Diagnosis Of Serous Cavity Effusions - Beware The Mesothelial Cell!

“Effusion = Confusion”

Diagnostic Accuracy of Serous Effusion Cytology

- Sensitivity: 50% (62.4%) Average 58%
- Specificity: 97% (98%)
- PPV: 95.7% (100%)
- NPV: 86.4% (88.3%)

Problem: “GOLD STANDARD”?

* Motherby et al, Diagn Cytopathol 1999

Serous Effusion Cytopathology

“Diagnostic Issues”

- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinoma
- Non-epithelial, Non-mesothelial Malignances Mimicking Adenocarcinoma
- Sarcomatous Effusions
- Effusions In Children
- Determination of the primary site of a metastatic carcinoma
- Abdomino-Pelvic Washings
- Lymphocytic Effusions (Benign/reactive, lymphoproliferative disorders)

Malignant Mesothelioma

“A Potential Litigation Diagnosis”

@ Google.com – “Mesothelioma + Attorney”
- 33,200 Sites

www.mesotheliomaattorneyforyou.com
Long microvilli of mesothelioma are conspicuous in pleural effusions processed by UFP

- Centrally-placed nuclei
- “Two Tone” Cytoplasm (denser)
- Bi/multinucleation
- Macronucleoli
- Fine Cytoplasmic Vacuoles
- Cytoplasmic Processes

Courtesy, Dr. Grace Yang, Cornell, NYC
A 22 yr-old pregnant woman with H/O pelvic thrombophlebitis. She presented with fever, chest pain and a right-sided pleural effusion.

p53 Immunostaining in Mesothelial Hyperplasia Vs. Cancer
- mo AB Do - 7
- Positivity in Malignancy - 32% To 55%
- None Of The Benign Effusions Stained
- Highly Specific (100%)
- Moderately Sensitive

Serous Effusion Cytopathology
"Diagnostic Issues"
- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinoma
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
- Sarcomatous Effusions
- Effusions In Children
- Determination of the primary site of a metastatic carcinoma
- Abdomino-Pelvic Washings
- Lymphocytic Effusions (Benign/reactive, lymphoproliferative disorders)
- Cytochemical Staining
- IPOX Studies

- Mucicarmine
- PAS, D-PAS
- Alcian Blue, Alcian Blue With Hyaluronidase, (Colloidal Iron)
- Oil Red O

- Mesothelioma – Acidic (mesenchymal) mucin, hyaluronic acid
- Adenocarcinoma – Neutral (epithelial) mucin

Mesothelioma Vs. Adenocarcinoma

- Cytoskeletal Proteins
- Cell Surface Glycoproteins
- Oncoplastic Antigens
- Myelomonocytic Antigens
- Intracellular Calcium-binding Proteins
- Cadherins
- Other Antigens

Cytoskeletal Proteins (Intermediate Filaments)

- Cytokeratins
- Vimentin

- CK (AE1/AE3, CAM 5.2)
  * Almost All Mesotheliomas And Adenocarcinomas Are Positive
  * Vimentin
  * Mesothelioma (Epithelial) - Scant Or Undetectable Reaction,
    * Adenocarcinoma - Seldom (Lung) To 50% Positivity
  * Very Confusing Profile - Limited Value
### Cell Surface Glycoproteins

- **Epithelial Membrane Antigen (EMA)**
- **B72.3**
- **Ber-EP4**
- **Others (HEA-125, MOC-31, 44-3A6, And BG Antigens)**

- Polymorphic Epithelial Mucin
- Mesothelioma - 5% To 42%
- Adenocarcinoma - 50% To 100%
- Membranous/Spiky Staining Pattern In Mesothelioma, Focal Staining In Benign Mesoethelium
- Limited Practical Value

### Oncoplastical Antigens

- **Carcinoembryonic Antigen (CEA)**
- **Placental Antigens (PLAP)**

- Oldest, And Most Widely Used Antibody
- Mesothelioma - 15% To 45% - pCEA, ~3% -mCEA
- Adenocarcinoma - 85% To 95% (Lung)
- Papillary Serous Carcinoma - 16%

### Myelomonocytic Antigens

- **Leu-M1 (CD15)**
- **LN2 (CD74)**

- Monoclonal Ab, Recognizes Glycolipid Sugar Sequence
- Hodgkin Lymphoma Marker
- Mesothelioma - 0% To 32%
- Adenocarcinoma - 42% To 94%
- Highly Useful And Specific Marker (Although Comparatively Less Sensitive)
IC Ca++ Binding Proteins

- S-100 Protein
- Calretinin
  - 29 Kda Ca++ Binding Protein
  - Expressed By Neurons, Gonads, Adipose Tissue, Kidney, Sweet Glands, Thymus And Mesothelium
  - Mesothelioma - 42% To 100% (~80%)
  - Adenocarcinoma - 8% To 30% (Focal)
  - Most Useful Positive Marker For Mesothelium

Combined E-Cadherin And Calretinin Immunostaining

<table>
<thead>
<tr>
<th></th>
<th>E-cad (Rct Meso (16))</th>
<th>Calret (MM (9))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0/16(0%)</td>
<td>16/16(100%)</td>
</tr>
<tr>
<td></td>
<td>9/9(100%)</td>
<td>8/8(100%)</td>
</tr>
<tr>
<td></td>
<td>45/52(86.5%)</td>
<td>0/81(0%)</td>
</tr>
</tbody>
</table>

