SEROUS FLUIDS
BODY CAVITY FLUID CYTOLOGY
Schematic representation of the three body cavities
Collection and preparation of specimen

- **Heparinized bottles**
  - (3 units heparin/ml)
  - Unfixed

- **Alcohol-fixed**
  - **Papanicolaou-stained**

- **Cytocentrifuge preparation**
  - Alcohol-fixed
  - Papanicolaou-stained
  - Air-dried cytocentrifuge preparation
  - Diff-Quik
  - (Hematologic malignancy is suspected)

- **Cell block**
  - Adding plasma and thrombin solution
  - Wrapped in filter paper
  - Placed in a cassette
  - Embedded in paraffin
  - Cut and H&E stain
## Differences Between a Transudate and an Exudate

<table>
<thead>
<tr>
<th>Feature</th>
<th>Transudate</th>
<th>Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross appearance</td>
<td>Watery, clear</td>
<td>Cloudy, reddish</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>&lt;1.015</td>
<td>&gt;1.015</td>
</tr>
<tr>
<td>Protein</td>
<td>&lt;3.0 g/dl</td>
<td>&gt;3.0 g/dl</td>
</tr>
<tr>
<td>Clots</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cells</td>
<td>Few; usually benign</td>
<td>Many; can be malignant</td>
</tr>
</tbody>
</table>

**Transudate**

- Increased hydrostatic pressure: Congestive heart failure
- Decreased oncotic pressure: cirrhosis, nephrosis, and malnutrition (decreased albumin)

**Exudate**

- Inflammation: Infection, infarction, hemorrhage
- Tumor
Body cavity fluid cases represents a significant number of non-gyn specimens in typical cytology practice.

An effusion always represents an underlying pathology.

The Primary Goal: Reactive VS. Malignant.

A positive diagnosis indicates advance neoplastic
OBJECTIVE

- Differentiate the many faces of reactive cells and malignant cells in serous effusions
- Analyze selected common effusion cases with emphasis
- Potential diagnostic pitfalls and the cytologic approach in making diagnoses in fluid cytology
Benign elements

**Mesothelial cells**

- Usually dispersed as isolated cells
- Binucleation and multinucleation
- Occasional small clusters with “windows”
- Dense cytoplasm with clear outer rim (lacy skirt)
Serous membranes
PLEURAL EFFUSION
Panorama of mesothelial cells

“Effusion = Confusion”
CRITERIA

- Dual population: Meso- Plus Atypical One
- Ball-like/Papillary-like 3-D clusters
- Pleomorphisms
- Nuclear hyperchromasia
- Nuclear membrane irregularities
- Large nucleoli
Warning Flags

- High cellularity,
- 3D cell groups with loss of polarity
- Vacuolated cells with nuclear atypia
- No spectrum (monotonous population with atypia)
- Necrosis; apoptosis
Low magnification

- Inflammatory, clustering, one or two cell population
- Background: Mucinous tumor/Serous tumor/necrosis/apoptosis
- Higher magnification: nuclear details
Adenocarcinoma
Reactive mesothelial cell
- Pleomorphic and enlarged nuclei
- Hyperchromasia
- Prominent nucleoli
- Mitotic figures

<table>
<thead>
<tr>
<th>Benign Mesothelial cells that mimic cancer cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign Formation</strong></td>
</tr>
<tr>
<td>Three Dimensional cell balls</td>
</tr>
<tr>
<td>Papillae</td>
</tr>
<tr>
<td>Indian files carcinoma</td>
</tr>
<tr>
<td>Cell in cell</td>
</tr>
<tr>
<td>Signet ring</td>
</tr>
<tr>
<td>Single cell</td>
</tr>
</tbody>
</table>
Non-neoplastic conditions

**Acute serositis**
- Bacterial infection: pleural empyema, bacterial peritoneal
- Color of the fluid: creamy pale yellow (purulent)
- Cytology preparation: high cellular and polymorphonuclear leukocytes

**Eosinophilic effusions**
- Thoracic trauma, pneumothorax, hemothorax, pulmonary infarcts
- Cytology preparation: high number of eosinophils
- Eosinophilic pleural effusions more common
- Charcot-Leyden crystals
**Tuberculous pleuritis**
- Color of the fluid: turbid and greenish-yellow
- Cytology preparation: high cellular of lymphocytes (T cells)
- Differential diagnosis: inflammatory effusion of non-tuberculous origin

**Rheumatoid pleuritis**
- Necrotizing granulomatous inflammation (joint disease)
- Cytology preparation: clumps of granular debris
  - multinucleated macrophages
Malignant effusions---primary tumors

Malignant mesothelioma

• Clinical history: asbestos exposure, persistent pleural effusions, chest pain
• Epithelial (carcinomatous) pattern

