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Workup of Metastatic Cancer of Unknown Primary

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Patient M presentation

- 50 year old woman
- Good past health
- Left thigh pain for 6 months
- Pain worsens with movement, not relieved at rest



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Patient M: Lateral Femur on Plain X ray

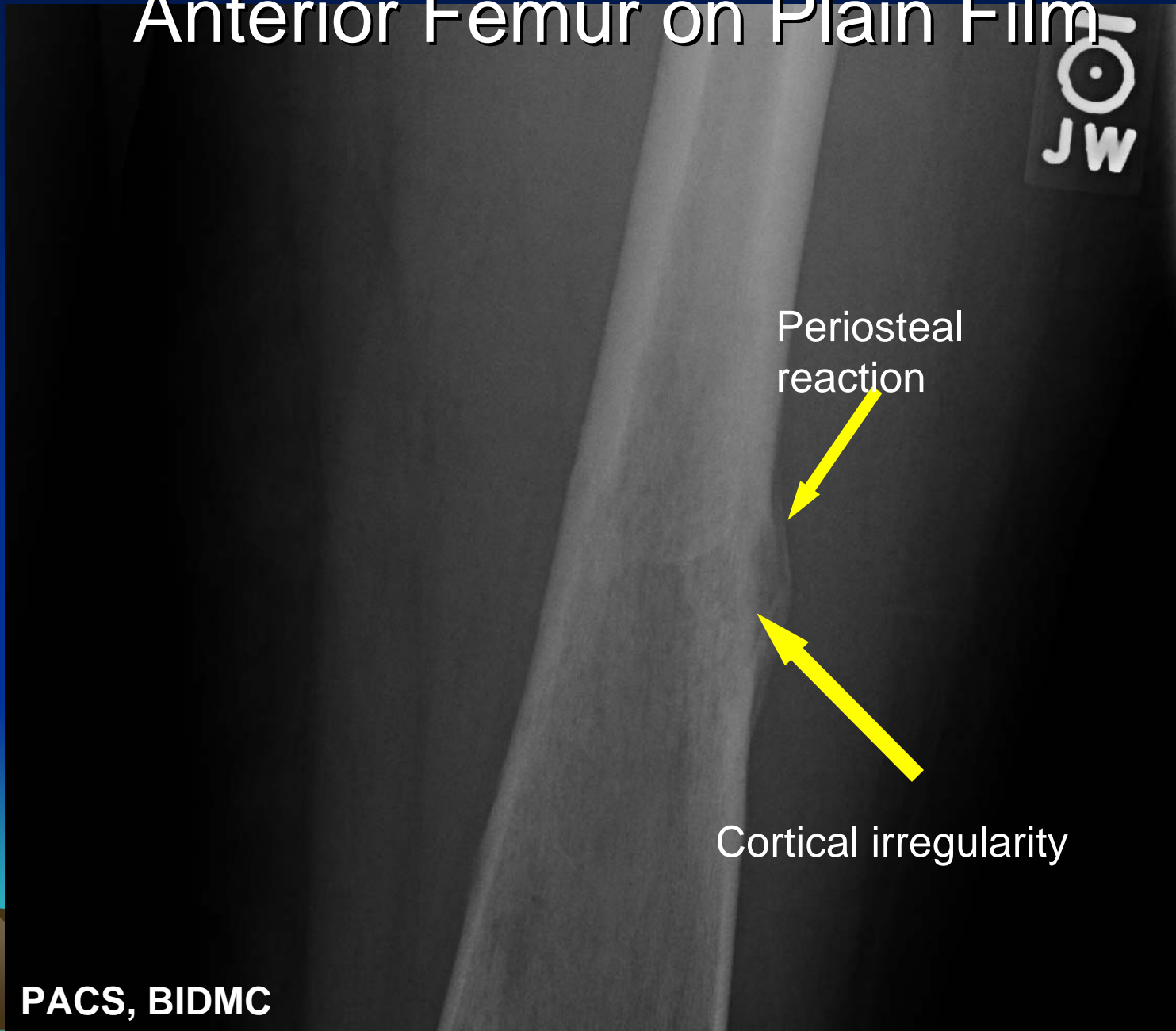
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Patient M:

