Urine CYTOLOGY

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Outline

- Introduction
- Specimens & processing
- Reporting and adequacy
- Accuracy
- Normal elements
- Benign
- Ancillary tests
Introduction

- Bladder cancer is the ninth most common cancer worldwide
- The age standardized incidence for north Africa is >5.3 and <9.2 /100,000 population
- The incidence is higher in Sudan and Saudi Arabia
- Egypt and Sudan also have a higher proportion of squamous cell carcinoma due to Schistosoma hematobium
Introduction

• At this point, there is no routine, effective bladder cancer screening test.
• However, urine cytology (consult) can be used as a surveillance tool for:
  – populations at high risk
  – symptomatic patients
  – patients with known prior urothelial malignancy.
• Urine cytology is feared because of low predictive values
• The low efficiency of urine cytology is inherent in the features of the urothelial lesions
CLINICAL INDICATIONS OF URINE CYTOLOGY

- Hematuria
- Follow up for patients treated for UC
- Patients at high risk for bladder cancer
<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voided urine</td>
<td>Noninvasive</td>
<td>Low cellularity</td>
</tr>
<tr>
<td></td>
<td>No instrumentation artifact</td>
<td>Vaginal contamination</td>
</tr>
<tr>
<td></td>
<td>High cellularity</td>
<td>Poor preservation</td>
</tr>
<tr>
<td>Catheterized</td>
<td></td>
<td>Invasive</td>
</tr>
<tr>
<td>Bladder washing</td>
<td>High cellularity</td>
<td>Instrumentation artifact</td>
</tr>
<tr>
<td></td>
<td>Good cell preservation</td>
<td>Poor preservation</td>
</tr>
<tr>
<td></td>
<td>High cellularity</td>
<td>Invasive</td>
</tr>
<tr>
<td>Upper tract washing</td>
<td>Good preservation</td>
<td>Instrumentation artifact</td>
</tr>
<tr>
<td></td>
<td>Selective sampling</td>
<td>Invasive</td>
</tr>
<tr>
<td>Brush cytology</td>
<td>Selective sampling</td>
<td>Invasive</td>
</tr>
<tr>
<td>Ileal loop</td>
<td>Permits screening for recurrent</td>
<td>Low cellularity</td>
</tr>
<tr>
<td></td>
<td>bladder cancer</td>
<td>Poor preservation</td>
</tr>
</tbody>
</table>
PROCESSING

- Fresh (1-12 hours), otherwise need fixation
- Refrigeration if more
- Fixation with equal volume of alcohol (50-70% ethanol).
- Cytocentrifugation, LBC, Cell block, smears
- Papanicolaou stain (H&E)
ADEQUACY

- No standards
- Unsatisfactory specimen:
  - Vaginal cells only
  - Obscuring inflammation or lubricant
  - Blood only
  - Marked degeneration
ACCURACY

• **URINE:**
  - Sensitivity: 25-75% for all grades
  - Sensitivity increases when suspicious & with more than one specimen (3X)
  - Grade dependent
  - Post treatment (RT & CT), less detection (FISH)
  - Specificity is high (95-100%)
  - False +ve: stones, CT, Polyoma V
  - LG papillary vs HG & CIS
ACCURACY

- **BLADDER WASHINGS:**
  - Sensitivity: 66-77%
  - More false positive than urine
  - Ureter and pelvic washings 70-80% sensitivity
CONVENTIONAL WISDOM

“Low grade urothelial carcinoma are usually missed by the cytologist but seen by the urologist; while high grade carcinoma are easily identified by the cytologist but difficult to locate by the urologist”
NORMAL ELEMENTS:

- Urothelial cells:
  - intermediate and superficial (umbrella) cells (voided urine)
  - intermediate, superficial, and basal cells (catheterized urine, washings)
- Squamous cells
- Seminal vesicle epithelial cells (rare)
- Degenerated intestinal epithelial cells (ileal conduit specimens)
NORMAL URINE
Normal
DEGENERATED UROTHELIAL CELLS
(MELAMED-WOLINSKA BODIES)
BASAL CELLS
SEMINAL VESICLE EP CELLS
Lubricant
Triple phosphate crystals

