The Longer I Practice Pathology,
The Less I Like Immunohistochemistry:
Genitourinary Pitfalls

Arthur Purdy Stout Society
Annual Meeting 2017
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Immunohistochemistry Pitfalls in GU

General Rules
• Morphology driven IHC
  • Adjunct
    • No immunostain is infallible
    • When you need IHC most... it helps the least

Antibody Specificity Over Time

Immunohistochemical “Pitfalls” in GU Pathology
• Diagnosis
  • Prostate Cancer Diagnosis
  • Renal Neoplasia Classification
  • Germ Cell Tumor Classification
• Tissue of Origin
  • Prostate vs Urothelial
  • Urothelial vs Renal
  • Metastatic RCC
  • Metastatic Germ Cell
Diagnosis of Minimal Prostate Cancer

- Blind IHC pre-staining of prostate core biopsies is at best *inadvisable*
  - Difficult to interpret
  - Stains are neither 100% sensitive, nor 100% specific
  - More pitfalls... increases atypical diagnosis rate
  - Overutilization of resources
  - In violation of Palmetto Local Coverage Determination (LCD)

Benign Prostate: p63 + AMACR

Prostate Bx: HMWCK + AMACR

Prostate Bx: p63 + HMWCK + AMACR
**Immunohistochemistry Pitfalls in GU**

**Diagnosis of Minimal Prostate Cancer**

- Antibodies
  - Cancer “specific”
  - AMACR
  - ERG
  - Basal cell markers
    - P63
    - HMWCK
    - CK5/6

  **Interpretation?**
  **Specificity?**
  **Sensitivity?**

**Partial Atrophy**

- P63+HMWCK+AMACR

**AMACR Immunoreactivity**

- Partial Atrophy
- Adenosis
- HGPIN

**Nephrogenic Adenoma**

- AMACR + p63
- HMWCK

**AMACR is NOT a Prostatic Epithelial Marker**

- Papillary RCC
- Colorectal AdenoCA
- Ovarian AdenoCA
- Breast AdenoCA
- Urothelial CA
- Etc…..
Basal Cell Markers

• Pattern of reactivity?
• "Aberrant" nuclear p63 in carcinoma
• Non-specific cytoplasmic HMWCK

Immunohistochemistry Pitfalls in GU

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Prostatic Adenocarcinoma with p63 Expression

HMWCK and Prostate CA

Cytoplasmic blush with some clones

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PROSTATIC vs UROTHELIAL

Prostatic vs. Urothelial Carcinoma

Prostatic
• PSA
• PSAP
• PSMA
• NKX3.1
• ERG

Urothelial
• p63
• HMWCK
• CK7/CK20
• GATA3
• Uroplakin antibodies
• Thrombomodulin
• CK7+/CK20+
**CK 7 and CK 20 Profiling: Probability, Not Absolute**

- **Unlikely**
- **Even Chance**
- **Likely**

1-in-6 Chance

4-in-5 Chance

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**Immunohistochemistry Pitfalls in GU**

**Optimal Panel?**
1. NKX3.1 and GATA-3
2. PSA and p63

**Poorly Differentiated Prostatic Adenocarcinoma**

**Lymphocytes or Tumor Cells?**

Breast Carcinoma | Paragangioma

Lymphocytes or Tumor Cells?

**GATA-3 Immunoreactivity**

- **Expected Positive**
  - Urothelial carcinoma
  - Breast carcinoma
  - Paragangioma
  - Subset of T lymphocytes
  - Trophoblasts
  - Skin adnexal tumors
  - Parathyroid

- **Often Positive**
  - Mesothelium
  - Skin squamous cell carcinoma
  - Chromophobe RCC

- **Rare Positive**
  - Lung CA
  - Gastric CA
  - Colorectal CA
  - Endometrial CA
  - Ovarian CA
  - Squamous cell CA: cervix, larynx, lung
  - Renal oncocytoma
  - Other RCC
  - Synovial sarcoma
RCC vs. Urothelial Carcinoma (renal pelvis)

RCC
- PAX-8
- p63
- HMWCK
- CK7/CK20
- GATA3
- Uroplakin antibodies
- Thrombomodulin

Urothelial

GATA3 Reactivity in Renal Neoplasia

Abstract #975

GATA-3 in CC-P RCC

| Marker | Normal chromophobe | Anaplastic chromophobe | Clear cell HLRCC
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>GATA-3</td>
<td>18/35 (51%)</td>
<td>6/35 (17%)</td>
<td>3/154 (2%)</td>
</tr>
</tbody>
</table>

PAX8 in Upper Tract Urothelial Carcinoma

- 15-30% express PAX-8!!
- May be strong and diffuse

Poorly Differentiated Carcinoma with Destructive, Permeative Growth

Diff Dx is key!!
- Urothelial
- Urothelial
- Urothelial Metastasis
- HLRCC
- CDC
Additional inspection and more sections of the renal pelvis may be more helpful than IHC!!

