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Genitourinary Pathology in 2016.....
Epidemiology

Due to long natural history of bladder cancer, the prevalence is high (500,000 - 600,000)

~$3 billion/year is spent for bladder cancer treatment

Most expensive cancer to treat!

In 2018...
more than 81,000 will be diagnosed
over 17,000 will die

4th most common cancer

11th most common cancer
Incidence of bladder cancer is increasing due to smoking!
Case 1

• A 58 year old male presented with hematuria. On workup was found to have 3 cm polypoid mass involving the anterior bladder wall. The patient underwent transurethral resection.
Diagnosis

- Non-invasive low grade urothelial carcinoma with endophytic growth
- Non-invasive high grade urothelial carcinoma with endophytic growth
- Inverted papilloma
- Nested urothelial carcinoma, including large nested
Case 2

• A 65 year old male presented with hematuria and dysuria. On workup was found to have 2 cm mass involving the anterior bladder wall.
Diagnosis

- Inverted papilloma
- Invasive high-grade urothelial carcinoma
- Nested urothelial carcinoma
- Invasive micropapillary urothelial carcinoma
Case 3

• A 60 year old female presented with hematuria and dysuria. On workup was found to have 2 cm polypoid mass involving the distal urethra.
Diagnosis

- Invasive adenocarcinoma, NOS type
- Urachal adenocarcinoma
- Nephrogenic adenoma
- Clear cell adenocarcinoma
Case 4

- A 58 year old male presented with elevated PSA of 8 ng/ml. He underwent an extended prostate biopsy. The right base biopsy showed abnormality which is enclosed for review.
Diagnosis

• Intraductal carcinoma of the prostate
• Prostate adenocarcinoma, Gleason score 5+5=10
• Noninvasive high-grade urothelial carcinoma with spread into prostatic ducts; pTa
• High-grade urothelial carcinoma with spread into prostatic ducts and invasion of prostatic stroma; pT2
Agenda: Discuss Important Changes in Bladder Cancer Classification, Grading, Staging and Reporting

- **New/Updated entities**
  - Divergent differentiation and Variants, Urothelial proliferation of uncertain malignant potential (hyperplasia), Tumors of Mullerian-type

- **Classification and Grading**
  - 2004 ISUP grading classification universally adopted
  - Molecular taxonomy for classification/prognostication

- **Staging**
  - Substaging tumors invading the lamina propria
  - Staging of tumors involving prostatic stroma
## WHO Classification of Infiltrating Bladder cancer:
Differences between the 3rd and 4th editions

### Third edition
- Infiltrating urothelial carcinoma
  - With squamous differentiation
  - With glandular differentiation
  - With trophoblastic differentiation
  - Nested
  - Microcystic
  - Micropapillary
  - Lymphoepithelioma – like
  - Lymphoma – like
  - Plasmacytoid
  - Sarcomatoid
  - Giant cell
  - Undifferentiated

### Fourth edition
- Infiltrating urothelial carcinoma  
  - With divergent differentiation
  - Nested, including large nested
  - Microcystic
  - Micropapillary
  - Lymphoepithelioma – like
  - Plasmacytoid/Signet ring cell/diffuse
  - Sarcomatoid
  - Giant cell
  - Poorly differentiated
  - Lipid rich and Clear cell
Why it matters to accurately classify Histologic variants?

- Some associated with a different clinical outcome
- Some require different therapeutic approach
- Awareness of certain histologic variants critical in avoiding diagnostic misinterpretations in superficial biopsies
- Distinction of variant histology from metastasis may be difficult when pure
- Variant histology poses higher risk of under-staging in non-muscle invasive (T1) cancer
Dis-cohesive tumor cells in diffuse infiltrative growth

Non-gland/nest-forming, poorly cohesive cells
PLASMACYTOID UROTHELIAL CARCINOMA
(Signet ring cell/diffuse)

Signet ring like cells; No extracellular mucin

Pan keratin
Plasmacytoid Urothelial Carcinoma

• Rare highly aggressive variant; often present with extensive spread in peritoneal cavity
• Can be pure or mixed
• Variable # of signet ring cells without extracellular mucin included
• D/D: Plasmacytoma, Signet ring cell carcinoma, metastatic lobular ca and Urothelial carcinoma with rhabdoid features
• Immunohistochemical profile
  – Pankeratin positive
  – Loss of membranous E-cadherin
  – CD 138 expression
  – P63 negative, GATA-3 positive
PLASMACYTOID UROTHELIAL CARCINOMA

Figure 2. OS. A, 17.7 months in all 31 patients. B, 45.8 vs 13.4 months for stage I–III vs IV (p < 0.001).