Urate crystals
Sperms

Corpora amylacea
INFECTIONS

- Bacteria, including malakoplakia
- Fungi (especially *Candida*)
- Herpes simplex virus
- Cytomegalovirus (CMV)
- *Trichomonas vaginalis*
- Polyomavirus
- Human papillomavirus (HPV)
Acute cystitis
BK virus “Polyoma”
Malakoplakia “MG bodies”
NONINFECTIOUS FINDINGS AND CONDITIONS:

- Crystals
- Casts
- Nonspecific reactive urothelial cell changes
- Chemotherapy effect
- Radiation therapy effect
- Urothelial atypia associated with urinary calculi
CYTOMORPHOLOGY OF NONSPECIFIC REACTIVE CHANGES:

- Enlarged nuclei
- Prominent nucleoli
- Coarsely vacuolated cytoplasm
REACTIVE UC (CATHETERIZED URINE):
STONE ATYPIA: BE VERY CAREFUL
CURRENT WORLD HEALTH ORGANIZATION AND INTERNATIONAL SOCIETY OF UROLOGIC PATHOLOGISTS CLASSIFICATION SYSTEM FOR UROTHELIAL NEOPLASMS:

- **Flat lesions:**
  - Dysplasia ???????????
  - Carcinoma in situ

- **Papillary lesions**
  - Papilloma
  - PUNLMP
  - Low-grade UC
  - High-grade UC
<table>
<thead>
<tr>
<th></th>
<th>Papilloma</th>
<th>Papillary neoplasm of low malignant potential</th>
<th>Low-grade papillary carcinoma</th>
<th>High-grade papillary carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Architecture</strong></td>
<td>Delicate</td>
<td>Delicate; occasionally fused</td>
<td>Fused, branching, and delicate</td>
<td>Fused, branching, and delicate</td>
</tr>
<tr>
<td>Papillae</td>
<td>Identical to normal</td>
<td>Polarity identical to normal; any thickness; cohesive</td>
<td>Predominantly ordered, yet minimal crowding and minimal loss of polarity; any thickness; cohesive</td>
<td>Predominantly disordered with frequent loss of polarity; any thickness; often dyscohesive</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>Identical to normal</td>
<td>May be uniformly enlarged</td>
<td>Enlarged with variation in size</td>
<td>Enlarged with variation in size</td>
</tr>
<tr>
<td>Nuclear size</td>
<td>Identical to normal</td>
<td>Elongated, round-oval, uniform</td>
<td>Round-oval; slight variation in shape and contour</td>
<td>Moderate-marked pleomorphism</td>
</tr>
<tr>
<td>Nuclear shape</td>
<td>Fine</td>
<td>Fine</td>
<td>Mild variation within and between cells</td>
<td>Moderate-marked variation both within and between cells with hyperchromasia</td>
</tr>
<tr>
<td>Nuclear chromatin</td>
<td>Fine</td>
<td>Fine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Absent</td>
<td>Absent to inconspicuous</td>
<td>Usually inconspicuous*</td>
<td>Multiple prominent nucleoli may be present</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Absent</td>
<td>Rare, basal</td>
<td>Occasional, at any level</td>
<td>Usually frequent, at any level</td>
</tr>
<tr>
<td>Umbrella cells</td>
<td>Uniformly present</td>
<td>Present</td>
<td>Usually present</td>
<td>May be absent</td>
</tr>
</tbody>
</table>

* If present, small and regular and not accompanied by other features of high-grade carcinoma.

