Urinary Cytopathology – Urothelial, Squamous and Beyond

Value
- Cheap
- Quick
- Reliable

Technique
- Sedimentation and smear
- Membrane filter
- Cytocentrifuge
- Liquid-based
  - ThinPrep
  - SurePath
- Stain - Papanicolaou

Specimen types
- Voided
  - Non-invasive
  - No instrumentation artifact
  - Low cellularity
  - Vaginal contamination
- Catheterized
  - High cellularity
  - Invasive
  - Intrumental artifact
- Bladder irrigation
  - Same as above

Voided Urine
- Three specimens
- Three consecutive days
- Avoid early morning specimen
  - Low pH
  - Cellular Degeneration (due to hypertonia)

Urine - Normal Cytology
Diagnostic Categories
- Benign (Negative for malignancy)
- AUCUS, NOS
- High grade
- Malignant
  - Low grade UC
  - High grade UC
  - Other
- Unsatisfactory

Benign
- Cystitis cystica et glandularis
- Granulomatous cystitis
- Infections
- Benign Neoplasms
  - Papilloma
  - Inverted papilloma
Infections

- Bacterial
- Fungal
- Viral
- Parasitic
Malignant Tumors

- Primary Cancers
  - UC
  - Squamous Cell Carcinoma
  - Small Cell Carcinoma
  - Rhabdomyosarcoma or Leiomyosarcoma (<5%)
Malignant Tumors

- Metastatic/Secondary Neoplasms
  - Regional
    - RCC, Prostatic & endometrial adenocarcinoma
  - Distant
    - Adenocarcinoma of lung, breast, other sites
  - Hematologic
    - NHL, HL
    - Myeloma

Urothelial Carcinoma - Some Facts

- Disease of older patients (over 65yrs) – 3%
  under age 44 yrs, 8% in 45-54 yrs
- Non-specific symptoms, most common-gross
  hematuria (80% of patients)
- 80% located at the bladder base
- 60% are single, 50% are <2.5 cm
- 70% have superficial papillary tumors, 20% have
  invasive and 10% have metastasis at presentation

1999 WHO ISUP Classification System

- Papilloma
- Grade 1 TCC
- Grade 2 TCC
- Grade 3 TCC
- Papilloma
- Dysplasia
- PUN of LMP
- Low-grade UC
- High-grade UC

Grading Urothelial Cancers – Role of Urinary Cytology

- Non-invasive, inexpensive
- Used for both, tumor detection and long term surveillance
- High specificity (94%-99%)
- Low sensitivity for low-grade tumors (50% or <)
Papillary Neoplasm Of Low Malignant Potential

Low-grade Urothelial Carcinoma

Criteria for Low-grade Neoplasm

• Architectural
  – Fibrovascular Cores (100% accurate, Post-voided)
  – Irregular Vs. Smooth Fragments

• Cytologic
  – Cytoplasmic homogeneity
  – High N/C ratios
  – Irregular nuclear membrane
High-grade Urothelial Carcinoma
Denuding Cystitis (DC)

- DC is a non-specific descriptive term, often denoting urinary bladder biopsies devoid of surface mucosa (pseudocystitis, erosive cystitis)
- Often encountered in tissue biopsies of bladder mucosa performed by either cold cup forceps or wire loop electrocautery to evaluate hematuria or to rule out recurrent urothelial carcinoma
- Used to describe partially or totally denuded urothelium, which can occur as a result of exfoliation of malignant epithelial cells
- DC in bladder biopsies has been recognized in association with flat carcinoma in-situ (CIS) since the original description of this entity by Melicow and Hollowell in 1952
Denuding Cystitis (DC)

- JHH experience; 
  - n=48
- Urinary Cytology
  - Positive – 26 (54%)
    - Flat CIS - 11
    - Non-invasive HG papillary – 9
    - Non-invasive LG papillary – 3
    - Invasive urothelial carcinoma – 3
  - Negative – 22 (46%)