Immunophenotypic Possibilities

<table>
<thead>
<tr>
<th>IHC Phenotype</th>
<th>Favored: Renal vs Urothelial</th>
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<tbody>
<tr>
<td>PAX8+/GATA3-/p63-</td>
<td>Renal</td>
</tr>
<tr>
<td>PAX8+/GATA3+/p63-</td>
<td>?</td>
</tr>
<tr>
<td>PAX8+/GATA3+/p63+</td>
<td>Urothelial</td>
</tr>
<tr>
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<td>Urothelial</td>
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</tbody>
</table>

Diagnosis of Angiomyolipoma/PEComa

- Differential Diagnosis:
  - Renal Cell Carcinoma
  - Melanoma
  - Liposarcoma
Immunohistochemistry Pitfalls in GU

**Angiomyolipoma**

- Sclerosing
- Epitheloid
- Lipid-rich

**PAX-8 Negative**

**IHC in Angiomyolipoma: Negative or Focal?**

- **HMB45**
- **SMA**
- **MART-1**
- **Cathepsin-K**

**Lipid-Predominant Angiomyolipoma**

**Expected Positive**

- Melanocytic Markers
  - HMB45
  - S-100 protein
  - Melan-A
  - Cathepsin-K

**Expected Negative**

- Epithelial markers
- Cytokeratins
- PAX-8

**Angiomyolipoma/PEComa**

**What is positive?**

- Smooth Muscle Markers
- Smooth muscle actin

**Diagnosis of Metastatic RCC**

- Markers of purported renal specificity
  - **PAX-8**
  - PAX-2
  - CD10
  - RCCma
Immunohistochemistry Pitfalls in GU Diagnosis of Metastatic RCC

- PAX-8 Expression Expected (Antibody Specific)
  - Gynecologic
  - Thyroid
  - Upper Tract Urothelial (15-30%)!!!
  - Pancreatic Neuroendocrine (polyclonal Ab)
  - Seminal Vesicle
  - Thymic Epithelium/Thymoma
  - Merkel Cell Carcinoma

- PAX-8 Sensitivity
  - Clear Cell 95%
  - Papillary 95%
  - Chromophobe 85%
  - Other??? 90%

Diagnosis of Metastatic RCC: General Rules

- Renal mass or history of RCC?
- Does it look like RCC histologically?

- Known mimics in the anatomic site biopsied?
  - Know sensitivity and specificity of markers used

Biopsy: soft tissue mass
Patient also has 5 cm renal mass!

Biopsy: Supraclavicular lymph node
Patient has remote history of "Clear Cell RCC"!
**Immunohistochemistry Pitfalls in GU**

**Original Nephrectomy**

**Biopsy: Retroperitoneal lymph node**

*Patient with history of “Clear Cell RCC”!*

**PAX-8**

**B CELL LYMPHOMA**

**CD20**

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**Differential Diagnosis of Clear Cell Tumors in a Given Anatomic Location?**

*True Peripheral Chordomas Exist!!*

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**Diagnosis of Testicular Germ Cell Tumors**

<table>
<thead>
<tr>
<th>Germ cell</th>
<th>Sex Cord Stromal</th>
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<tbody>
<tr>
<td>OCT3/4</td>
<td>Inhibin</td>
</tr>
<tr>
<td>SALL4</td>
<td>Calretinin</td>
</tr>
<tr>
<td>PLAP</td>
<td>SF-1</td>
</tr>
<tr>
<td></td>
<td>SF-1</td>
</tr>
<tr>
<td></td>
<td>FOXL2</td>
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**Sex Cord Stromal (Sertoli)**

*SF-1*
**Immunohistochemistry Pitfalls in GU**

**Seminoma vs Lymphoma?**

- **Seminoma**
  - OCT3/4 Immunoreactivity: Expected Positive • Seminoma • Embryonal carcinoma • Renal medullary carcinoma
  - Rare Positive • B cell lymphomas • Acute myeloid leukemias

- **DLBCL**
  - OCT3/4 Immunoreactivity: Expected Positive • B cell lymphomas • Acute myeloid leukemias
  - Commonly Positive • “Pan” germ cell • Serous carcinoma (GYN) • Malignant rhabdoid tumor • Gastric adenocarcinoma • Urothelial carcinoma

**OCT3/4 Immunoreactivity**

- **Expected Positive** • Seminoma • Embryonal carcinoma • Renal medullary carcinoma
- **Occasionally Positive** • B cell lymphomas • Acute myeloid leukemias

**SALL4 Immunoreactivity**

- **Commonly Positive** • Hepatocellular carcinoma • Mammary carcinoma • Prostatic adenocarcinoma • Leukemia
- **Rare Positive** • “Pan” germ cell • Serous carcinoma (GYN) • Malignant rhabdoid tumor • Gastric adenocarcinoma • Urothelial carcinoma

**Subtyping of Testicular Germ Cell Tumors**

- **Seminoma**: OCT3/4, PLAP, cKIT
- **Embryonal**: OCT3/4, CD30
- **Yolk Sac**: Glypican3, AFP, GATA3
- **ChorioCA**: BhCG, GATA3

**Primitive Carcinomas and SALL4: e.g., Esophageal Adenocarcinoma with Fetal Gut Differentiation**

**Immunohistochemistry Pitfalls in GU**
Summary

• Diagnosis
  • Prostate Cancer Diagnosis
  • Renal Neoplasia Classification
  • Germ Cell Tumor Classification

• Tissue of Origin
  • Prostate vs Urothelial
  • Urothelial vs Renal
  • Metastatic RCC
  • Metastatic Germ Cell

Thank You