Challenges in Diagnostic Cytomorphology 2

Dina Mody, MD
Richard DeMay, MD
David Wilbur, MD
Eva Wojick, MD

There are no disclosures necessary.
Update for Cervical Cytology
Atypical Glandular Cells
Unusual HSIL Presentations
Biomarkers

David C. Wilbur, M.D.
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Topics to be discussed

1) Endocervical neoplasia and mimics
2) “High risk” variants of HSIL
3) Biomarkers and their utility

Incidence of Endocervical Carcinoma

• 9 US SEER databases
    • 19,703 squamous cell carcinoma (▼ 20%, CIS ▲ 1.4x)
    • 3,895 adenocarcinoma (▲ 2x, AIS ▲ 7x)
    • 956 adenosquamous
    • 2,457 type unspecified
• Worldwide
  – Some countries show declines in ACA
    • Finland, France, Italy
Atypical Endocervical Cells

Follow Up Studies – “Rule of Thumb”

<table>
<thead>
<tr>
<th>Category</th>
<th>Probability</th>
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<tbody>
<tr>
<td>Benign/Reactive</td>
<td>40%</td>
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<tr>
<td>Squamous Neoplasia</td>
<td>50%</td>
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<tr>
<td>Endocervical Neoplasia</td>
<td>10%</td>
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Topic 2
Adenocarcinoma in situ/Invasive

- AIS – prototypical WD EC neoplasia
- Invasive EC ACA – well to poor differentiation
- Architectural features
- Cytologic features
- Cellularity
- Background

EC Adenocarcinoma in Situ

1) Hyperchromatic crowded groups
2) Increased nucleus to cytoplasmic ratio
3) Nuclei large (75 um2)
4) Even chromatin with coarse granularity
5) Micronucleoli
6) Rosettes
7) Feathering
8) Strips with pseudostratification
9) Mitoses, apoptotic bodies
10) Amphophilic granular cytoplasm
11) Clean or inflammatory background
Endometrioid AIS

• Smaller cells than usual type AIS
• Absence of EM stroma and stromal fragments
• Most commonly missed AIS
• AGC is acceptable

Villoglandular Adenocarcinoma

• Usually occur in younger population (35 y mean)
• 62% history of oral contraceptive use
• Usually well-circumscribed, minimally invasive
• Behavior favorable
• LN metastases rare
• Conservative management (cone only) for pure Gr1 lesions with minimal invasion, LVI-, margins-
Topic 3
Adenoma Malignum

- Rare
- Often not HPV associated
- Presents with mass
- Histologically bland
- Cytologic atypia common
Adenoma Malignum
“too many EC cells”
Adenoma Malignum
“too many EC cells”

Topic 4
Tubal Metaplasia

- Benign metaplasia of EM and upper EC canal
- Architectural mimic of AIS
- May have mitotic activity
- Bland nuclear features
- P16/Ki67 neg or spotty +
Tubal Metaplasia - Cytologic Features

1) Incomplete features of AIS
2) Chromatin (texture/distribution)
3) Nuclei “washed-out”
4) Nuclear pleomorphism
5) N/C increased
6) Mitoses/rare apoptosis
7) Large stripped nuclei
8) Cilia/terminal bars
Topic 5
Endocervical Polyps

1) Common
2) Bleeding
3) Surface ulceration
4) EC proliferation - abundant cellularity - HCG’s
5) Reactive changes - enlargement, nucleoli, mitoses
6) Inflammation - reparative changes
7) Can mimic either EC or EM neoplasia

AEC associated with biopsy site
**Topic 6**
**Directly Sampled Endometrium**

1) tight groups or 2-dimensional sheets  
2) Small reniform nuclei  
3) Small nucleoli/chromocenters  
4) “Wispy” granular cytoplasm  
5) Some cytoplasmic vacuoles  
6) Tubule and gland formation  
7) Mitoses/apoptosis common

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**Directly Sampled Endometrium**

- Present as pseudostratified strips of cells  
- Nuclei are generally coarsely granular  
- Good look-alike for AIS  
- Stromal fragments can be HCG’s  
- Stromal fragments attached to EM epithelium  
- Caveat – small cells with small nuclei
Size Matters!!

