FNA Cytology of Metastatic Malignancies of Unknown Primary Site

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Pathologic Diagnosis of Metastasis

- Smaller specimens, less invasive techniques
- FNA cytology is highly accurate
- Determine primary site
  - No previous history of malignancy
  - Prior pathology not available
  - Unpredictable pattern of metastasis
- Accurate Dx \( \rightarrow \) modify patient management
Metastatic Malignancies of Unknown Primary Site (MUP)

- 8th most common malignancy
- 5-10% of all non-cutaneous malignancies
- Up to 15% of new referrals to hospital based oncology centers
- Standard panel of multi-agent chemotherapy
- Poor prognosis. Median survival \(\approx 4-12\) mo.
Definition: Bx confirmed. 1º site not found after rigorous, but limited initial clinical and radiographic evaluation
– careful Hx, physical exam, lab, x-rays, etc.
Is Workup of MUP Necessary?

- Optimal management may be organ-specific, and rely on accurate determination of primary site
- Inability to ID a primary → major clinical challenge
  - Patient anxiety:
    - ? Inadequate evaluation by physician
    - ? Prognosis improved if primary is found
Cost Effectiveness of Pathologic Workup

- Extensive radiological exams & serum tumor markers – often unsuccessful in finding 1° site
- Pathologic evaluation (including extended IHC panel) is more cost effective than clinical workup

<table>
<thead>
<tr>
<th></th>
<th>Cost per patient</th>
<th>Success rate</th>
<th>Theoretical cost-effectiveness ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical tests alone</td>
<td>$ 18,000 *</td>
<td>20 %</td>
<td>$ 250,000</td>
</tr>
<tr>
<td>IHC panel**</td>
<td>$ 2,000</td>
<td>70 %</td>
<td>$ 2,900</td>
</tr>
</tbody>
</table>

* excluding physician charges

** panel of 6 tests

Wick et al 1999
Cost Effectiveness of Pathologic Workup

- Overutilization occurs in individual cases or by individual pathologists
  - Too many Ab’s in 30% of cases
  - Unnecessary IHC in 10% of cases
FNA Diagnosis of MUP

A Clinico-pathologic approach

1. Cytomorphologic features
2. Ancillary studies: IHC
3. Clinical patterns of metastases
FNA Diagnosis of MUP

A Clinico-pathologic approach

1. Cytomorphologic features
   • *Histologic types* (specific cell lineage): adenoca, squamous ca, melanoma, etc.
   • *Morphologic patterns* (non specific cell lineage): small cell, large cell, oncocytic, spindle, etc.

2. Ancillary studies: IHC

3. Clinical patterns of metastases
CYTOMORPHOLOGIC PATTERNS OF MUP

Specific Cell Lineage
- Squamous CA
- Sarcoma
- Melanoma

Cell Pattern / Type
- Adenocarcinoma
- Lymphoma
- Small Cell
- Oncocytic/Granular
- Clear Cell
- Pleomorphic/Giant Cell
- Spindle cell
- Polygonal, Large Cell
Case 1

- CT guided FNA biopsy of a kidney mass in a 68 year old woman.
Diagnosis: Metastatic adenocarcinoma. A lung primary was subsequently found.
Adenocarcinoma

- Most common MUP (60%)
- W-M differentiated adenocarcinoma → median survival ≈ 3-6 months
- Lung & pancreas: most common (40%)
  - GI tract
  - Liver
- Nonspecific diagnosis → 1º vs. MET
Morphologic Patterns of Differentiated Adenocarcinoma (W-M)

Adenocarcinoma

Columnar/ductal
  - Low grade
    - Pancreas
    - Bile duct
    - Colon
    - Lung (BAC)
    - Breast
    - Carcinoid
  - High grade
    - Hyperchromatic
      - COLON
      - Endometrioid
      - CA
    - Hypochromatic
      - Lung
      - Pancreas
      - Prostate
      - Bile duct
      - Stomach

Microacinar

Mucinous
  - Breast
  - Ovary
  - Pancreas
  - GIT
  - Chordoma

Papillary
  - Thyroid
  - Ovary
  - Kidney
  - Endometrium
  - Breast
  - Lung
Adenocarcinoma