<table>
<thead>
<tr>
<th>Malignant Mesothelioma</th>
<th>Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td>“More and bigger cells, in more and bigger clusters”</td>
<td>• Increased bi/multinucleation</td>
</tr>
<tr>
<td>Group</td>
<td>• Nuclear enlargement and pleomorphism</td>
</tr>
<tr>
<td>• Irregular papillae and Knobby three-dimensional clusters</td>
<td>• Macronucleoli</td>
</tr>
<tr>
<td>• Cell-in-cell arrangements</td>
<td>Cytoplasm</td>
</tr>
<tr>
<td>• Indian files</td>
<td>• Windows, skirts (lacy appearance)</td>
</tr>
<tr>
<td></td>
<td>• Dense, many two-tone staining</td>
</tr>
<tr>
<td></td>
<td>• Fine vacuoles (lipid, glycogen)</td>
</tr>
</tbody>
</table>
More and bigger cells, in more and bigger clusters

Cell-in-cell pattern

"More and bigger cells, in more and bigger clusters"
## Malignant effusions---metastatic tumors

<table>
<thead>
<tr>
<th>The Most Common Tumor that Cause Malignant Effusion, by Site and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Malignant</strong></td>
</tr>
<tr>
<td>Pleural</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Peritoneal (includes gastric and pancreatic)</td>
</tr>
<tr>
<td></td>
</tr>
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<td></td>
</tr>
</tbody>
</table>
Adenocarcinoma

- Large nucleoli
- Secretory vacuoles
- Three dimensional aggregates
- Increased N/C ratio
- Irregular nuclear membranes

<table>
<thead>
<tr>
<th>The patterns of Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
</tr>
<tr>
<td>- Cannonball (no vacuole)</td>
</tr>
<tr>
<td>- Indian files</td>
</tr>
<tr>
<td>- Signet ring cells (small)</td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
</tr>
<tr>
<td>- Psammoma bodies</td>
</tr>
<tr>
<td>- Cannonball (vacuole)</td>
</tr>
<tr>
<td><strong>Stomach cancer</strong></td>
</tr>
<tr>
<td>- Signet ring cells (large)</td>
</tr>
<tr>
<td><strong>Kidney cancer</strong></td>
</tr>
<tr>
<td>- Clear cells</td>
</tr>
<tr>
<td><strong>Thyroid cancer</strong></td>
</tr>
<tr>
<td>- Psammoma bodies</td>
</tr>
</tbody>
</table>
Breast cancer
- Cannonballs:
  - Tight packed large balls of cells
  - Smooth borders
- Indian files

Lung cancer
Ovarian carcinoma
• Irregular clusters of cells
• Large and clear vacuoles

Gastric carcinoma
• Signet ring cell pattern
Clear cell carcinoma of kidney cancer

• Clear or granular and vacuolated cytoplasm

Papillary carcinoma of the thyroid

• Psammoma bodies
Squamous cell carcinoma
• Keratinized or non-keratinized
• Tadpoles and bizarre shape

Small cell carcinoma
• Isolated and molded cells
• Scant cytoplasm, inconspicuous nucleoli
Non-Hodgkin lymphoma

Large cell lymphoma
• Nuclei large than histiocyte
• Eccentric nuclei
• Abundant blue cytoplasm
• Best appreciated in Diff-Quik

Follicular lymphoma
• Irregular nuclear contours
• Scant cytoplasm
Lymphoblastic lymphoma

• Small to medium sized lymphocytes
• Fine powdery chromatin
• Scant cytoplasm

Small lymphocytic lymphoma

• Differential diagnosis:
  chronic inflammation (tuberculosis)
**Hodgkin lymphoma**
- Reed-Sternbery cells:
  - Multinucleated cell with huge inclusion-like nucleoli

**Multiple myeloma**
- Single, lack cohesive aggregate
- Numerous malignant plasma cells
- Immunocytochemistry stain:
  - kappa and lambda light chain (+)
  - CD138 (+)
**Melanoma**
- Isolated round cells with prominent nucleoli
- Fine brown cytoplasmic pigmentation
- Intranuclear pseudoinclusions
- Immunocytochemistry stain: S-100(+), HMB-45(+)

**Sarcomas**
- Isolated cells

- **Pleomorphic sarcoma**
  - Osteosarcoma
  - Liposarcoma
  - Large and bizarre shaped

- **Round cell sarcoma**
  - Rhabdomyosarcoma
  - Neuroblastoma
  - Small and uniform shaped

- **Spindle cell sarcoma**
  - Fibrosarcoma
  - Leiomyosarcoma
  - Spindle shaped
### Differences Between Adenocarcinoma and Mesothelioma

