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 → 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 ≈ 4-12 mo.
Metastases of Unknown Primary Site

Definition: Bx confirmed. 1° 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><strong>Clinical tests alone</strong></td>
<td>$ 18,000 *</td>
<td>20 %</td>
<td>$ 250,000</td>
</tr>
<tr>
<td><strong>IHC panel</strong></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): adenocarcinoma, squamous cell carcinoma, 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

Adenocarcinoma
- Lymphoma

Cell Pattern / Type
- 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
  - Prostate
  - NEC
  - Thyroid
  - Granulosa CT
- Mucinous
  - Breast
  - Ovary
  - Pancreas
  - GIT
  - Chordoma
- Papillary
  - Thyroid
  - Ovary
  - Kidney
  - Endometrium
  - Breast
  - Lung
Adenocarcinoma

Columnar/ductal

Low grade

Hyperchromatic

High grade

Hyperchromatic

Hypochromatic
Adenocarcinoma: Low Grade Columnar/ductal

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

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

- Pancreas
- Breast
- Bile duct
- Lung (BAC)
- Colon
- Carcinoid

Carcinoid

Cholangiocarcinoma
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
  - High grade
    - Hyperchromatic
    - 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
- Columnar/ductal, high grade

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

![Diagram]

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
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
Signet-Ring Melanoma

Ballon Cell

Spindle Cell

Small Cell MM
Pigmented dendritic histiocytes
SARCOMA

• Very unusual unknown primary
• Primary site usually obvious
• Diff Dx: Sarcomatoid carcinoma / melanoma
• Spindle, epitheliod, pleomorphic, small cell, myxoid
Case 2

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
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

<table>
<thead>
<tr>
<th>Cell Pattern / Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Cell</td>
</tr>
<tr>
<td>Oncocytic/Granular</td>
</tr>
<tr>
<td>Clear Cell</td>
</tr>
<tr>
<td>Pleomorphic/Giant Cell</td>
</tr>
<tr>
<td>Spindle cell</td>
</tr>
<tr>
<td>Polygonal, Large Cell</td>
</tr>
</tbody>
</table>
# Small Cell Tumors

<table>
<thead>
<tr>
<th>Neuroendocrine tumors</th>
<th>Poorly differentiated carcinomas</th>
<th>Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoids / Islet cell tumors, etc.</td>
<td>Squamous cell carcinoma (Basaloid SCC)</td>
<td>Small blue cell tumors of childhood</td>
</tr>
<tr>
<td>Small cell (neuroendocrine) carcinoma</td>
<td>Adenocarcinoma</td>
<td>Some sarcomas (synovial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melanoma variant</td>
</tr>
</tbody>
</table>
Lymphoma
Basaloid Squamous Cell

CK7/20 -; P63, CK5/6 and K903 +
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
Leiomyosarcoma

MFH
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
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
Prostate CA

PSA +
Hyaline Globules

- Carcinoma (Rhabdoid)
  Wide variety, often PD malignancies
- Sarcomas
- Lymphoma
- Melanoma (Rhabdoid)
- Hepatocellular, renal, ovary
Melanoma
Pleomorphic Giant Cell - Pancreas
Single Cell

Adeno CA
BREAST
Pancreas
Stomach
Prostate

Other Tumors
Small Cell CA
Mesothelioma
Carcinoids
Melanoma
Hematopoietic
Non-Hodgkin Lymphoma
Papillary Neoplasms

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

- Plasma Cells
- Carcinoid / Islet
- Melanoma
- Breast CA
- Pleomorphic adenoma
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
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
<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

Adenocarcinoma 72.5%
Squamous carcinoma 10%
Large cell carcinoma 25.8%
Large cell neuroendocrine carcinoma 75.0%
Typical carcinoid 30.5%
Atypical carcinoid 100%
Small cell carcinoma 94.1%
Alveolar adenoma 100%