Columnar/ductal

Low grade

High grade

Hyperchromatic

Hypochromatic
Adenocarcinoma: Low Grade Columnar/ductal

- Cohesive clusters and geographic flat sheets
Low Grade Columnar/Ductal

- Uniform cell population with bland appearance
- Low N/C ratio, finely granular chromatin, small nucleoli
- Round to elongated nuclei, luminal borders
Low Grade Columnar/Ductal Adenocarcinoma

- Pancreas
- Breast
- Bile duct
- Lung (BAC)
- Colon
- Carcinoid
High Grade Columnar/Ductal Adenocarcinoma

• Cohesive clusters and flat sheets
High Grade Columnar/Ductal Adenocarcinoma

- Nuclear overlapping, haphazard arrangement, significant pleomorphism.
- Acinar formation may be seen.
Adenocarcinoma

Columnar/ductal

Low grade

Hyperchromatic

High grade

Hypochromatic
High Grade Columnar/Ductal Adenocarcinoma

- Hypochromatic
  - Lung
  - Pancreas
  - Bile duct
  - Prostate
  - Stomach
High Grade Columnar/Ductal Adenocarcinoma

- Hyperchromatic
  - COLON
  - Endometrioid CA (endometrium, ovary, cervix)
  - Bile duct
• High grade, columnar/ductal
Metastatic lung CA to bone
Metastatic pancreatic CA to liver
• High grade, columnar/ductal

Metastatic colon CA to liver
CYTOMORPHOLOGIC PATTERNS OF METASTASIS OF UNKNOWN PRIMARY ORIGIN

Specific Cell Lineage

- Squamous CA
- Sarcoma
- Melanoma

Adenocarcinoma

Lymphoma

Cell Pattern / Type

- Small Cell
- Oncocytic/Granular
- Clear Cell
- Pleomorphic/Giant Cell
- Spindle cell
- Polygonal, Large Cell
CARCINOMA

- Adenocarcinoma (60%)
- Squamous cell carcinoma (10%)
- Undifferentiated CA/P.D.
- Small cell/NE carcinoma
- Melanoma

Modified from DeMay p493-530
Squamous Cell Carcinoma
MELANOMA

- Metastasis to unusual sites
- Mimics other malignancies
- Primary occult or not apparent by history
Malignant Melanoma Variants

- Rhabdoid
- Signet-ring
- Spindle
- Myxoid
- Desmoplastic
- Ballon Cell
- Small Cell
Pigmented dendritic histiocytes
SARCOMA

• Very unusual unknown primary
• Primary site usually obvious
• Diff Dx: Sarcomatoid carcinoma / melanoma
• Spindle, epithelioid, pleomorphic, small cell, myxoid
An 81 year old woman was identified as having a right hilar lung mass. FNA biopsy was performed.
Case 2

DIAGNOSIS

Metastatic Hurthle cell carcinoma of the thyroid
Case 3

A CT guided FNA biopsy of a single mass involving the anterior right lobe of liver was performed in a 72 year old female
Case 3

DIAGNOSIS

Metastatic small cell variant of malignant melanoma to the liver
Case 4

53 year old male presented with a 6 cm sacral mass and pain in his legs. A FNA biopsy was performed.
Case 4

DIAGNOSIS

Metastatic conventional clear cell carcinoma of the kidney
CYTOMORPHOLOGIC PATTERNS OF METASTASIS OF UNKNOWN PRIMARY ORIGIN

- Cell Pattern / Type
  - Small Cell
  - Oncocytic/Granular
  - Clear Cell
  - Pleomorphic/Giant Cell
  - Spindle cell
  - Polygonal, Large Cell
Small Cell Tumors

• Neuroendocrine tumors
  Carcinoids / Islet cell tumors, ect.
  Small cell (neuroendocrine) carcinoma

• Poorly differentiated carcinomas
  Squamous Cell Carcinoma
  Adenocarcinoma

• Lymphomas

• Small blue cell tumors of childhood

• Some sarcomas (synovial)