AIS

Direct-sampled EM

ASCCP Flowchart

http://www.asccp.org/pdfs/consensus/algorithms_cyto_07.pdf
Atypical Glandular Cells

Quality Control/Quality Assurance
1) Prevalence of AGC (<1%)
2) Clinical history
3) Communication
4) Criteria Application
5) Retrospective Review
6) Cytology/Histology Correlation

AGC Prevalence

Range 0.11 – 2.1% (mean = 0.48, median = 0.27)
CAP Data - mean = 0.35%, median = 0.3%
Rule of thumb < 1%

Variant Presentations of HSIL
Patterns of HSIL/CA

- Classic – single cell, syncytia
- Involving glands
- In atrophy
- Stripped nucleus
- EM stroma-like/repair-like
- Hypochromatic
- Keratinizing

4) Stripped Nucleus Pattern

- Individual stripped nuclei
- Small groups of stripped nuclei loosely aggregated
- Nuclei may be enlarged, irregular, and hyperchromatic
- Nuclei may be relatively bland
- Mimic is cytolysis

Papanicolaou & Traut 1943
5) EM stroma/repair-like

- Bloody background simulating menses
- Small tightly packed groups of cells
- Small isolated cells with high N:C
- Prominent spindle cell component
- Cytoplasm spindles from group margins
- “Taffypull” cytoplasm
- +/- nucleoli
- May be associated with “classic” HSIL
P16/Ki67 uses: Squamous lesions

- To reduce interobserver variability in cervical biopsy interpretation
- To differentiate HSIL from
  - Atrophy
  - Immature squamous metaplasia
  - Reactive epithelial changes
- To differentiate AIS/EC dysplasia from benign EC
- To evaluate cauterized margins
- To evaluate thin dysplasias
- To evaluate the presence of invasion
- To screen putatively negative biopsies after HSIL Paps
- Screening Pap/Anal Pap tests
p16/ProExC in Pap tests

HSIL - Positive staining

Sweeney et al, ASC Meeting 2009

p16/ki67 in Anal Specimens

Thank You!!

Questions??
Body Cavity Fluids

Exudates:
Can be malignant
...but are always pathologic

Transudates: Exudates:
Usually benign Can be malignant

Mesothelial Cells

Mesodermally-derived epithelial cells
Line body cavities: Pleura, pericardium, peritoneum
Normal: Single layer, flat (squamous) cells
Effusions: “Reactive”
Cells: plump, cuboidal
Nuclei: active
DDx: Cancer - Common dilemma
Mesothelial Cells

Mostly single Small lobulated groups

Windows Hugging Histiocytes

Mesothelial Cells

Cells: Rounded, variable size
Nuclei: Reactive changes common
Cytoplasm: Dense center, lacy skirts

Vacuoles

Common, though often nonspecific
- Degenerative
- Lipid
- Glycogen
- Mucin => adenocarcinoma
Marked Reactive Changes

- Pulmonary embolism or infarct
- Active cirrhosis or hepatitis
- Uremia
- Pancreatitis
- Long-term dialysis
- Radiation, chemo-Rx, surgery
- Also: Pericardial effusions

*Repeat tap can be helpful!*

Histiocytes

- Practically ubiquitous
- Nuclei: beans, mitoses!
- Cytoplasm: lacy throughout, phagocytosis typical
- DDx: Mesothelial Cells
  - No: Molding, hugging, windows, tight groups

Other Inflammatory Cells

Eosinophils
- Usually => prior tap
- Infx, infarct, allergy, idiopathic
- Not: Cancer, Hodgkin

Lymphocytes
- Common, usually nonspecific

Neutrophils
- Nonspecific, but often infectious
  - => markedly reactive meso’s
- Rarely numerous in malignant effusions
Psammoma Bodies