“Deceptively Bland” Carcinomas

Invasive urothelial carcinomas described as “deceptively bland” and “underdiagnosed”

• Nested Carcinoma, including large nested
• Tubular Carcinoma
• Microcystic Carcinoma
Disorderly proliferation of small nests mimicking Von Brunn's nests

Haphazard proliferation of nests with banal cytology

Nested Urothelial Carcinoma
Nested Urothelial Carcinoma

• 30 nested urothelial carcinoma
• A component of conventional UC was present in 60% of cases
• Mixture of nests, cordlike, cystitis cystica and tubular growth patterns frequently present
• Immunophenotype (CK7/20, p63, HMWCK 903) identical to usual UC
• Nested UC associated with advanced disease and metastasis, compared to pure conventional UC (p<0.001) regardless of whether nested UC was pure or mixed (nested with conventional components)

Nephrogenic Adenoma with Nested Features
“Deceptively Bland” Carcinomas

• Differential Diagnosis
  – Proliferative Von Brunn nests
  – Nephrogenic adenoma

Disorderly/Haphazard proliferation of nests in superficial biopsy should prompt one to consider Nested carcinoma
Large Nested urothelial carcinoma

D/D: Non-invasive urothelial carcinoma with prominent inverted growth pattern
- Muscularis propria invasion
- Irregularly infiltrating nests
- Stromal reaction
Case 4: Large Nested urothelial carcinoma
Neuroendocrine Tumors

- Well-differentiated NE neoplasm (Carcinoid)
- Small Cell Carcinoma
- Large Cell NE Carcinoma
Chromatin finely stippled; inconspicuous nucleoli

Sheets/Nests of cells with scant cytoplasm and high N:C ratio

Chromatin finely stippled; inconspicuous nucleoli
Small cell carcinoma

- Male predisposition 5:1
- Conventional urothelial component common (50%)
- Chromogranin/Synaptophysin positivity >60%
- CD56 is the most sensitive marker
- Dot-like positivity for cytokeratin
- TTF1 positive ~40%
- High Ki-67 index (>80%)
- Systemic disease with 5 year survival of 8 to 40%
- Tumor responds to platinium based chemotherapy
Small cell carcinoma

D/D:
- Poorly differentiated carcinoma
- High grade lymphoma
- Solid alveolar rhabdomyosarcoma

! Important to rule out these differentials in absence of positivity for neuroendocrine markers
Large Cell Neuroendocrine Carcinoma
“Slender, delicate filiform processes or tight papillary clusters reminiscent of papillary serous carcinoma of ovary”

Male predominance
Tumors with similar morphology described at other sites
Conventional Treatment Approach

• Several published studies independently reported high stage presentation with frequent nodal metastasis

• On TURBT
  – If: pT1 (no invasion of muscularis propria) with Micropapillary morphology, re-staging biopsies performed with intravesical BCG therapy
• 44 nonmuscle invasive Micropapillary carcinoma
• Not responsive to intravesical BCG therapy
• Surgery offered the best chance of cure
• Some US centers treat T1 micropapillary urothelial carcinomas aggressively with cystectomy
• For pathologists strict diagnostic criteria warranted to avoid over interpretation
Interobserver Reproducibility Study of Micropapillary carcinoma: Sangoi et al, AJSP 2010

- Overall agreement
  - Moderate (kappa: 0.54)

- 10 “classic” MP cases
  - 93% [130 of 140: 10 cases x 14 reviewers] diagnosed as micropapillary