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, Renal
- GATA-3- Breast, Urothelial

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
Breast CA / ER +
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)
## IHC WORKUP OF UNDIFFERENTIATED/POORLY DIFFERENTIATED MALIGNANCY

<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 cancers, cervix, melanoma
- **Vascular**: venous pathways
  - head & neck, bone, kidney cancers → 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 sources 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
• Nasopharynx > hypopharynx > base of tongue → cervical spinal region
• Anterior part of oral cavity and lips → submandibular
• Metastatic basaloid squamous cell carcinoma to upper cervical lymph node
• Hypopharyngeal primary was found
### 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>Rt 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>
FNA left upper cervical lymph node, 51 year old man. No previous HX of malignancy
Squamous CA arising in left Tonsil

<table>
<thead>
<tr>
<th></th>
<th>Squamous CA</th>
<th>Small Cell CA</th>
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</thead>
<tbody>
<tr>
<td>CK5/6</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>P63</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>TTF1</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Synaptophysin, CD 56</td>
<td>-</td>
<td>±</td>
</tr>
</tbody>
</table>

TTF1
CK5/6
P63
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
  – 16/19 Pelvic & 6/6 Abdominal 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 Lt supraclavicular LN. The patient is a 65 year old man with a remote history of malignancy
Diagnosis: Metastatic urothelial carcinoma. The patient had a previous history of bladder CA
Mimickers in Lymph Node Mets
• 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
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%
Multiple lung nodules in 49 yr old woman. No previous malign.

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

DX: Metastatic adeno CA c/w colon 1°
Multiple lung nodules, 76 y M, no previous hx of malignancy

- 5-10% of PD prostate CA are PSA- or PAP- (best use both)
- PSMA and P501S = can pick up some PSA-/PAP- cancers
- NKX3.1 (nuclear stain) = 99% sensitivity
FNA right solitary lung mass in a 91 year old woman. Hx of breast ca x 10 years.
Metastatic malignant melanoma. Primary site not found.
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 inadvertently sample benign liver tissue
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 those 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
Pancreas

• Metastasis may be radiographically and clinically indistinguishable from a primary neoplasm
• Lung, breast & kidney are most common
• Stomach, intestine, biliary tract → Direct extension
• *Benning 1992*: 19 metastases that mimicked primary pancreatic carcinoma
  – 11% of all malignant pancreatic FNA
  – cytology foreign to pancreas is a helpful clue
66 YO woman presented with obstructive jaundice. Subsequent therapy shrunked the tumor and improved the jaundice

- Small cell carcinoma is usually metastatic
- Metastatic adenocarcinoma is difficult to distinguish from primary pancreatic ca
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 (mimickers):
  – 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
Gene Expression Profiling

1. Theros CancerType ID®
2. ResponseDX: Tissue of Origin Test®
3. Agendia cupPrint assay
- microassay data base of 22,000 genes from primary and met tumors
- Genetic algorithm to search for combination optimal for multi-tumor classification.
- 92 gene/ RT-PCR assay
- 39 tumor types
- FFPT, CNB, FNA
- Agreement/accuracy 84%
- O/N microarray measure expression pattern >1500 met genes
- Compares expression to 15 known tumor tissue sites (>90% of mets)
- Frozen tissue/FFPT, No CNB or FNA
- Accuracy 89%, spec 99%

### ResponseDX: Tissue of Origin Test®

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Similarity Score</th>
<th>Low</th>
<th>5</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>88.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>4.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Small Cell Lung</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>2.1</td>
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Agendia CupPrint® assay

- Marketed predominately in Europe
- Profiles 495 genes in custom oligonucleotide microarray
- 43 different tumor classes
- Uses FFPE tissue, CNB, FNA; accuracy is 88%
- Excellent in breast & colon; poor in lung, pancreas, stomach

*Oien 2008, Horlings 2008*
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 CancerType ID)
    - 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!!

Oien 2008
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
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