Urinary Cytology: Current Practice and Future Directions

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Advantages & limitations of urinary cytology

Advantage of diagnosing
- High grade urothelial carcinoma

Limitation in diagnosis of:
- Low-grade papillary urothelial tumors

Urine Cytology

- Urine cytology has high specificity for detection of UC
- High sensitivity for high-grade tumors ~80%
- Poor sensitivity for low-grade tumors ~25%

Diagnostic Categories in Urine Cytology
Currently Used Terminologies

- Negative
- Atypical, rate of malignancy is 30%
- Suspicious, rate of malignancy is 70%
- Positive

Koss & Hoda, Springer Press, 2012
Diagnostic Categories in Urine Cytology
Paris Classification System, 2015

- Nondiagnostic or Unsatisfactory
- Negative for malignancy
- Atypical Urothelial Cells of Uncertained Significance (AUC-US)
- Atypical Urothelial Cells Suspicious for High Grade Urothelial Carcinoma (AUC-HG)
- Low Grade Urothelial Carcinoma (LGUC)
- High Grade Urothelial Carcinoma (HGUC)
- Other Malignancies Priamary and Metastatic

Case 1
Catheterized urine in a 65-year-old man with frequency

Clusters of urothelial & squamous cells, inflammation

Cytologic Diagnosis
Negative for Malignant Cells

Urine Collection Techniques
- Voided
- Catheterized
- Bladder, ureteric & renal pelvic washings & brushings
- Retrograde catheterization of ureters & renal pelves
- Ileal conduit

Structure of the Urothelium
dilated  contracted

Desmosomes
AUM
Tight junctions
Normal Cells
Voided Urine - Various Types of Umbrella Cells
Voided Urine - Eosinophilic Inclusions
Catheterized urine
Clusters of Normal Urothelial Cells
Washings & Brushings
Clusters
Intermediate, basal & umbrella cells
High cellularity
Well-preserved
Iliac Conduit Uline
Summary

- A thorough knowledge of the differences in cellularity, cell types and architectural features seen among the various collection techniques is important for accurate interpretation.

Case 2

Voided urine in a 59-year-old man with pelvic pain & gross hematuria

Vacuolated cytoplasm with a cytoplasmic collar

Courtesy: Dr. Eva Wojcik

Inflammation, pseudopapillary clusters

Cytologic Diagnosis

Atypical Urothelial Cells

Differential Diagn- Atypical Urothelial Cells

- Urolithiasis
- Treatment effect
- Reactive urothelial cells
- Mislabeling of specimen type
- Low grade papillary urothelial tumors

This diagnosis should be used sparingly
**Urolithiasis in Voided Urine**
- Resemble effects of instrumentation
- Inflammatory background
- Occasional crystals or calcifications
- Spherical 3-D, pseudopapillary clusters

**Benign**

**LGUC**

**Case 3**
Renal pelvic wash in a 68-year-old man with a filling defect

**Summary**
- Reactive changes due to stones, instrumentation, or inflammation maybe misinterpreted as LGUC
- Clinical history of stones is helpful
Bladder Carcinoma

- The 6th most common cancer in US
- Etiology: smoking
- Hematuria, most common presenting sign
- 80% of new cases >60 yrs, >white men

> Arsenic in well water has been indicated as a bladder carcinogen in Argentina, Chile, & Taiwan in smokers


74,690 new cases & 15,580 men & women will die of disease in the USA in 2014

Bladder ca incidence among men in South America is highest in Argentina, >10.7/100,000-WHO

2004 WHO Classification of Bladder Tumors

- **Flat Lesions**
- **Papillary Neoplasms**
  - Papilloma
  - Inverted papilloma
  - Papillary neoplasm of low malign. potential
  - Papillary carcinoma, low-grade
  - Papillary carcinoma, high-grade
- **Invasive Neoplasms**
  - Lamina propria invasion
  - Muscularis propria invasion

Histological Types of Bladder Ca

- Urothelial ca >90%
- Squamous cell ca <10%
- Adenocarcinoma <2
- Small cell ca rare
- Poorly differentiated ca rare
Urothelial Carcinoma

Papillary In Situ & Invasive

Non-invasive, LGUC

In situ & Invasive, Papillary UC

Papillary Urothelial Ca
Visualized on Cystoscopy- Polypoid Tumors

Papillary Urothelial Ca
Ureter
Kidney

Low Grade Papillary Urothelial Carcinoma
• Comprises 75-80% of Urothelial ca
• >75% recur
• 30% progress to muscle invasion
• <5% death

Low-Grade Papillary Urothelial Ca
Fibrovascular Core- Most Reliable
Cytological Features of LGUC (including LBP)

- Increased N/C
- Irregular nuclear borders
- Cytoplasmic homogeneity
- Other Features
  - Increased cellularity
  - 3-D groups
  - Large, eccentric nuclei