- Not diagnostic of cancer!
  - Mesothelial hyperplasia
  - Endosalpingiosis

Cancer: Ovary most common in women
Other, eg, papillary adenocarcinomas

Collagen Balls

- Usually peritoneal washes, females
  - Also, other sources, men
- Associated with mesothelial cells
  - Benign proliferation
  - Malignant mesothelioma
- Rare in adenocarcinoma

Odds & Ends

- Ciliocytophilia
- Megakaryocyte
- Sickle cell
- LE Cell
- Hematoxylin Body
- Pick up
- Curschmann spiral

Page 4
**Tuberculosis**

Turbid, yellow or metallic green (pseudochylous effusion)

Classic cytologic findings:
- Lymphs abundant
- Mesothelial rare
- Histiocytes present, giant cells rare
- TB, T cells; Lymphoma, B cells

=> flow cytometry (TGFF)

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**Rheumatoid Effusion**

Pseudochylous (metallic) classic

Cyto: Rheumatoid Granuloma
- Necrotic debris, "diagnostic"
- Epithelioid histiocytes
- Multinucleated giant cells
- Mesothelial cells sparse
- Bizarre cells, yet benign!

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**Malignant Effusions**

Any cancer can cause an effusion
- Common: Lung, Breast, Ovary, GI tract

In oncology pts, most are malignant
- Can be benign (eg, CHF, Cirrhosis, Rx)

Site of effusion clue to primary site
- Lung & breast usually ipsilateral
- Abd/pelvic → Ascites before pleural
Diagnosis of Malignant Effusions

Key: Foreign Cells

“When cytology is easy, it is very, very easy...”

But when it’s difficult...

Some malignancies mimic benign cells, like *Invasion of the Body Snatchers*
“Mesothelial Pattern” Carcinoma

When it’s difficult...

Two helpful suggestions

- Mucicarmine stain
- “Submit more material, if fluid reaccumulates”
  - If doesn’t, probably benign
  - Improves cellular preservation
  - Benign atypia tends to resolve
General Features Malignant Effusions

Key: Foreign cells with foreign features
   ie, discrete or extra population of cells

Some possible exceptions:

- Mesothelioma: Native cells, can be bland
- Tumor mimics reactive mesothelial cells
  eg, breast cancer, serous ovarian tumors

Tumor Diagnosis: No single feature

- Cell Groups
- Group Contours
- Cell Shape
- Nuclei
- Cytoplasm
- Cell Surface
- Background
  + clues to primary

Cell Groups

- Large groups: Suspicious
  - Cell balls, papillae, glands
- Single tumor cells:
  - Lymphoma (classic)
  - Breast or Gastric CA
  - [Sarcoma, Melanoma, Mesothelioma]
Cannonballs

Suggest Breast CA
... in a woman

Papillae

Pleural: Lung, Breast
Ascites: Ovary, GI tract
(Mesothelial hyper/neoplasia)

“Caterpillars” - Single file chains

Breast, Pancreas, Gastric, Uterus
[Lung (small cell), Mesothelioma]
Cell Shape

All cells tend to round up in fluids (makes differential dx difficult)

Bizarre shapes => malignancy

except rheumatoid effusion

Nuclei

Malignant nuclei = *sine qua non*

Classic cytologic criteria:
- Enlarged, pleomorphic
- High N/C ratios
- Irregular membranes
- Abnormal chromatin
- Large/abn nucleoli

Hyperchromasia variable

May not be prominent due to proliferation

Mitoses not helpful: Unless numerous or abnormal

Intracytoplasmic Lumens (ICLs)

Suggests breast cancer

...in women
Signet Ring Cells

- Stomach or Breast
- Other Adenocarcinomas

Extreme Vacuolization

- Ovary, Pancreas

Cell Surface

- Well-defined cell borders:
  - Favor malignancy
- Ill-defined cell borders:
  - Favor benign (Mesos or histiocytes)
- Cilia: Strongly favor benign
  - Exclude prominent microvilli
  - Ciliated carcinoma very rare
Colorectal Carcinoma

