Cytopathologist’s perspective

- Emerging & re-emerging infectious diseases
- Threat of bio-terrorism
- Ever-growing population of patients with
  - Iatrogenic
  - Inherited
  - Acquired immunodeficiency

Specific role
- Patients with incompletely defined clinical problems
- As an adjunct to other diagnostic modalities.
- Help in identifying the pattern of tissue injury

Advantage
- Rapid & convenient (bedside)
- Sample can cover large areas

SELECTION TAILORED TO CLINICAL SITUATION
Clues to a viral infection

- **Cytopathic changes**
  - Inclusion bodies with margination of chromatin on the nuclear membrane
  - Cowdry type A (herpes)
  - Cowdry type B (adenovirus or poliovirus)
  - Multinucleation
  - Ground glass appearance

- **Tissue Tropism** – organ specific distribution
  - CMV, HSV, VZV, polyomavirus, Adenovirus – multisystem infection in immunocompromised.
Tissue Tropism

Gynecological infection

- HPV
- HSV
- CMV
- Molluscum contagiosum

Pulmonary infection

- Atypical community acquired infections
  - RSV
  - Parainfluenza virus
  - Influenza virus
  - Adenovirus

- Immunocompromised
  - CMV
  - HSV/ VZV
  - Measles

Viral Lymphadenitis

- EBV
- HIV
- HSV
- CMV
- RSV
- Adenovirus
- Measles
- influenza
Case I

- 62-year-old male
- DM / HT / CAD / CKD (ESRD) on HD with CVA
- 1 episode of GI Bleed
- Endoscopy –
  - Esophagitis with ulcer (?CMV/HSV) with gastric ulcer
Case II

- S - 26F, Tzanck smear
Case III

32 year old female – PAP Smear
Herpes simplex virus

- HSV-1 & 2
- Pap smears
- GIT
- Respiratory specimens (Immunocompromised patients)
- HSV-1  Respiratory tract.
- HSV-2  Sexual activity
- Conspicuous nuclear changes - Infected cells
- PAP stain - most desirable
Three M’s of Herpes

- Multinucleation – Cowdry type A ("eggs in a basket")
  (Acta Cytol 1994;38:43)
- Moulding
- Margination
- Mononucleated cells – Early disease
  (DeMay: The Pap Test: Exfoliative Gynecologic Cytology; 2005)
- Confirmation – culture, ICC, IF, and ISH techniques
CASE IV

- PAP Smear for screening

Large defined perinuclear halos, binucleation, and slight nuclear atypia, with smudged chromatin.
 Koilocytes – “Koilos” (hollow or cavity)

 Recognition is based on:
   - marked density of the cytoplasm peripheral to the cavity,
   - amphophilic cytoplasm, and
   - enlarged hyperchromatic nucleus.

 Other features:
   - bi- and multinucleation,
   - plaques or aggregates of parakeratosis and hyperkeratosis,
   - anucleate squames
The 2014 Bethesda System

- Squamous Epithelial Cell Abnormalities
  - Dichotomous reporting terminology for LSIL and HSIL is maintained
  - Natural history of HPV-related infections –
    - low-grade changes represent productive, largely transient HPV infection
    - high-grade morphology represents a precancerous lesion.
CASE V

- Solitary cells.
- Enlarged nuclei with nuclear inclusions
  - almost fill the nucleus
  - thin rims or halos.

Urine sample in Renal allograft Recipient
Decoy cells

- Typical intranuclear viral inclusion bearing epithelial cells in the urine.
- Different morphologic variants (types 1 through 4)
- Easily identified and quantifiable in
  - routine Papanicolaou stained urine cytology specimens.
  - unstained urinary sediment by phase contrast microscopy.
- Ancillary techniques - IHC, EM, and FISH.
Decoy cells

- Parameter to assess the risk for disease in RAR – BKN
- Sensitivity and specificity of decoy cells for diagnosing BKN is 99% and 95%, respectively
- PPV varies between 27% to 90%
- NPV is 99%.
- Detection of decoy cells – comparable to PCR and EM (assess the activation of polyomaviruses in the urine).

Polyomaviruses and Human Diseases - Advances in Experimental Medicine and Biology, Volume 577, pp 201-212
PULMONARY VIRAL INFECTIONS

HSV/VZV – Cowdry type A and B inclusions in Metaplastic squamous cells & Multinucleated giant cells

CMV – Large intranuclear and small cytoplasmic inclusions, multinucleation rare

Adenovirus - Intranuclear inclusions (smudge cells) and ciliocytophthoria.

Respiratory syncytial virus — syncytial giant cells.

Parainfluenza — syncytial giant cells with cytoplasmic inclusions and ciliocytophthoria.

Measles - multinucleated giant cells with cytoplasmic and intranuclear Cowdry type A inclusions.
<table>
<thead>
<tr>
<th>Virus</th>
<th>Nuclear Features</th>
<th>Inclusions</th>
<th>Other Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex and herpes zoster</td>
<td>Multinucleation; molding; peripheral margination of chromatin</td>
<td>Eosinophilic, intranuclear (Cowdry type A)</td>
<td>—</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Enlargement</td>
<td>Large intranuclear, basophilic, with halo; small cytoplasmic, basophilic</td>
<td>Cytoplasmic enlargement</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Multinucleation</td>
<td>Eosinophilic, intranuclear; multiple eosinophilic intracytoplasmic</td>
<td>Giant cells</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Multinucleation</td>
<td>Cytoplasmic, basophilic, with halo</td>
<td>Giant cells; necrosis</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Smudged appearance as a result of large inclusion that fills entire nucleus</td>
<td>Large intranuclear, basophilic</td>
<td>Ciliocytophthoria</td>
</tr>
</tbody>
</table>
## Viral lymphadenitis – Cytological clues

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>CYTOLOGICAL FEATURES</th>
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<tbody>
<tr>
<td>EBV - Infectious mononucleosis</td>
<td>Immunoblasts with atypia</td>
</tr>
<tr>
<td>HIV</td>
<td>Polymorphous lymphoid cell pattern, plasma cells, Opportunistic infections.</td>
</tr>
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<td>HSV</td>
<td>3 M’s</td>
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<td>CMV</td>
<td>Large cells – Owl’s eye inclusion.</td>
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<td>VZV</td>
<td>Rare intranuclear inclusion</td>
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<tr>
<td>Measles</td>
<td>Polykaryocytes</td>
</tr>
</tbody>
</table>
Ophthalmic viruses

- Superficial viral eye diseases
  - 21 of 38 patients with suspected HSV
  - 3 of 4 patients with suspected VZV
  - 2 of 10 patients with suspected Adenovirus infection.

Improved impression cytology techniques for the immunopathological diagnosis of superficial viral infections