• Melanoma variant
Lymphoma
CK7/20 -; P63, CK5/6 and K903 +

Basaloid Squamous Cell
Pleomorphic / Giant Cells

- Carcinomas
  - Lung, Pancreas, Liver, Thyroid, etc.
- Sarcomas
  - i.e., Malignant fibrous histiocytoma, etc.
- Germ cell tumors
  - Choriocarcinoma
- Neuroendocrine tumors
  - Pheochromocytoma
- Lymphoreticular neoplasms
  - Anaplastic large cell lymphoma (Ki-1)
- Melanoma
Pleomorphic Large Cell Lung

Pancreas - Pleomorphic Giant Cell CA
Spindle Cells

- Sarcomas
  - Fibrosarcoma
- Sarcomatoid Carcinomas
  - Renal Cell CA; Spindle Squamous CA
- Pseudosarcomas
  - Nodular fasciitis, fibromatosis, repair, etc.
- Neuroendocrine tumors
  - Paraganglioma
- Melanoma
Sarcomatoid Squamous Cell CA
Sarcomatoid Renal Cell
Granular Cell Neoplasms

• Carcinomas (Adenomas)
  Kidney, Liver, Salivary Gland, Glassy Cell (cervix)
• Oncocytic / Hurthle Neoplasms
  Kidney, Thyroid, etc.
• Apocrine - Breast, Sweat Gland
• Neuroendocrine Tumors - Carcinoid, Paraganglioma
• Soft Tissue Tumors - Granular Cell Tumor
  Others: Muscle, Alveolar Soft Parts Sarcoma
• Melanoma
• Hilar / Leydig Cell Tumor

DDX: Nonspecific degeneration

Modified from DeMay
Islet Cell Tumor
Oncocytic Neuroendocrine

Warthin’s
Clear cell Tumors

- Carcinomas
  - KIDNEY, also Ovary, Liver, Adrenal, Salivary Gland, lung GYN, Thyroid
- Oncocytic neoplasms
- Acinic / Acinar Tumors
- Neuroendocrine Tumors (i.e., paragaglioma)
- Soft Tissue Tumors (i.e., clear cell sarcoma)
- Lymphoma - very rare
- Germ Cell Tumors
- Melanoma (ballon cells)
Paraganglioma
Intranuclear Cytoplasmic Inclusions

• Thyroid
  Papillary CA, others

• Lung
  Bronchioloalveolar CA

• Liver
  Favors HCC

• Melanoma

• Many others
Microacinar Complexes

- Prostate
- Thyroid
- Carcinoid / Islet (Rosettes)
- Others - Granulosa cell tumor, other SRCT of childhood
Prostrate CA

PSA +

Prostrate CA
Hyaline Globules

- Carcinoma (Rhabdoid)
  - Wide variety, often PD malignancies
- Sarcomas
- Lymphoma
- Melanoma (Rhabdoid)
- Hepatocellular, renal, ovary
<table>
<thead>
<tr>
<th>Single Cell</th>
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<tbody>
<tr>
<td><strong>Adeno CA</strong></td>
</tr>
<tr>
<td><strong>BREAST</strong></td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Non-Hodgkin Lymphoma
Gastric CA
Adrenal Cortex
Papillary Neoplasms

- Ovary
- GI Tract, Pancreas
- Lung (Bronchioloalveolar)
- Thyroid
- Renal
- Others
Papillary TC
Plasmacytoid Cells

• Plasma Cells
• Carcinoid / Islet
• Melanoma
• Breast CA
• Pleomorphic adenoma
Multiple Myeloma
Multiple Myeloma

Breast CA
Colloid (Mucinous) Neoplasms

- Colloid Carcinomas
  - GI tract, Breast, Ovary, Pancreas
- Pseudomyxoma peritonei (appendix)
- Myxoid sarcomas
- Melanoma (Rare)
Colon - Colloid CA
Mucin Positivity excludes:

- LYMPHOMA / LEUKEMIA
- SARCOMA (except chordoma)
- MELANOMA

Modified from DeMay
Case 5

72 year old male presented with a single lung mass. FNA biopsy was performed
Case 5

DIAGNOSIS

Metastatic colon cancer to the lung
Which Cytokeratin to use?