"Terminal bars"
(Striped border)
Cigar-shaped nuclei
Dirty necrosis

Small Cell Carcinoma

Caterpillars: Usually easy diagnosis
Clusters: Can be difficult to detect
in "busy" inflammatory background
Also: Single cell pattern, mimics lymphoma

Pseudomyxoma Peritonei

Mucus in peritoneum ("jelly belly")
Source: Mucinous GI Tract lesions,
esp appendix (not ovary)
Neoplastic glands in mucous lakes
Adenomucinosis (bland)
Mucinous carcinomatosis
Other cells sparse / absent
(i.e., meso’s, histiocytes, WBCs)
Cell blocks can be helpful in prep
Squamous Cell Carcinoma

Common cancer, rarely sheds <5% malignant effusions
More keratinization => easier Dx
Most = NK SCC (DDx Rx mesos, AdCA)
Dense cytoplasm, pearls, bizarre shapes
DDx: Sarcomas, rheumatoid effusion
Also benign squames: cyst, fistula, contamination

Lymphoma/Leukemia

Effusions usually late, dx established
Often → chylous effusion
Single cells; no tissue aggregate
Larger cells => easier dx
Clues to look for:
▪ Irregular membranes (eg, cleaves, knobs)
▪ Massive karyorrhexis (apoptosis)
Flow cytometry for difficult cases (TGFF!)

Primary Effusion Lymphoma

Immunocompromised pts
▪ Mostly homosexual men with AIDS
Also, HIV (+), usually elderly men
Confined to body cavities
without solid tumor formation
Particularly “big & ugly” lymphoma cells
Bridges immunoblastic & anaplastic NHL
plasmacytoid ± RS-like cells
HHV-8, EBV, germ line c-myc characteristic
CD30 frequently (+)
### Hodgkin Lymphoma

- Effusions common, diagnostic cells rare
  - Reed-Sternberg cells
  - Hodgkin cells
- Eosinophils rare!
- DDx: Large Cell NHL; Metastatic Malignancy
- Clinical history!

### Melanoma

- Dark brown/black fluid
- Big, ugly tumor cells
- Binucleation common
- Macronucleoli; INCI
- Melanin often sparse
- Problems: Mimics many tumors, late recurrence, unknown 1°

### Sarcoma

- Effusions: Primary usually well known
  - Pleomorphic (e.g., TFFKA-MFH)
  - Round (e.g., Neuroblastoma)
  - Spindle (e.g., Leiomyosarcoma)
- DDx: Mesothelioma, SCC, Rheumatoid
- All cells round up in fluid => DDx wide
Germ Cell Tumors

Suspect diagnosis:
“Big Ugly Tumor cells”
in young patient
Important diagnosis,
may respond to Rx
Mesothelioma

- Epithelioid
- Sarcomatoid
- Biphasic

Other epithelial subtypes:
- clear cell, oncocytoid or granular cell, tubulopapillary, large polygonal cell, polyhedral
- mucin-producing, "medullary," small cell, lymphohistiocytic

Mesothelioma: Fluid Cytology

- Often first diagnostic specimen
- Fluid highly viscous (hyaluronic acid)
- Exudate with high cell count
- Remains high after repeated taps

Combination:
- High hyaluronic acid (>8mg/dL) plus
- Atypical mesothelial cells
- Suggests diagnosis of mesothelioma

Cytodiagnosis of Mesothelioma

In theory, easy—
- Malignant cells ~ mesothelial
- Morphologic kinship
- No foreign cells

In practice, difficult—
- WD - looks benign
- PD - difficult to classify
Cytodiagnostic Features

Cellularity
Cell groups
Cells
Nucleus
Cytoplasm
Vacuoles
Cell borders
Background

Not every feature is present in every case!