<table>
<thead>
<tr>
<th>Cytologic Differences Between Adenocarcinoma and Mesothelioma</th>
<th>Adenocarcinoma</th>
<th>Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groupings</strong></td>
<td>Community borders</td>
<td>Irregular knobby outline</td>
</tr>
<tr>
<td></td>
<td>Windows unusual</td>
<td>Windows common</td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>Columnar shape</td>
<td>Blebs, skirts</td>
</tr>
<tr>
<td><strong>Nucleus</strong></td>
<td>Usually eccentric</td>
<td>Usually central</td>
</tr>
<tr>
<td></td>
<td>Pleomorphic and bizarre</td>
<td>Less pleomorphic and not</td>
</tr>
<tr>
<td><strong>Cytoplasm</strong></td>
<td>Delicate, homogeneous</td>
<td>Dense with lacy edges</td>
</tr>
<tr>
<td></td>
<td>Uniform stain</td>
<td>Two-tone staining</td>
</tr>
<tr>
<td><strong>Vacuoles</strong></td>
<td>Secretory</td>
<td>Degenerative</td>
</tr>
<tr>
<td><strong>Multinucleated Giant cells</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lymphoma  Mesothelial and lymphs
Lung Ca

Reactive Meso
Squamous cell Ca  Mesos
Hodgkin Lymphoma (CHL)
Lung AdenoCa
Reactive Meso

Ovarian Ca
PE with DLBCL
PE with DLBCL
Primary effusion lymphoma
Burkitt Lymphoma
Mantle cell lymphoma
CSF – Patient with leukocytosis and Dx; AML
CSF – Mantle Cell Lymphoma
EXAMPLES
Lymphoid leukocytosis.
80-year-old man was hospitalized with symptoms of progressive cough, fever, and dyspnea over a period of 5 days.
clues of SL neoplastic cells in the PB. May-Grunwald-Giemsa magnification ×630.

**HCL:** lymphocytes with oval eccentric nuclei and reticular chromatin showing abundant pale cytoplasm with fine, evenly distributed projections.

**SMZL:** medium sized lymphocytes with round nuclei, dispersed chromatin and abundant pale cytoplasm showing thick polar vell.

**MCL:** medium sized lymphocytes with indented nuclei, condensed chromatin and indistinct nucleoli (left); larger blastoid cells with reticular chromatin and one or two nucleoli (right).

**LPL:** large plasmacytoid lymphocytes with round nuclei, finely dispersed chromatin and rich basophilic cytoplasm (left); small round lymphocytes with denser chromatin and scanty cytoplasm (right).

**B-PLL:** medium to large cells with moderately condensed nuclear chromatin and prominent vesicular nucleoli, regular nuclear outline and weakly basophilic cytoplasm.

**FL:** small atypical lymphocytes with condensed chromatin, markedly irregular nuclear contours and deep nuclear grooves ("buttock cells").

**T-LGL:** medium sized cells with round nuclei and condensed or "ropey" chromatin, and ample cytoplasm with variable numbers of azurophilic granules.

**HSTL:** medium sized-to-large atypical lymphocytes with irregular nuclear contour, prominent nucleoli, and abundant cytoplasm that may contain scattered granules (right).
Algorithm for evaluation of chronic anemia based on the CBC (continued).

Low Hct/Hgb: Are reticulocytes increased?

- Yes
  - Hemolysis?
    - ↑ Bilirubin, LDH
    - ↓ Haptoglobin
    - Blood smear
      - Fragmented RBCs?
        - Yes: Microangiopathy; Pos. DAT?
          - Yes: AIHA; Cold Aggl.
          - No: Membrane Defect (HS;PNH)
            Enzymopathy (G6PD,PK)
            Hemoglobinopathy
        - No: Blood donor
  - No: Previous normal Hct/Hgb?
    - Yes
      - Hemoglobinopathy
        Thalassemia
        Congenital Anemia
        Fanconi; DBA
    - No
      - Macrocytosis?
        - Yes
          - ↓ Cobalamin, Folate?
            Rx - AZT, MTX, TMS?
            - Yes: Myelodysplasia
              Hypothyroidism
              Congenital Anemia
              Fanconi; DBA
            - No: Fe Deficiency?
              Hypothyroidism
              Inflammation
              PRCA
        - No: Microcytosis?
          - Yes
            - Blood Loss
              GI; GU
              Blood donor
          - No: Renal Failure
            Hypothyroidism
            Inflammation
            PRCA
          - Hemoglobinopathy
            Thalassemia
            Congenital Anemia
            Fanconi; DBA

- No: Blood Loss
  - GI; GU
  - Blood donor
  - Inflammation
    - Thalassemia
    - Sideroblastic Anemia
Algorithm for evaluation of chronic anemia based on the CBC. Bottom right: “Low Hct/Hgb: Are reticulocytes increased?” is the same as top box in Figure 3.
CSF
THANK YOU

? QUESTIONS