Complex keratin (K903, 34BE12) - Basal cell and squamous cell

CK 5/6 - Squamous cell, mesothelium, urothelium

CK 7/20 - Adeno CA of unknown primary
IHC MARKERS FOR INTESTINAL CA

• CK 7/20

• Villin - Colorectal, pancreas. Occasionally in non-GI i.e. endometrial, RCC (brush border staining)

• CDX2 - Intestinal tumors, also bladder adeno, ovarian mucinous

Strong uniform CDX-2 +/with or without villin

- favors colorectal
## Organ-specific and Organ-associated Markers

<table>
<thead>
<tr>
<th>Antibodies to:</th>
<th>Identifying:</th>
<th>Also identifies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatic specific antigen (PSA)</td>
<td>Prostrate Carcinoma</td>
<td>-----</td>
</tr>
<tr>
<td>Prostatic acid phosphatase (PAP)</td>
<td>Prostrate Carcinoma</td>
<td>Neuroendocrine carcinomas</td>
</tr>
<tr>
<td>Gross cystic disease fluid protein -15</td>
<td>Breast Carcinoma</td>
<td>Salivary gland, sweat gland tumors</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>Thyroid carcinoma</td>
<td>-----</td>
</tr>
<tr>
<td>Thyroid transcription factor-1 (TTF-1)</td>
<td>Thyroid and Lung carcinomas</td>
<td>Rare other carcinomas</td>
</tr>
<tr>
<td>Uroplakin</td>
<td>Urothelial carcinomas</td>
<td>-----</td>
</tr>
<tr>
<td>Inhibin</td>
<td>Adrenal</td>
<td>Sex cord / stromal, granular cell</td>
</tr>
<tr>
<td>Hep PAR-1</td>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>LCA, B&amp;T</td>
<td>Lymphoid</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Pathol case Review 4(6), p254, 1999
Pathol case Review 4(6), p150, 2001
**IMMUNOHISTOCHEMICAL DETECTION OF TTF-1 IN LUNG TUMORS**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>72.5%</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>10%</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>25.8%</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>75.0%</td>
</tr>
<tr>
<td>Typical carcinoid</td>
<td>30.5%</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>100%</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>94.1%</td>
</tr>
<tr>
<td>Alveolar adenoma</td>
<td>100%</td>
</tr>
</tbody>
</table>

TTF-1 + / Adeno CA

TTF-1 + / Small Cell CA
NUCLEAR TRANSCRIPTION FACTOR ANTIBODIES

- MyoD1 and Myogenin - Skeletal Muscle
- TTF-1 - Lung and Thyroid
- CDX2 – Intestinal
- Microphthalmia transcription factor (MITF)
  - Melanoma
- WT1- Serous CA, Mesothelial
- Pax8/Pax2- Mullerian, Thyroid

Advantages - All or none positive; no false positive, cytoplasmic positive due to biotin, etc.; not related to differentiation
# Hormone Receptor Expressions in Carcinomas

<table>
<thead>
<tr>
<th>ER and/or PR Positive Carcinomas (Subset)</th>
<th>ER and/or PR Negative Carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast, Ovarian, Endometrial</td>
<td>Lung non-small cell (antibody dependent)</td>
</tr>
<tr>
<td>Cervical</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Skin sweat gland</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine (e.g., carcinoid)</td>
<td></td>
</tr>
</tbody>
</table>

**ER** = estrogen receptors; **PR** = progesterone receptors

Pathol Case Review 4(6), p254, 1999
IHC Panel for the Workup of METS
X known Primary

• Cytokeratins: CAM 5.2, CK7, CK20, PAN CK, AE1/3, CK 5/6
• EMA, CEA
• S-100, HMB-45, etc.
• LCA, etc.
• Specific-PSA, Thyroglobulin, TTF-1, GCDFP-15, inhibin, Hep par 1, CDX-2
• NE markers-NSE, Synatophysin, CD56, Chromogranin, MAP-2, etc.
• Germ Cell-CK, PLAP, Oct 3/4, CD30, C-kit
• Hormonal (ER/PR)
<table>
<thead>
<tr>
<th></th>
<th>AE-1/3</th>
<th>CD – 45</th>
<th>S-100</th>
<th>PLAP</th>
<th>Additional markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Differential keratins, EMA</td>
</tr>
<tr>
<td>Melanoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>HMB 45, Melan A</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>CD 20, CD 3, CD 30 etc</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>EMA, OCT-4, CD-30</td>
</tr>
</tbody>
</table>
Clinical Patterns of Metastasis
FNA Workup of MUP