Anterior Femur on Plain Film



Periosteal
reaction

Cortical irregularity

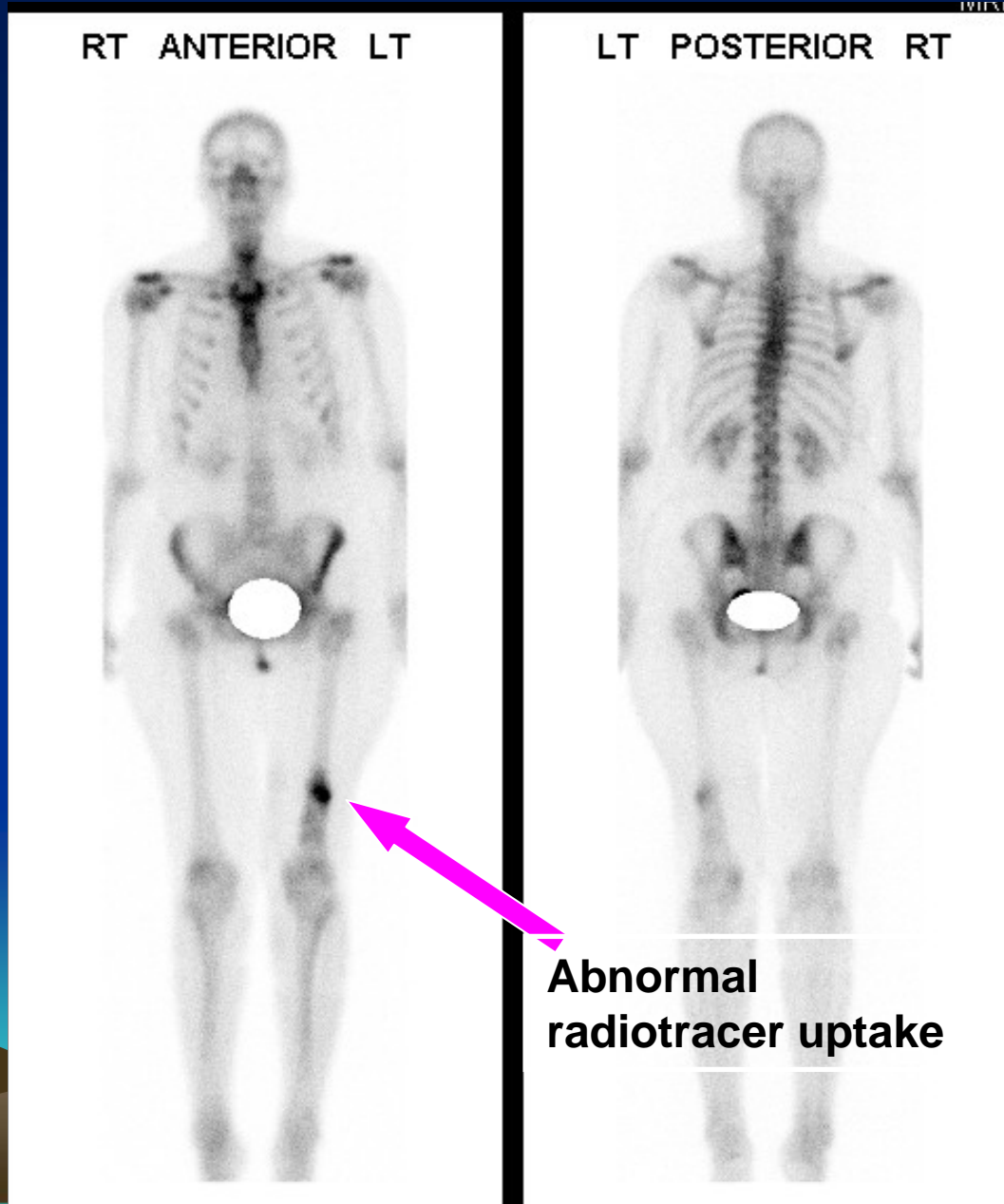


Differential Diagnosis

- Healing fracture (if history of trauma)
- Osteomyelitis
- Inflammation
- Neoplasm (primary Vs metastasis)