- 20 “non-classic” MP cases
  - Marked variability
Recommended Restricted Criteria

Major feature
  Multiple small nests in same lacunar space

Frequently seen features
  Epithelial ring forms
  Back to back lacunae
  Peripheral nuclei
  Cytoplasmic vacuolization
Multiple nests in same lacunar space

Epithelial ring forms and back-to-back lacunae
NOT Micropapillary

Large nests (> 5 cells across narrowest width)  Epithelial confluence and branching
Case 2: Invasive high-grade urothelial carcinoma
Variant histologic differentiation in urothelial carcinoma (UC) is under-recognized in community practice: Impact of mandatory central pathology review

- Variant histologic differentiation was not reported by the referring institution in 44% of cases with variant histology at central review, of which 47% were extensive
- Increased awareness required

Shah RB et al, Urologic Oncology: Seminars and Original Investigations, 2012
### WHO Classification of Non-invasive Urothelial Neoplasias: Differences between the 3rd and 4th editions

**Third edition**

*Noninvasive urothelial neoplasias*
- Urothelial carcinoma in situ
- Papillary urothelial carcinoma, low grade
- Papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma

**Fourth edition**

*Noninvasive urothelial neoplasias*
- Urothelial carcinoma in situ
- Papillary urothelial carcinoma, low grade
- Papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
- **Urothelial proliferation of uncertain malignant potential (hyperplasia)**
- **Urothelial dysplasia**
Histological Comparison of Grading Systems for Papillary Urothelial Tumors

<table>
<thead>
<tr>
<th>WHO 1973</th>
<th>ISUP/WHO 2004</th>
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<tbody>
<tr>
<td>Papilloma</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Grade 1</td>
<td>PUNLMP</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Low Grade</td>
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<tr>
<td>Grade 3</td>
<td>High Grade</td>
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</tbody>
</table>

- Eliminates Grade 1 UCC category which is not cancer
- Better stratifies high grade UCC for intravesical BCG
- Removes ambiguity of 5 grades by pathologists: Grade 1, 1-2 (?), 2, 2-3 (?), 3
- Higher % classified High grade
How much HG do you need?...any, 5%, 10%?
Tent-shaped broader folds, lack of well defined delicate fibrovascular cores, Hyperplastic epithelium but benign cytology
PAPILLARY UROTHELIAL PROLIFERATION OF UNCERTAIN MALIGNANT POTENTIAL (UPUMP)

Urothelial hyperplasia

- Thickened urothelium with minimal or no cytological atypia
- Undulations but no true papillary fronds
- Most frequent in patients with history of prior carcinoma or adjacent to papillary lesions
- Likely lateral extension (“shoulder lesion”) of a papillary neoplasm
- May be seen de novo and in this setting the clinical relevance unknown

*High incidence of chromosome 9 deletions and lesser but significant FGFR3 abnormality*

- Potential to confuse it with PUNLMP
- Overuse/misuse must be avoided
# MULTIPLE FACES OF ADENOCARCINOMA OF THE UROTHELIAL TRACT

<table>
<thead>
<tr>
<th>Bladder</th>
<th>Urachus</th>
<th>Mullerian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric features predominate</td>
<td>Enteric features predominate</td>
<td>Clear cell and endometrioid features predominate</td>
</tr>
<tr>
<td>Mixed histology common</td>
<td>Mixed histology less common</td>
<td>Mixed histology rare</td>
</tr>
<tr>
<td>Arises from surface urothelium</td>
<td>Arises from Urachal epithelium</td>
<td>Arises from Mullerian rests within or outside bladder</td>
</tr>
<tr>
<td>Standard bladder staging</td>
<td>Staging varies depending on site of urachal involvement</td>
<td>Not well defined</td>
</tr>
</tbody>
</table>
CASE 3: CLEAR CELL ADENOCARCINOMA