Cellularity

Important diagnostic clue:

More and bigger cells...
...in more and bigger clusters

Cell Groups

Knobby
Complex, irregular
Single Cells
Papillae
Caterpillars
**Cell Arrangements**

- Hugging
- Collagen cores

**Cells**

Tumor cells look mesothelial:
Key diagnostic feature!

- Gigantocyte
- Spindle + epithelioid
- Spindle

- Histiocytoid
- Mesothelioid
Nucleus
N/C ratio maintained → Uniformity

Cytoplasm

Vacuoles
Lipid
Glycogen
Hyaluronic Acid
Mesothelioma: Ultrastructure

Bushy (vs stubby) microvilli
### 2-Part Mesothelioma Immunopanel

1st Part: Mesothelial Markers (+)
- Calretinin, WT-1 (front line)
- CK 5/6, CAM 5.2* (secondary)
  *Does not exclude carcinoma, but helps detect
calretinin, CK 5/6 (−) cases, often sarcomatoid

2nd Part: Epithelial Markers (−)
- CEA, Ber-Ep4, BG-8, MOC-31
to exclude adenocarcinoma

*Strongly recommend cell blocks!!!*

### Primary Peritoneal Carcinoma

- Usually elderly women, normal ovaries
- Origin: Mesothelium vs Fallopian tube
- Most: Papillary serous morphology
- DDx: Mesothelioma
  - Epithelial markers, eg, MOC-31 vs
  - Mesothelial markers, eg, calretinin
- Ovarian carcinoma
  - Gross ovarian disease, invasion

### Two take home points...

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**Page 6**
Metastases

Foreign cells with foreign features
“One of these things is not like the other…”

Mesothelioma

Malignant cells that look mesothelial in origin
“More & bigger cells, in more & bigger clusters”

Thank you
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Urine – the most frustrating cytology specimen

Eva M. Wojciech, MD
Professor and Chair of Pathology
Loyola University, Chicago, IL

Main purpose of urine cytology

To detect bladder cancer

Why frustrating?

- Urologist sees a tumor – urine cytology report is negative
- Urologist doesn’t see a tumor – urine cytology report is positive
- Great chance that the tumor will recur – Which patient? When?
- All urines are “atypical”
**Frustrating for whom?**

- Cytotechnologist
- Cytopathologist
- Surgical pathologist
- Urologist
- Epidemiologist
- Insurance
- Molecular markers industry
- Patient

**Bladder cancer - current status**

- Worldwide - 7th most common cancer
- 250,000 new cases each year in men
- 76,000 new cases each year in women
- Man - 1 in 30; woman - 1 in 90 (USA)
- Highest incidence - Western Europe, North America, Australia
- ~50% detected by routine cytology
- ~75% superficial bladder cancers
- ~50% - 70% - recurrence
- ~5% - 10% - progression
- >500,000 people in the US are survivors of this cancer
- The fifth most expensive cancer to treat
- ~$3.4 billion/year is spent for bladder cancer treatment (USA; 2003)
Classifications

WHO 1973

<table>
<thead>
<tr>
<th>Papilloma</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
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<tbody>
<tr>
<td>Papilloma</td>
<td>Low Grade</td>
<td>High Grade</td>
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</table>

WHO/ISUP 2004

Urothelial papilloma

- ~1% of papillary urothelial tumors
- < 50 years of age: F: M - 2:1
- Delicate fibrovascular stalks covered by cytologically and architecturally normal urothelium → Cytology negative
- May recur but no progression
- Molecular findings:
  - Дilet на low proliferative rate
  - P53 mutation ~ 75%
  - Ch 20 - superficial cells

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

"papillary urothelial lesion with orderly arranged cells within papillae with minimal architectural abnormalities and minimal nuclear atypia" www.uo-invest.net
- Cytology negative
- Increased urothelial thickness, preserved polarity
- Mitoses - very rare, basal
- M:F (3:1), > 65 years old
- Local recurrence ~ 30%, progression ~ 5%
- Molecular findings:
  - Дilet на low proliferative rate
  - P53 mutation ~ 85%
Low grade urothelial carcinoma