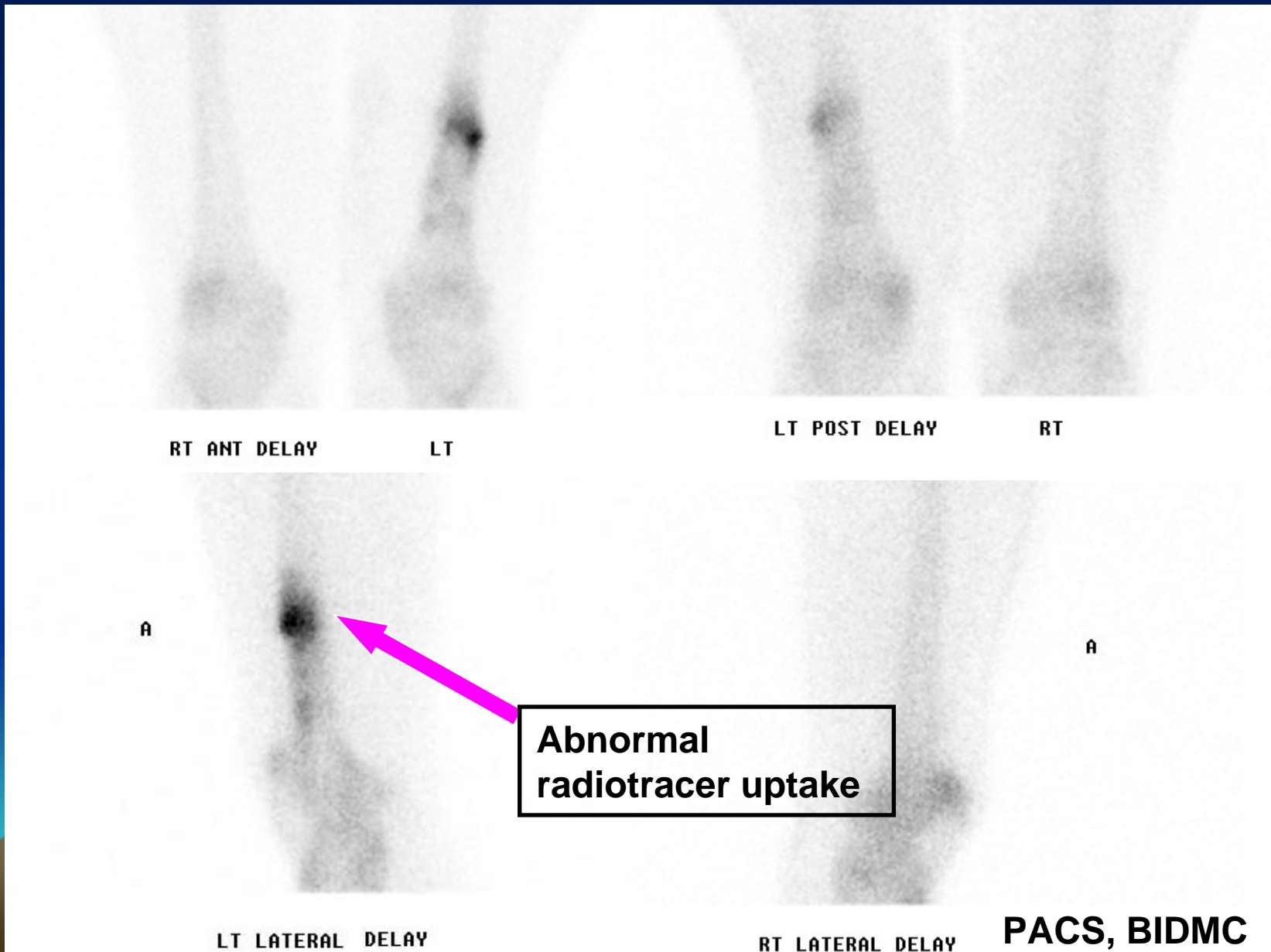


Our Patient: Radionuclide Bone Scan



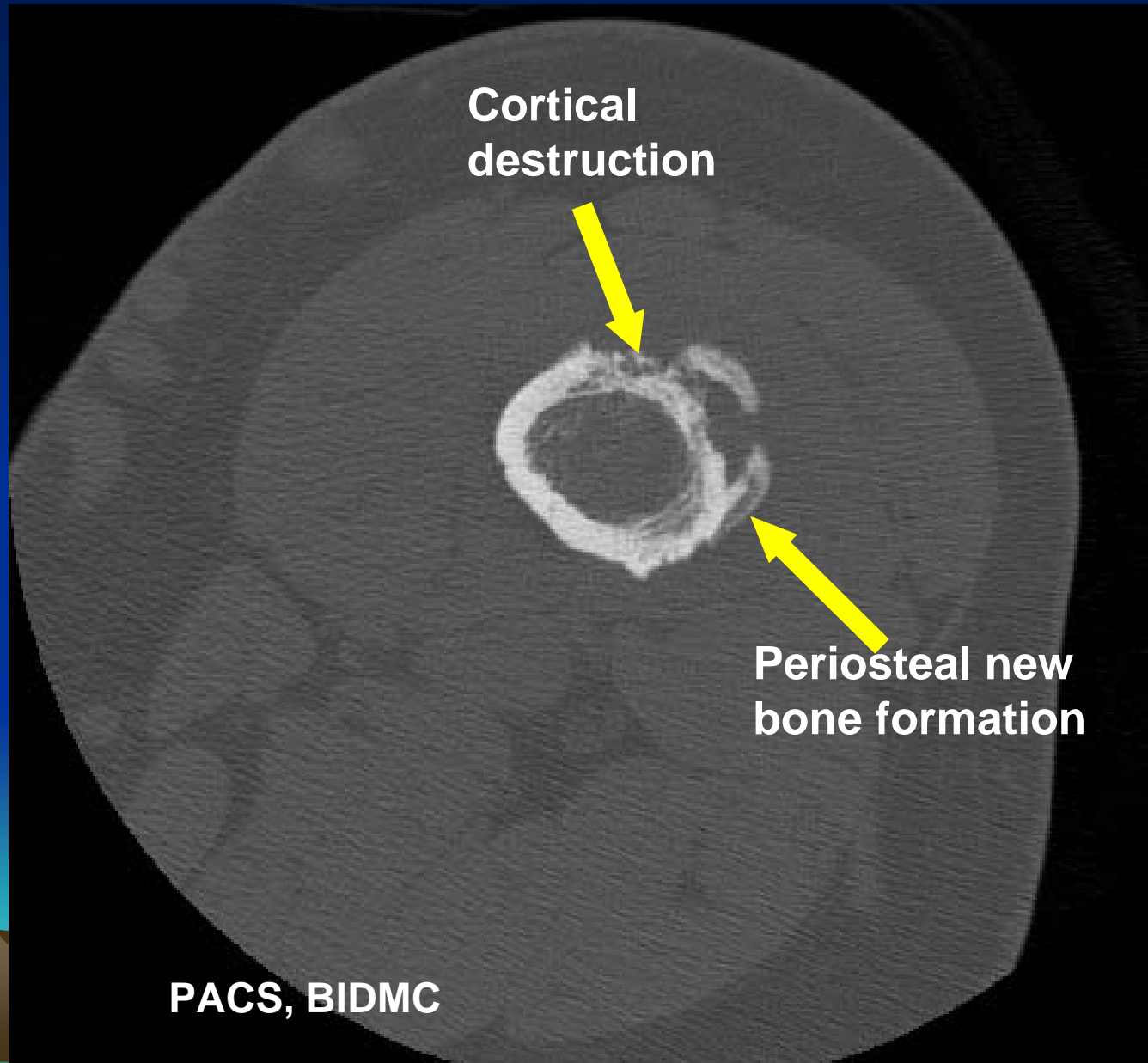