A Clinico-pathologic approach

1. Cytomorphologic features
2. Ancillary studies: IHC
3. Clinical patterns of metastases
   - Common metastatic sites
   - Uncommon metastatic sites
Metastatic Malignancies

- Determination of primary site is facilitated by familiarity with cytologic features of the malignancy and selected use of ICC
- Still, a primary site may not be determined because of non-specific cytologic & IHC features, or an atypical pattern of dissemination
Patterns of Metastases

- Usual patterns of METS to common sites: lung, lymph nodes, liver
- Cancer may occasionally metastasize to unusual sites: breast, spleen, pancreas
- This unpredictable pattern of METS may pose diagnostic problems for clinicians and pathologists → misdiagnosis as a primary neoplasm
- Familiarity with variable patterns of metastasis → a more specific diagnosis
Initial Sites of Metastasis

- Parallel natural drainage pathways of primary malignancy, i.e. related to anatomic location of tumor
- Lymphatic: regional lymph nodes
  - head & neck, cervix, melanoma
- Vascular: venous pathways
  - head & neck, bone, kidney → lung
  - pancreas, stomach, colon → liver
  - prostate → axial skeleton via paravertebral veins
Common Sites of Metastasis

- Most common sites of metastasis:
  - Lymph nodes
  - Lung
  - Large bones
  - Liver

- Most common primary sites of MUP:
  - Lung
  - Pancreas
  - Colon
  - Liver
  - Stomach

Reyes 1998, FNA of 116 MUP

- Most common sites of metastasis
  - Lymph nodes
  - Liver

- Most common primary sources
  - Lung
  - Prostate
  - Kidney
  - Colon
Lymph Nodes

- Most common site for metastasis
- Diagnostic accuracy for metastatic carcinoma is 82-99%
- Knowledge of exact location of involved lymph node is of prime importance
Lymph Node Metastasis

<table>
<thead>
<tr>
<th>Lymph nodes</th>
<th>Common/Probable primary site or malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Head and neck, lung, melanoma, breast</td>
</tr>
<tr>
<td>Right supraclavicular</td>
<td>Lung, breast, lymphoma</td>
</tr>
<tr>
<td>Left supraclavicular</td>
<td>Lung, breast, cervix, prostate, lymphoma</td>
</tr>
<tr>
<td>Axillary</td>
<td>Breast, lung, arm, regional trunk, GI tract</td>
</tr>
<tr>
<td>Inguinal</td>
<td>Melanoma, trunk, leg, vulva, prostate, anorectal, bladder</td>
</tr>
</tbody>
</table>
• Metastatic basaloid squamous cell carcinoma to upper cervical lymph node
• Hypopharyngeal primary was found
METS to Cervical Lymph Nodes

- Head & neck squamous CA, melanoma: most common
- Adenocarcinoma
  - Primaries arising in supra-clavicular organs
    - Thyroid
    - Salivary glands
  - Primaries arising in infra-clavicular organs
    - Lung
    - GI tract
    - Breast
    - Ovary
    - Prostate
Supraclavicular Lymph Nodes

- Primary sites involving left SCLN (*Virchow’s Node*) are different from those involving right SCLN
- *Cervin et al 1995*, FNA of 96 SCLN
  - Pelvic (16/19) & abdominal (6/6) malignancies → LSCLN
  - Thorax, breast, head/neck → no difference in metastatic pattern to LSCLN or RSCLN
  - Most common primaries: lung/breast > pelvis/testis > abdomen
Case 7. FNA biopsy of left supraclavicular lymph node. The patient is a 65 year old man with a remote previous history of malignancy.
Diagnosis: Metastatic urothelial carcinoma. The patient had a previous history of bladder CA
• PD carcinoma may mimic lymphoma
• Diff Dx: large cell lymphoma, neuroendocrine CA, melanoma

Dx: Metastatic large cell CA, lung 1º, involving cervical lymph node
• Lymphoma may mimic carcinoma

DX: Anaplastic large cell lymphoma (Ki-1), involving RSCLN
Lung Metastases

- Breast, GIT- common
- Any malignancy → lung
- Multiple nodules, most commonly
  - **Miliary:**
    - Melanoma, kidney, ovary, thyroid medullary CA
  - **Cannon ball:**
    - Sarcoma, kidney, melanoma, colorectal CA
Multiple lung nodules (cannon ball) in 49 yr old woman.
No previous malign.

