Workup of Metastatic Cancer of Unknown Primary

Faith Ho, MBBS
University of Hong Kong
Harvard Medical School
Gillian Lieberman, MD
May, 2007
Patient M presentation

• 50 year old woman
• Good past health
• Left thigh pain for 6 months
• Pain worsens with movement, not relieved at rest
Patient M: Lateral Femur on Plain X ray
Patient M: Anterior Femur on Plain Film

Cortical irregularity

Periosteal reaction

PACS, BIDMC
Differential Diagnosis

- Healing fracture (if history of trauma)
- Osteomyelitis
- Inflammation
- Neoplasm (primary Vs metastasis)
Our Patient: Radionuclide Bone Scan

Abnormal radiotracer uptake
Our Patient: Radionuclide Bone Scan

Abnormal radiotracer uptake
Our Patient: Femur on CT scan

Cortical destruction

Periosteal new bone formation

PACS, BIDMC
Summary of Findings on Our Patient

• Plain X ray
  ✓ Poorly-defined lucency in medial distal left femur with cortical irregularity and periosteal reaction

• Bone scan
  ✓ Single focus of abnormal radiotracer localization in the left distal femoral metaphysis

• CT scan
  ✓ Focal cortical destruction and periosteal new bone in left distal femoral metaphysis
Differential Diagnosis

Aggressive bone lesion:
- Metastasis
- Osteosarcoma
- Lymphoma
Our patient:
CT Guided Femur Bone Biopsy
Histology:

Metastatic Adenocarcinoma
Further Investigation

- Mammogram
- Breast USG
- Chest CT

All Negative
Where is the primary cancer?
Cancer of unknown origin

- Cancer of unknown origin (CUP) definition: Histologically proved metastatic disease without evidence of a primary tumor
- 5 – 10% of all cancer patients
- 7\textsuperscript{th} - 8\textsuperscript{th} most common type of cancer
- 4\textsuperscript{th} cause of cancer death in both sex
Cancer of unknown origin

- Male: female = 5 : 4
- Median age at diagnosis is 65
- Only 10% at diagnosis is younger than 50
Hypothesis of CUP

1) Slow growing tumors with a genotype favoring metastatic capability over local tumor growth
2) Tumors involute during disease
3) Invasive cancers, not switching to the angiogenic phenotype, are unable to grow beyond 1-2 mm
Cancer of unknown origin

Most common metastatic site for CUP is lymph node:

1) Head and neck lymph nodes
2) Axillary lymph nodes
3) Inguinal lymph nodes
Cancer of unknown origin

Preferential site for extra-nodal metastasis:

- Lung
- Bone
- Liver

- Most patients have multiple metastases at presentation
- Metastatic dissemination pattern differs from that of tumors of known origin
Cancer of unknown origin

- Histological categories
  1) Adenocarcinoma 60%
  2) Poorly differentiated carcinoma 30%
  3) Squamous cell carcinoma 5%
  4) Poorly differentiated neoplasm 5%
Cancer of unknown origin

- Median survival ~ 6-9 months
- Survival more depends on organ of presentation than that of origin
- Subsets of patients may have much longer survival. (23 months in Raber MN. series)
- Patients with poorly differentiated carcinoma or metastatic adenocarcinoma have poor prognosis.
Cancer of unknown origin

• All oncological staging and treatment depend on the origin of primary tumor

*Important to diagnose the primary site in patients with favorable prognosis if specific treatment could be given!!!*
How often can primary site be identified?

- Common imaging investigations including: chest X ray, abdominal and pelvic CT, mammography in women, can only identify 20-27% of CUP cases.
- PET scan is able to identify the primary lesion in 24% -40% of patients with negative conventional imaging studies.

How about PET/CT scan?
Role of PET/CT scan in CUP

1. Identify the small occult primary site by increased FDG avidity with correlation to anatomical location.
2. Guide further diagnostic procedures by determination of other sites of metastatic dissemination.
Companion Patients: Transverse images in a 41-year-old woman with right axillary lymph node metastases (patient 17).

A, CT image does not depict the primary tumor. B, PET image and C, PET/CT images depict breast cancer (arrow), which was later confirmed at pathologic examination.