The WHO / ISUP Consensus Classification of Urothelial Neoplasms of the Urinary Bladder
LOW GRADE UROTHELIAL CARCINOMA
CYTOLOGIC CRITERIA FOR DIAGNOSING LOW-GRADE LESIONS:

- Cytoplasmic homogeneity
- High nuclear-to-cytoplasmic ratio
- Irregular nuclear membranes
LOW-GRADE UC
LOW-GRADE UC
HIGH GRADE UROTHELIAL CARCINOMA
CYTOMORPHOLOGY OF CARCINOMA IN SITU AND HIGH-GRADE UROTHELIAL CANCER:

- High nuclear-to-cytoplasmic ratio
- Marked nuclear hyperchromasia
- Coarsely granular chromatin
- Irregular nuclear outline
- Large nucleoli (some cases)
HIGH GRADE UC
High grade urothelial carcinoma
VARIANTS:
SQUAMOUS
GLANDULAR
DIFFERENTIATION
DIFFERENTIAL DIAGNOSIS OF CARCINOMA IN SITU AND HIGH-GRADE UROTHELIAL CARCINOMA:

- Polyomavirus
- Stone atypia
- Normal upper tract washings or brushings
- Treatment effect
- Nonspecific reactive changes
BILATERAL URETERAL WASHINGS
CYTOMORPHOLOGY OF SQUAMOUS CELL CARCINOMA:

- Cytoplasmic keratinization
- Pearls
- Bridges
- Angulated hyperchromatic nuclei
SQUAMOUS CELL CARCINOMA
SMALL CELL CARCINOMA
ADENOCARCINOMA
RENAL CELL CARCINOMA
PROSTATE CARCINOMA
Metastatic breast carcinoma
COMMON PATTERNS OF ATYPICAL URINE SPECIMENS:

- Cell clusters in voided urine: diagnose as negative
- Cytologic or architectural criteria for a low-grade lesion: diagnose as negative
- Rare small highly atypical cells: diagnose as suspicious
- Degenerated atypical cells with intact nuclear outlines: diagnose as suspicious
- Rare mildly atypical cells: try to diagnose as negative
HIGH GRADE CELLS HIDDEN
“COY CELLS”
DEGENERATED HIGH GRADE CELLS

A

B
ANCILLARY TESTING OF CYTOLOGICAL SAMPLES

Less specific
More sensitive
Used in conjunction with cytology
ANCILLARY TECHNIQUES:

- DNA aneuploidy (flow cytometry, image analysis)
- Bard bladder tumor antigen (BTA)™ test
- Nuclear matrix protein NMP22 test
- Telomerase assays
- Microsatellite instability assays
- Hyaluronidase and hyaluronic acid
ANCILLARY TECHNIQUES:

- Growth factors
  - acidic fibroblast growth factor (FGF)
  - basic FGF
  - autocrine motility factor
  - epidermal growth factor
  - transforming growth factor-β

- Cell adhesion molecules
- Fibrinogen degradation products
- Tumor-associated and blood group antigens
- FISH
UroVysion™ test

- Multicolored FISH test
- Detects aneuploidy in Chr 3, 7, 17 and loss of 9p21 (p16)
- FDA approved for monitoring patients with h/o TCC and for detection in patients with hematuria.
UroVysion™ test

- Normal UroVysion™ test
  CEP 3 = red
  CEP 7 = green
  CEP 17 = aqua
  LSI 9p21 = gold

- Abnormal UroVysion™ test
  Chr 3 = 2 copies
  Chr 7 = 4 copies
  Chr 17 = 4 copies
  9p21 = 1 copy
SUMMARY:

- Most urine samples for hematuria are negative
- The value of urine cytology for high grade lesions are undisputed
- Criteria for low grade lesions lack specificity
- Urothelial clusters per se are of limited value to diagnose low grade lesions
SUMMARY:

• The term *DYSPLASIA* should be avoided in cytology
• Upper tract lesions: be very conservative
• Separation of high risk from low risk patterns maybe of value to decrease atypical diagnosis
• FISH test (*UroVysion™*) is a promising adjunct to detect UC
THANK YOU
Normal kidney on FNA: glomerulus and renal tubules
Benign renal cysts (FNA)
Oncocytoma
Oncocytoma
Oncocytoma
Renal cell carcinoma
RCC, High Fuhrman grade
RCC, High Fuhrman grade
RCC, papillary type
Urothelial carcinoma of renal pelvis on FNA