- CK7-, CK20+
- CDX2+, TTF1-

DX: Metastatic adeno CA c/w colon 1°
Lung Metastases (cont.)

• Diffuse infiltrate or solitary coin lesion (more problematic) → rule out primary lung carcinoma

• Diffuse (6-8 % of pulmonary mets):
  – Lung, breast, GI tract, pancreas

• Solitary MET (3-9 % of all solitary pulmonary nodules):
  – Melanoma, breast, colon, kidney, sarcoma, non-seminomatous GCT

• FNA sensitivity =89%, specificity =96%
• Solitary lung mass, 68y F
• Hx breast ca X 1 month, SBR I, 0/18 nodes
• IHC: CK 7+, CK 20-, TTF1-, ER+, PR+

Diagnosis: Metastatic breast ca
Lung

53 year old male presented with a solitary 3 cm lung mass. Patient also had an indistinct kidney mass.
FNA of right lower lobe lung masses may also inadvertently sample benign liver tissue
Lung

- Multiple lung nodules, 76 y M
- No previous hx of malignancy

5-10% of PD prostate CA either PSA- or PAP- (best to use both)
Unusual Sites of Metastasis

- Include breast, thyroid, pancreas, kidney, small bones, eye, spleen
- Uncommonly encountered
- May pose diagnostic difficulties and lead to confusion with primary neoplasms arising in these sites
Mechanisms of Metastasis to Unusual Sites

• Initial sites of metastasis → lymph nodes or venous (lung, liver)
• Subsequent (2°) widespread dissemination from initial metastatic site via arterial system → brain, endocrine glands, small bones, spleen
METS to Thyroid

- Unusual site of involvement in clinical practice; although autopsy series report 2-26% of patients with malignancy
- Solitary mass or multiple small nodules
- Direct extension – head & neck squamous cell CA, adenoid cystic CA
- Kidney > colon, lung, breast > melanoma
METS to Thyroid (2)

- Alien cytology
- Differential diagnosis:
  - Renal CC, clear cell type vs. thyroid CA with clear cells
  - RCC, granular type vs. Hurthle cell neoplasm
    - RCA, TTF-1, thyroglobulin
  - Plasmacytoma + amyloid vs. Medullary CA
    (EMA, kappa/lambda, Calcitonin, CEA)
- Dx of metastasis may prevent inappropriate thyroidectomy
FNA right thyroid nodule, 76 year old female.

Patient had previous Hx of malignancy X 15 yrs

• Diagnosis: Metastatic Renal cell CA
Summary
Cytopathologic Workup of MUP

• Clinico-pathologic approach
  1. Cytomorphologic patterns
     • Cell lineage: adenoca, squamous, etc.
     • Cytomorphologic classification: small cell, large cell, etc.
  2. Ancillary studies – IHC
  3. Clinical patterns of metastasis
     • Common metastatic sites
     • Uncommon metastatic sites
Gene Expression Profiling in MUP

• Confirm existing suspicions or provide new info?
  - High agreement with already available CP data
    – ? superiority to IHC + clinical info in unresolved cases: *not helpful (Personal experience w AviaraDx)*
    – Cost: $ 3,350 - 3,750

• Prospective studies are needed to assess:
  - Effect on patient outcome
  - Which profiling methodology /gene panel is best?

• IHC remains crucial component of workup. GEP may play supportive role in unresolved cases. 
  Promising future
General Principles Considered in Analysis of Suspected Metastasis

- Familiar with cytologic features of common malignancies originating in a primary site
- Unusual/alien cytology for a primary site
- Knowledge of common and unusual metastatic patterns of malignancies & possible diagnostic pitfalls
- Produce a potential short list of possible primary sites
- Cytomorphology and IHC can then help arrive at a more specific diagnosis
General Principles Considered in Analysis of Suspected Metastasis (2)

• Clinical history of previous malignancy
• Review of previous pathology material
• Tissue confirmation in unresolved cases before definitive treatment