Other Antibodies For Mesothelioma

- CK7 +, CK 20 – (Breast, Lung, Ovary)
- CK 5/6 (Epithelial Mesothelioma)
- WT-1
- Thrombomodulin
- Mesothelin
- AMAD-2
- D2-40

Serous Effusion Cytopathology

"Diagnostic Issues"

- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinoma
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
- Sarcomatous Effusions
- Effusions In Children
- Determination of the primary site of a metastatic carcinoma
- Abdomino-Pelvic Washings
- Lymphoctic Effusions (Benign/reactive, lymphoproliferative disorders)
Serous Effusion Cytology

“Diagnostic Issues”

- Reactive Mesothelial Hyperplasia vs. Malignant Mesothelioma
- Malignant Mesothelioma vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinoma
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
- Sarcomatous Effusions
- Effusions in Children
- Determination of the primary site of a metastatic tumor (unknown cancer or multiple primaries)
- Abdominal-Pelvic Washings
- Lymphoctic Effusions (Benign/reactive, lymphoproliferative disorders)
Serous Effusion Cytopathology

“Diagnostic Issues”

- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenoarcoerina
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma

Sarcomatous Effusions

- Effusions In Children
- Determination of the primary site of a metastatic carcinoma
- Abdomino-Pelvic Washings
- Lymphocytic Effusions (Benign/reactive, lymphoproliferative disorders)

Sarcomatous Effusions

- NEVER Present As Occult Metastases
- Objective Of The Cytologic Examination Is To
  - Document The Presence Or Absence Of Cancer
  - Confirm The Morphologic Resemblance With The Known Primary Sarcoma
- IMPERATIVE To Review/Compare With The Original Resection Specimen
- Perform Ancillary Studies

- Large Pleomorphic Cells
  - MFH, Liposarcoma, Undifferentiated Embryonal Sarcoma, MMMT
- Epithelioid/Round Cells
  - Osteosarcoma, Chondrosarcoma, Clear Cell Sarcoma
- Small Round Blue Cells
  - Ewing Sarcoma, PNET, Endometrial Stromal Sarcoma, Embryonal Rhabdomyosarcoma
- Spindle/Fusiform Cells
  - Leiomyosarcoma, PNST
No, it's not a melanoma

Desmin

EMA

Serous Effusion Cytopathology

"Diagnostic Issues"

- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinoma
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
- Sarcomatous Effusions

Effusions In Children

- Determination of the primary site of a metastatic carcinoma
- Abdomino-Pelvic Washings
- Lymphocytic Effusions (Benign/reactive, lymphoproliferative disorders)
Small Round Blue Cell Tumors
- Ewing Sarcoma, PNET, Neuroblastoma, Embryonal Rhabdomyosarcoma
- Hematologic Neoplasm
- Lymphomas And Leukemias
- Other Tumors
- Rhabdoid Tumor

Serous Effusion Cytopathology

"Diagnostic Issues"

- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinoma
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
- Sarcomatous Effusions
- Effusions In Children

Determination of the primary site of a metastatic carcinoma

- Abdomino-Pelvic Washings
- Lymphocytic Effusions (Benign/reactive, lymphoproliferative disorders)
Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
Unusual Phenotypes of Metastatic Adenocarcinomas
Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
Sarcomatous Effusions
Effusions In Children
Determination of the primary site of a metastatic carcinoma

Serous Effusion Cytopathology

**Diagnostic Issues**

- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinomas
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
- Sarcomatous Effusions
- Effusions In Children
- Determination of the primary site of a metastatic carcinoma

**Abdomino-Pelvic Washings**

- Lymphocytic Effusions (Benign/reactive, lymphoproliferative disorders)

---

123 Out of 3335 Effusions* (3.7%)
- 112 Abdominal (91%)
- 10 Pleural (8%)
- 1 Pericardial (0.8%)

Malignant Abdominal Effusions With PB
- Carcinoma Of The Ovary Or The Endometrium And MMMT
- 37% Of Abdominal Effusions With PB Are Benign
- Endosalpingiosis, Endometriosis, Papillary Mesothelial Hyperplasia, Cystadenoma/Adenofibroma
Serous Effusion Cytopathology

“Diagnostic Issues”

- Reactive Mesothelial Hyperplasia Vs. Malignant Mesothelioma
- Malignant Mesothelioma Vs. Metastatic Adenocarcinoma
- Unusual Phenotypes of Metastatic Adenocarcinoma
- Non-epithelial, Non-mesothelial Malignancies Mimicking Adenocarcinoma
- Sarcomatous Effusions
- Effusions in Children
- Determination of the primary site of a metastatic carcinoma
- Abdomino-Pelvic Washings
- Lymphocytic Effusions (Benign/reactive, lymphoproliferative disorders)

Flow Cytometry in Serous Cavity Effusions

- 3 OR 4 Color Analysis
- CD45, CD71, CD33, CD22, CD19, CD20, Kappa, Lambda, CD5, CD3, CD10, CD56
- 17% (16/96) - Significant Modification Of The Pre-Flow Diagnosis*
- Cannot Diagnose Hodgkin Lymphoma

[* Czader and Ali, Diagn Cytopathol 2003]