Transverse images in a 61-year-old man with liver metastases

A, CT image does not show any evidence of the primary tumor.  
B, PET and,  
C, PET/CT images depict the primary tumor (arrow) at the lesser curvature of the stomach. Note additional vertebral metastases.
Transverse images in a 93-year-old man with right cervical metastasis

A, CT image reveals lymphadenopathy without characterizing the primary tumor. B, PET image shows FDG uptake (arrow). Side-by-side evaluation of A and B misinterpret the FDG uptake as a lymph node metastasis. C, PET/CT reveals focally increased glucose metabolism (SUV max, 5.9) in the right submandibular gland, which was diagnosed as the primary tumor. Diagnosis was later confirmed at histologic examination.

## Sensitivity and PPV of CT or PET alone

<table>
<thead>
<tr>
<th>Statistics</th>
<th>CT scan</th>
<th>PET scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity(%)</td>
<td>19.0</td>
<td>28.2</td>
</tr>
<tr>
<td>PPV* (%)</td>
<td>72.7</td>
<td>64.7</td>
</tr>
</tbody>
</table>

*PPV: positive predictive value
# Sensitivity and PPV of PET/CT

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity(%)</td>
<td>35.7</td>
<td>35.3</td>
<td>52.6</td>
</tr>
<tr>
<td>PPV* (%)</td>
<td>83.3</td>
<td>82.8</td>
<td>95.2</td>
</tr>
</tbody>
</table>

*PPV: positive predictive value
Limitation of PET/CT scan

- **Size**
  - Lesion smaller than 8mm in diameter cannot be accurately assessed

- **Tumor type**
  - Bronchioloalveolar carcinoma, carcinoid tumor, hepatocellular carcinoma, renal cell carcinoma typically have low FDG avidity due to low metabolic activity.
Limitation of PET/CT scan

- Histologic grade
  - Low grade tumors have low FDG uptake
- Physiological uptake region
  - Renal collecting system, urinary bladder, GI tract may be obscured by background physiological uptake to assess areas of focal uptake
# Algorithm of CUP workup

<table>
<thead>
<tr>
<th>Histology</th>
<th>Suspected primary</th>
<th>Diagnostic procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Breast, Lung, Thyroid, Colon, Gynecological tract, Prostate</td>
<td>MMG, USG, MRI, Chest X ray, Chest CT, USG, thyroid scan, Colonoscopy, Abdominal/Pelvis CT PSA, USG</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PSA: prostate specific antigen
Algorithm of CUP workup

<table>
<thead>
<tr>
<th>Histology</th>
<th>Diagnostic procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>Oto-rhino-laryngeal exam, endoscopy, cervical CT</td>
</tr>
<tr>
<td>Inguinal</td>
<td>Abdominal CT, cystoscopy and anoscopy</td>
</tr>
<tr>
<td>Poor differentiated carcinoma</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>Abdominal and thoracic CT</td>
</tr>
</tbody>
</table>

PET/CT scan acts as an effective “problem solver” in CUP cases

---

Faith Ho, MBBS
Gillian Lieberman, MD
Diagnostic Persistence in workup of CUP

- In most published series, we cannot identify the primary in up to 70% cases even in autopsy.

- The critical question is

  How far to go in subjecting the patient to further diagnostic studies?
Diagnostic Persistence in workup of CUP

• We should judiciously balance between the expected survival and patient’s idea and concern and the impact of known primary on disease management before extensive workup.
Our Patient: PET/CT Scan

Coronal scan of the lower limbs

PACS, BIDMC
Our Patient: PET/CT Scan

Coronal scan of the upper trunk

PACS, BIDMC
Our Patient: PET/CT Scan

Axial scan of the axillary lymph node

PACS, BIDMC
PET/CT scan Finding in Patient M

- Intense FDG uptake in left distal femur (SUV max of 11.1), corresponding to that biopsied and determined to be adenocarcinoma
- 13 mm left axillary lymph node demonstrates abnormal FDG uptake with SUV max of 5.7
PET/CT scan Finding in Patient M

- No abnormal FDG uptake in the head, neck, chest, breast and abdomen.
- Kidneys, bladder, GI tract are difficult to assess given physiologic uptake.
- Given the axillary lymph node involvement, MRI breast imaging is pending.
References

2) Pelosi E et al. Role of whole body PET/CT scan with FDG in patients with biopsy proven tumor metastases from unknown primary site. Q J Nucl Med Mol Imaging 2006; 50:15-22
Acknowledgements

- Gillian Lieberman, MD
- Gerald Kolodny, MD
- Jeff Velez, MD
- Pamela Lepkowskki
- BIDMC Radiology staff and residents