- LG UC – slender papillary branching frowns with minimal fusion
- Easily recognized variation in architectural and cytological features – nuclear enlargement
- Mitosis may be present, any level
- Cytology – mostly negative
- Local recurrence ~ 50 - 75%, progression >10%, death <5%
- Molecular findings:
  - Mostly diploid with low proliferative rate
  - FGFR3 mutation ~ 60%
  - Altered expression of CK 20, CD44, p16 and p53 may be seen

VS.

Cytologic cells
What features are necessary to make diagnosis of LGUC in urine cytology?
"Architecture"
- Fibrovascular cores
- Central capillary vessel
- Cellularity - "an ocean of cells"
**LG UC**

- Increased cellularity
- Presence of papillary, cohesive clusters
- Mild to moderate pleomorphism
- Increased N/C ratio
- Eccentric, mildly enlarged nuclei
- Mild irregularity in nuclear membrane
- Granular, even chromatin
- Homogenous cytoplasm
- Inconspicuous nucleoli

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**How significant is the fact that we made a diagnosis of LG UC?**

- If we made a diagnosis – tumor must be large or multiple
- Cystoscopic findings including lesion size ≥ 2cm or multiple lesions, together with concurrent positive or suspicious urine cytology, were associated with recurrence or progression

  J. Jackson, C. Barken, C. Middle

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**Take home message**

- Cyto dx of LG UC on instrumented urines is possible ("low power diagnosis" - cellularity, fibrovascular cores) but unlikely
- If you are considering LG UC on instrumented urine check if biopsy has been taken
- If cyto+ and bx LG UC – urologist will look for CIS
- Our job is to look for HG UC
High grade urothelial carcinoma

- Papillary fronds with obviously disordered arrangement (fusion) and cytologic atypia
- Pleomorphism, altered polarity, mitoses
- "Low-power diagnosis"
- Cytology positive
- Molecular findings:
  - Aneuploidy with high proliferative rate
  - Altered expression of CK 20, CD44, p53 and p63

HGUC

- Increased cellularity
- Presence of loose clusters and single cells
- Moderate to marked pleomorphism
- Eccentric, enlarged, pleomorphic nuclei
- Irregular nuclear membrane
- Coarse chromatin
- +/ prominent nucleoli
- Squamous or glandular differentiation
Urothelial carcinoma in situ

- Non-papillary (flat) lesion composed of malignant cells
- De novo - 3-8%
- Associated with papillary carcinoma (10-15%) and invasive carcinoma (15-50%)
- Anaplasia, loss of polarity, disorganization, mitoses
- Cytology - positive
Take home message

- If the urine is POSITIVE (in general) it is a high grade carcinoma
- We can not assess the stage - carcinoma in situ (Tis) looks the same as papillary HG non-invasive (Ta) or invasive (T1-T3)

Urothelial Carcinoma - Follow-up
Cystoscopy vs. Cytology
- Sensitivity – 73%
- Specificity – 37%
- Invasive procedure

Understanding urine cytology

Function of the urothelium
- Urine - blood barrier
- Ability to dilate and contract
Cells in the urine

- Urothelial cells - superficial (umbrella cells), intermediate/basal cells
- Squamous cells - GYN tract, trape, metaplasia, dysplasia
- Glandular epithelium - cystitis glandularis, metaplasia, prostatic glandular cells, seminal vesicle cells
- Rhabd tubular cells
- Hematopoietic cells

Umbrella cells

GYN contamination

Sq metaplasia - chronic irritation (etones)

Sq differentiation to HUC or para SqCCa

GYN contamination - LSIL
Type of urine specimens

- Voided urine:
  - Low cellularity – umbrella cells, few intermediate cells, squamous cells (women)
  - Rare cell clusters
  - Eosinophilic cytoplasmic inclusions - degeneration