- Inconclusive diagnosis of DC on tissue might be related to biopsy method and technique, small sample size, or biopsy of cystoscopically "abnormal" urothelium that is denuded

Squamous Cell Carcinoma

- 3% of all bladder cancers
- Association with Schistosoma Hematobium
- Most cases are mixed, Urothelial-Squamous Cell Carcinoma
Adenocarcinoma

- < 3% of bladder cancers
- Associated with extrophy and urachal remnants
- Intestinal and signet-ring subtypes
- Most cases mixed, urothelial-adenocarcinoma

Small Cell Carcinoma

- Rare
- High-grade, aggressive
- Cytology-similar to SmCC from other sites
- Mostly mixed, Urothelial-SmCC
Mimics of High Grade UC

- Polyoma Virus Infection
- Post-therapy
- Radiation

Ileal Loop (Neo-bladder) Urine
Ureteral washings Vs. Biopsy

- Sensitivity
  - Washings 79%
  - Biopsy 71%
  - Combined 100%

Atypia in Upper UT Specimens

- Very commonly reported in UUT cytology (128/321 or 40%), compared to 12%
- Cytopathologists have a lower threshold for UA in UUT
  - Due to a lack of well-defined, published morphologic criteria
  - Risk of definitive surgery in such cases without an intervening tissue biopsy
- Follow-up is evenly between subsequent UC, benign diagnoses and persistence of UA
- Majority of the neoplastic cases are high-grade UC

(Nikolaeva and Ali, unpublished data)
New Technologies

- DNA Ploidy
- Cell markers
- Cytogenetics
- UroVysion

DNA Ploidy

- FC or Image Analysis
- Aneuploidy – High Grade UC
- Diploid – LG UC
- Same sensitivity as cytology
- May allow longer cystoscopy intervals

Cytogenetics

- LG Lesions
  - Trisomy 1 and 7
  - Monosomy 9 (TS gene)
- HG lesions
  - Altered chromosomes 3, 5, 7, 11
  - Association with prognosis

UroVysion FISH Test

- The UroVysion® Bladder Cancer Kit (Abbott molecular)
- FDA approved
- Designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus via FISH
- Results intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis and subsequent monitoring for tumor recurrence
- Loss of signal to 9p21 is thought to be the first and most common deletion, which occurs in low grade papillary neoplasms
- Significant percentages of polysomic cells in the urine typically correspond to high grade urothelial cancers
- If UroVysion results are negative but standard clinical or diagnostic tests (e.g., cytology, cystoscopy) are positive, the standard procedures take precedence
Vysis UroVysion probe set looks for various colored fluorophores to specific DNA sequences matching the centromeres of chromosomes 3, 7, and 17. It uses a locus specific gold-colored fluoroprobe to 9p21 where several tumor suppressor genes, including p16, reside. Loss of signal to 9p21, trisomy 7, or need 11 or more cells (Gold probe). Polysomic cells need 4 or more cells with gains of 2 or more chromosomes.

Criteria For Interpretation

- Loss of signal to 9p21, trisomy 7
- Need 11 or more cells (Gold probe)
- Polysomic cells
- Need 4 or more cells with gains of 2 or more chromosomes

Limitations of UV FISH Test

- Genetic changes of some bladder cancers
- Ta stage solitary tumors smaller than 5mm
- Dependent on the amount of tumor cells deposited on the slide

Comparison of UroVysion FISH - Urinary Cytology

Meta-Analysis of Test
- 14 studies involving 2477 FISH tests
- The overall prevalence of urothelial cancers was 35%

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<thead>
<tr>
<th>FISH</th>
<th>Cytology</th>
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<tr>
<td>Sensitivity</td>
<td>72%</td>
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<tr>
<td>Specificity</td>
<td>83%</td>
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Urine Cytology Discrepancies

- Incidence – 41%
- Cause
  - Interpretation – 35%
  - Sampling – 63%
- 48.6% resulted in minimal or mild harm (repeated testing or diagnostic delays)
- Severe harm never observed

(Raab SS, et al. AJCP 2007)