Tubulocystic and papillary patterns

Clear cytoplasm, Hobnailing
# Immunohistochemical markers in D/D

<table>
<thead>
<tr>
<th></th>
<th>NA</th>
<th>Clear cell Adenoca</th>
<th>UCC</th>
<th>PCA</th>
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</thead>
<tbody>
<tr>
<td><strong>PAX2/8</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>AMACR</strong></td>
<td>+</td>
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<td>-/+</td>
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<tr>
<td><strong>GATA3</strong></td>
<td>-</td>
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<td><strong>PSA</strong></td>
<td>-</td>
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<td>-</td>
<td>+</td>
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<tr>
<td><strong>Basal markers</strong></td>
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<td>+</td>
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Nephrogenic adenoma; UCC=Urothelial carcinoma, PCA=prostate adenoca
Urothelial Carcinoma
Two Divergent Molecular Pathways

Normal Urothelium

Superficial UC

Urothelial Hyperplasia

HG Papillary Ur Ca

Invasive UrCa

Flat CIS

H-RAS/FGFR3

PUNLMP LG Papillary UrCa

P53/RB

Muscle Inv UC
MOLECULAR CLASSIFICATION OF BLADDER CANCER

Basal type: p63 activation, squamous diff, clinically aggressive but sensitive to neoadjuvant chemotherapy

Luminal type: activating FGFR3 mutations

P53 type: wildtype TP53 expression, resistance to neoadjuvant MVAC

Choi et al, Cancer cell, 2014

Clinical trial (COXEN) by SWOG
Pathologic Staging of Urothelial Carcinoma

**Superficial (70%)**
(Non-muscle invasive)

- pTa (50%)
  - Non-invasive
  - **pT1 (20%)**
    - Lamina Propria invasion
      - 35-40% progression in 3 yrs
      - Under staging 30%
      - Distant metastasis 5-15%

**Muscle Invasive (30%)**

- T2
  - pTIS (CIS)
  - Majority progress
  - Higher metastasis
  - Cystectomy
    - (?Neo or adjuvant chemo)
Substaging of pT1 disease

- AJCC Level of Evidence: II
- Numerous subcategories proposed
  - Above (T1a) or below (T1b) muscularis mucosae
  - Beyond the venous plexus (T1c)
  - Microinvasive (T1m) vs more deeply invasive (T1e)
- The method of T1 substaging not optimized

- Inherent lack of orientation of the specimen due to fragmentation and tangential sectioning
- Muscularis mucosae and venous plexus landmarks often not present
Substage according to the new system (T1m and T1e) was user-friendly, possible in 100% of cases, and very predictive of T1 bladder cancer behavior.
Substaging of pT1 disease

• Microinvasive vs. Advanced pT1 disease

• **Microinvasive disease**
  1) Invasive tumor <1 high power in content
  2) Greatest invasive tumor diameter of 1 mm
  3) Invasive tumor above the muscularis mucosae extending to a depth of 2 mm or less

• Microinvasive disease has better outcome than Advanced pT1 disease

• Recommended to categorize pT1 disease using one of the above methods
Microinvasive pT1 disease
Advanced pT1 disease
Prostatic stromal invasion via
Subepithelial invasion (Urethral surface or prostatic duct) pT2

Prostatic stromal invasion via
Transmural or Extravesical route pT4
Figure 2. Kaplan-Meier curves for CSS between pT4a and SSI (HR 0.28, 95% CI 0.14–0.55, p < 0.001).

Figure 3. Kaplan-Meier curves for OS between pT4a and SSI (HR 0.33, 95% CI 0.19–0.57, p < 0.0001).
CASE 4: HIGH-GRADE UCC WITH SPREAD INTO PROSTATIC DUCTS AND INVASION OF STROMA; pT2
Take Home Messages

• Recognize many faces of Urothelial carcinoma
• Nested, Micropapillary, Small cell and Plasmacytoid: UC variants to worry about in small biopsies
• Document in the report, including % if not pure
• 2004 WHO classification of non-invasive urothelial tumors has been universally adopted
• Better understanding of genomic profile of bladder cancer is likely to further improve therapeutic targeting
Take Home Messages

• An assessment of the depth and/or extent of subepithelial tissue invasion in T1 cases is recommended

• Prostatic stromal invasion is staged differently depending on subepithelial (T2) versus transmural invasion (T4)
thank you so much