommended Restricted Criteria**

Major feature
① Multiple small nests in same lacunar space

Frequently seen features
① Epithelial ring forms
② Back to back lacunae
③ Peripheral nuclei
④ Cytoplasmic vacuolization

**Features Suggesting NOT Micropapillary**

Major features
① Large nests (> 5 cells across narrowest width)
② Epithelial confluence and branching

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**Back-to-Back Lacunae**

Multiple Nests in Same Lacunar Space
Back-to-Back Lacunae
Multiple Nests in Same Lacunar Space

Epithelial Ring Forms
Back-to-Back Lacunae

Intracytoplasmic Vacuoles
Not Classic Micropapillary, But What Is It?

Urothelial CA with Distinct Mixed Features:
Quantitative Problem

"Even small foci of micropapillary differentiation portend a poor prognosis"
Micropapillary Immunophenotype?

<table>
<thead>
<tr>
<th></th>
<th>Micropapillary</th>
<th>Usual UC with Retrxn</th>
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<tbody>
<tr>
<td>MUC-1</td>
<td>96%</td>
<td>63%</td>
</tr>
<tr>
<td>CA-125</td>
<td>33%</td>
<td>13%</td>
</tr>
<tr>
<td>Her2/neu</td>
<td>25%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Sangol et al. Mod Pathol 2009; 22:660

Micropapillary Carcinoma

D2-40

No
Non-invasive Micropapillary Carcinoma (pTa)

- Included in studies proposing immediate surgery
- Criteria problems
  - Qualitative threshold
    • Definition?
  - Quantitative threshold
  - Glandular (villo glandular) differentiation

Non-Invasive Papillary Urothelial Carcinoma, Micropapillary
Non-Invasive Papillary Urothelial Carcinoma
Does Cribriform = Micropapillary?

Non-Invasive Papillary Urothelial Carcinoma
“Micropapillary” or “Villoglandular/Glandular”?

Micropapillary Reporting
Recommendation

1. Use restrictive criteria for invasive micropapillary carcinoma
2. Report presence of ANY invasive micropapillary component and give percentage
3. We do NOT currently diagnosis pTa carcinoma using “micropapillary” term
Sarcomatoid Carcinoma

- Most common malignant spindle cell neoplasm in adults
- May be histologically identical to a sarcoma
- Must always be excluded before accepting a primary vesical sarcoma
Sarcomatoid Carcinoma: Heterologous Elements

- CS
- OS
- RMS
- Myogenin

Sarcomatoid Carcinoma: Immunohistochemistry

- CK34BE12
- p63

Sarcomatoid Carcinoma

- Specific differential diagnostic scenarios
  1) Myofibroblastic vs. Malignant
  2) Leiomyosarcoma vs. Sarcomatoid CA
**Myofibroblastic Proliferations: Nomenclature**

<table>
<thead>
<tr>
<th>Diagnostic Term</th>
<th>Clinical Setting</th>
</tr>
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<tbody>
<tr>
<td>Postoperative Spindle Cell Nodule</td>
<td>History of bladder instrumentation</td>
</tr>
<tr>
<td>&quot;Myofibroblastic ____________&quot;</td>
<td>No association with trauma or carcinoma</td>
</tr>
<tr>
<td>Pseudosarcomatous Stromal Proliferation Associated with Neoplasia</td>
<td>Overlying carcinoma</td>
</tr>
</tbody>
</table>

**Morphologically Indistinguishable**

**Myofibroblast Morphology**

**Non-Trauma/Non-Tumor Related Myofibroblastic Proliferations**

- **Nomenclature**
  - Inflammatory pseudotumor
  - Pseudosarcomatous fibromyxoid tumor
  - Inflammatory myofibroblastic tumor
  - Pseudosarcomatous spindle cell proliferation
Non-Trauma/Non-Carcinoma Related Myofibroblastic Proliferations

• Inflammatory Myofibroblastic Tumor?
  – Myofibroblastic lesions
  – ALK + by IHC (up to 89 %)
  – ALK gene rearrangement by FISH

Myofibroblastic Proliferations of the Urinary Bladder

• Clinically Relevant: Prognosis
  – Recurrence (0-19%)
  – Metastasis (0%)
  – Death (1 case: untreated, died from urinary obstruction)

Myofibroblastic Proliferations of the Urinary Bladder

• Clinically Relevant: Differential diagnosis
  – Myofibroblastic vs Malignant
  – Leiomyosarcoma vs Sarcomatoid carcinoma
Myofibroblastic

Muscularis Propria Invasion
Myofibroblastic in Bladder: Immunohistochemistry

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<tr>
<th>Antigen</th>
<th>Reactivity</th>
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<tr>
<td>ALK-1</td>
<td>+/- (8-89%)</td>
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<tr>
<td>Actin</td>
<td>+/-</td>
</tr>
<tr>
<td>Desmin</td>
<td>+/- (&lt;50%)</td>
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<tr>
<td>Cytokeratin</td>
<td>+/- (36-84%)</td>
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<tr>
<td>EMA</td>
<td>-</td>
</tr>
<tr>
<td>Myogenin</td>
<td>-</td>
</tr>
<tr>
<td>h-Caldesmon</td>
<td>+/- (64%!!!)</td>
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</table>

Cytokeratin Immunoreactivity in Myofibroblasts

- Low molecular weight cytokeratin: Positive
- High molecular weight cytokeratin: Negative

Leiomyosarcoma

- Although rare, most common primary vesical sarcoma in adults
- Two main morphologic appearances
  - Uterine-like: Eosinophilic and tight fascicles
  - Myxoid: Overlap with myofibroblastic
Myxoid Leiomyosarcoma

Spindle Cell Algorithm (Adult)

- Spindle cell proliferation
- Other
  - Myofibroblastic
  - Malignant
    - Sarcomatoid CA
    - LMS

In Younger Patients: Botryoid Rhabdomyosarcoma

- Morphologic features
  - Cambium layer
  - Varying differentiation
    - Undifferentiated mesenchyme
    - Rhabdomyoblasts
    - Myxoid, hypocellular
Botryoid Rhabdomyosarcoma

Deceptively Bland Pattern

Myogenin!!
Myofibroblastic vs. Malignant

- Cytology is the one criteria reproducible from all the studies
  - Marked nuclear pleomorphism
  - Irregular chromatin condensation (hyperchromasia)
Malignant Myofibroblasts

Malignant Spindle Cell Neoplasm (Adult)

- Sarcomatoid Carcinoma
- Leiomyosarcoma

May be morphologically indistinguishable
Malignant Spindle Cell Neoplasm (Adult)

- Sarcomatoid Carcinoma
  - Concomitant CIS or invasive carcinoma
  - Prior history of high-grade urothelial carcinoma
  - Heterologous differentiation?

Malignant Spindle Cell Neoplasm
No history, no morphologic clues

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<td>Diffuse CK</td>
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<tr>
<td>Diffuse desmin</td>
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<tr>
<td>Diffuse actin</td>
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Malignant Spindle Cell Neoplasm
No history, no morphologic clues

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<tr>
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<tr>
<td>HMWCK</td>
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Summary

Invasive Urothelial Carcinoma: Selected Variants

- Plasmacytoid
- “Deceptively bland”/Nested
- Small cell
- Micropapillary

Spindle Cell Proliferations of the Urinary Bladder

- Malignant vs. Myofibroblastic
- Sarcomatoid Carcinoma vs. Leiomyosarcoma