*All features rarely present in every cell

Whishnant, Diagn Cytopathol 2003;28:186

Differential diagnosis of LGUC

- Instrumentation
- Hyperplasia
- Papilloma
- PUNLMP
- Calculi

- Poor recognition in urine by cytology
- Often diploid by DNA ploidy, FISH-

Koss & Hoda, Springer Press, 2012

Summary

- Diagnosis of LGUC may be possible on instrumented urines showing high cellularity & fibrovascular cores

Case 4

Voided urine in a 78-year-old man with gross hematuria

Single cells, clusters, enlarged cells, Nucleus enlarged, hyperchromatic, irregular

Diathesis
Cytologic Diagnosis
Urothelial Ca, High Grade

HGUC, Muscle-invasive (T2, T3, T4)
- Usually preceded by in situ ca
- Frequently metastasize
- Poor long-term outcome

Cytology of High Grade Urothelial Ca
- High cellularity
- Anaplastic cells
- Nuclei: Irregular, Dark
- High n:c
- Diathesis, inflammation, blood

Koss & Hoda, Springer Press, 2012

Low Grade UC       High Grade UC

Case 5
Voided urine in a 82-year-old man with urgency & hematuria
Single tumor cells

Cytologic diagnosis
Urothelial Carcinoma, Probably In Situ

CIS
- Comprises 20-25% of urothelial carcinoma
- Difficult to visualize by cystoscopy
- Tends to progress to invasive cancer
- Clean background
- Single enlarged cells with malignant nuclei

Treatment of Urothelial Carcinoma
- Superficial UC
  - Excision, BCG, other
  - Monitor with cystoscopy & cytology
- Invasive UC
  - Cystectomy
  - Nephroureterectomy

Surveillance for Urothelial Carcinoma
- Cystoscopy
  - Initially, every 3 months for 0-2 yrs
  - Then every 6 months for 2-4 yrs
  - Yearly, thereafter
- Cytology

Diagnostic Sensitivity Urothelial Carcinoma in Cytology
- Low Grade 16-39%
- High Grade 89-93%
Urine-Based Ancillary Tests

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Fluorescence In Situ Hybridization (FISH) for Bladder Ca Detection

Laudadio & Hoda, BJU 2005;96:1280
Veeramachaneni, Diagn Cyto 2003;28:301

UroVysion™

- Low grade tumors:
  - ↑no. chr.1 and 7 (trisomy)
  - changes of chr. 9 (deletion of part or all of chr9 or of 9p21 locus)

- High grade tumors:
  - ↑no. of chr.3, 4, 8, 11, 17, 18 (& virtually all others)

Scoring Criteria

- Gain of ≥ 2 chr in > 4 cells
- Isolated gain of single chr in ≥ 10% cells
- Homozygous loss of 9p21 in ≥ 12 cells
Applications of FISH

- A subsequent tumor is discovered x2 as often for those with (+) UV assay compared to those who are (–)
- FISH is > sensitive than & equally specific to cytology in the detection of urinary tract urothelial ca

Grutschwitz. Int Urol Nephrol. 2014 Apr 22
Sarosdy J Urol, 2002

DDX of High Grade Urothelial Carcinoma

- Polyomavirus
- Treatment effect
- Seminal vesicle cells

Polyomavirus


Seminal Vesicle Cells

Summary

- Sensitivity for diagnosing HGUC is high
- It may not be possible cytologically to distinguish CIS from invasive carcinoma
- Polyomavirus mimics high grade ca
Case 6

- 80-year-old male
- Gross hematuria
- Long-term smoker

Small blue cells, Crush artifact, Necrosis

High N:C, Scant cytoplasm, Nuclear molding, Coarse chromatin, Occasional nucleoli

Chromogranin

Ki-67

Small Cell Carcinoma of Urinary Bladder

Non-Urothelial Bladder Tumors

2004 WHO Classification

- Rare, <5%
- Epithelial, i.e. Carcinoma
  - Squamous cell ca, Adenoca, Small cell ca, Carcinosarcoma/sarcomatoid ca
- Non-Epithelial
  - Sarcomas, Lymphomas, Melanoma, Pheochromocytoma
Histological types of bladder ca

- Urothelial ca >90%
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Non-Urothelial Ca of Urinary Bladder

- Hematuria
- Frequency
- At diagnosis: generally invasive, in advanced stage with poor prognosis

Small Cell Carcinoma

- Rare, <1% of all bladder tumors
- Elderly men, History of smoking
- Present with hematuria
- ~2/3 may have co-existent urothelial ca
- 5-year survival, Stage II: 63%, III:15%, IV:10%


Treatment of Small Cell Carcinoma

- Radical cystectomy
- Systemic chemotherapy when metastatic

Squamous Cell Carcinoma

Adenocarcinoma, Urachal
Renal Cell Ca
Melanoma
Lymphoma
Ovary

Metastatic Tumors to Bladder

Eosinophilic inclusions

Cercariform cells

Features of Metastatic Urothelial Ca

Unusual findings in urinary sediment

Septate & brown hyphae
Stain contaminant

Alternaria

Human Papillomavirus (HPV)