- Instrumented urine:
  - High cellularity – umbrella cells and intermediate/basal cells
  - Better cellular preservation
  - Numerous cell clusters
  - Similar findings in urotheliums and low grade carcinomas

- Urinary diversion urine:
  - Rare cell, indistinct pustule, nephroblast
  - No upper urinary tract
  - Numerous poorly preserved glomerular cells

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Human Polyoma virus

- Small, non-enveloped, double-stranded DNA virus, BK and JC
- Infection occurs during childhood and is usually subclinical, > 90% of adults are carriers
- Infection is reactivated in individuals with various degrees of immunological deficits
- Human polyoma virus is demonstrable in 0.3% of healthy adults
- Human polyoma virus nephropathy - 1%-4% of renal transplants, loss of graft - 50% of cases
- Cytology: single, large, homogenous, pleomorphic inclusion body
- Metaplastic changes include papillary hyperplasia, metaplasia with squamous differentiation
- Urthelial cells affected by virus have an abnormal DNA content

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Diagnostic Categories

- Positive
- Suspicious
- Atypical
- Negative
- Unsatisfactory
Positive

Quality

Quantity

Negative

Voided Urine

Instrumented Urine

Suspicious

No Quality or No Quantity

But Almost There......
What is Atypia

Umbrella cells - Not Atypia

Instrumentation - Not Atypia
Atypical cytology by specimen type

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<tr>
<th>Total Number</th>
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<td>Bladder washing</td>
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<td>Voided urine</td>
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<td>TOTALS</td>
<td>15299</td>
<td>1320</td>
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Beyond Urine Cytology

Quest for ...
FISH - after UroVysion probe hybridization
FOUR COMBINED PROBES

- Diploid
  - 2 copies of chrom 3 (red)
  - 2 copies of chrom 7 (green)
  - 2 copies of chrom 17 (qua)
  - 2 copies of region 9p21 (gold)

- Aneuploid
  - 2 copies of chrom 3 (red)
  - 4 copies of chrom 7 (green)
  - 3 copies of chrom 17 (qua)
  - 1 copy of region 9p21 (gold)

UroVision – Review of the Literature

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<tr>
<th>Author</th>
<th>Cytology</th>
<th>FISH</th>
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<td>Haling et al.</td>
<td>58%</td>
<td>81%</td>
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<tr>
<td>Fredrich et al.</td>
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<td>Mian et al.</td>
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<tr>
<td>Skacel et al.</td>
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<td>Serosdy et al.</td>
<td>26%</td>
<td>71%</td>
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<tr>
<td>Haling KC</td>
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<td>81%</td>
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</tbody>
</table>
Correlation of FISH with Atypical Urine Cytology and its Progression to Malignancy

- Jan 2008 – Dec 2010 – all atypical urines – FISH
- A total of 251 atypical urine cytology specimens were analyzed for FISH over three years and 22% (55/196) had positive FISH results
- 23 true positives (TP), 32 false positives (FP), 177 true negatives (TN), and 19 false negatives (FN)

<table>
<thead>
<tr>
<th>Specimen Positive</th>
<th>Specimen Negative</th>
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<tr>
<td>FISH Positive</td>
<td>23 (12 HG, 6 LG, 1 ACC, 3 avo only)</td>
</tr>
<tr>
<td>FISH negative</td>
<td>19 (8 HG, 8 LG, 3 avo only)</td>
</tr>
</tbody>
</table>

- Sensitivity - 56.8%, Specificity - 84.7%
- Positive predictive value (PPV) - 41.8%, negative predictive value (NPV) - 90.3%

Final take home message

- Urine cytology is not that bad
- Better miss LG UC than overcall
- We can not be perfect all the time
- Look for a high grade – this one is clinically significant
- Not everything is atypical
- Apply adjuvant study judiciously
- Always correlate with morphology
Thank you