Our Patient: Radionuclide Bone Scan





Our Patient: Femur on CT scan





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



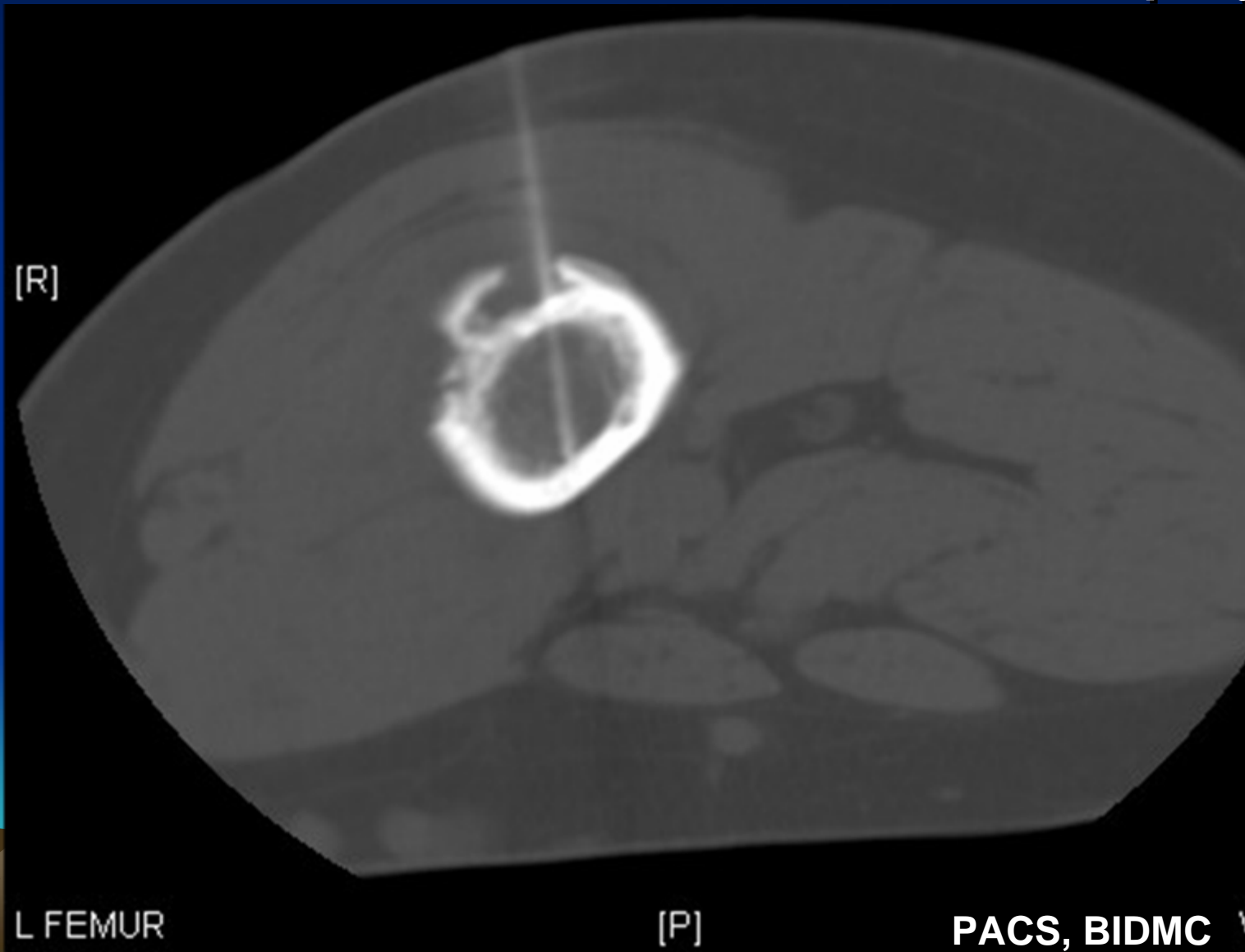
Differential Diagnosis

Aggressive bone lesion:

- Metastasis
- Osteosarcoma
- Lymphoma



Our patient : CT Guided Femur Bone Biopsy





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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
- 7th -8th most common type of cancer
- 4th 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?**

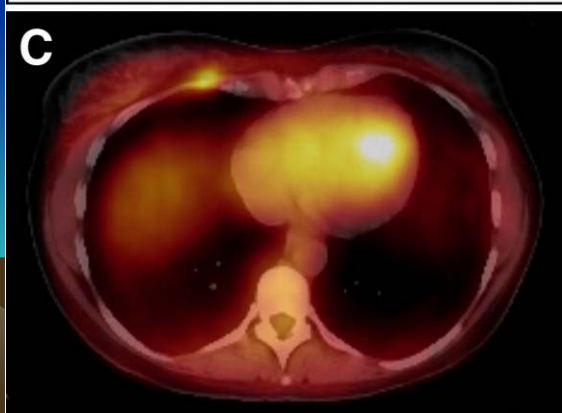
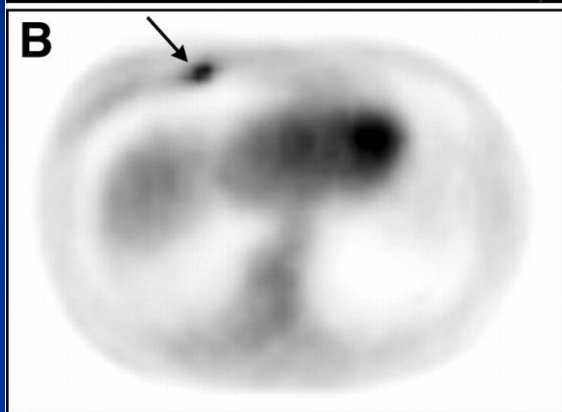


Role of PET/CT scan in CUP

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:



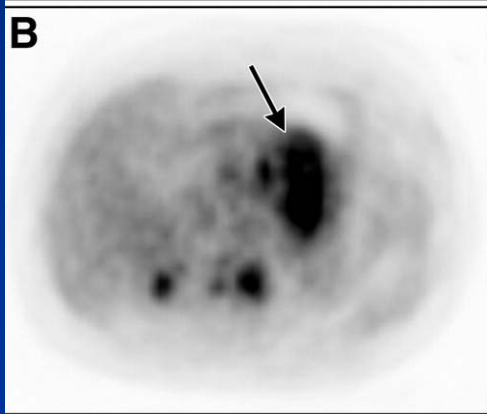
Transverse images in a 41-year-old woman with right axillary lymph node metastases (patient 17).

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.



Companion Patients:



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

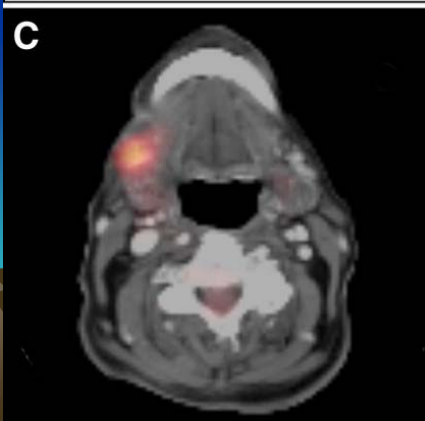
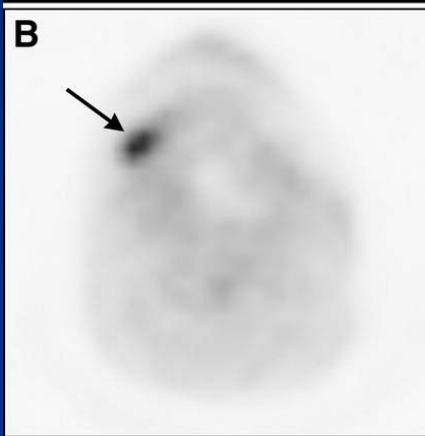
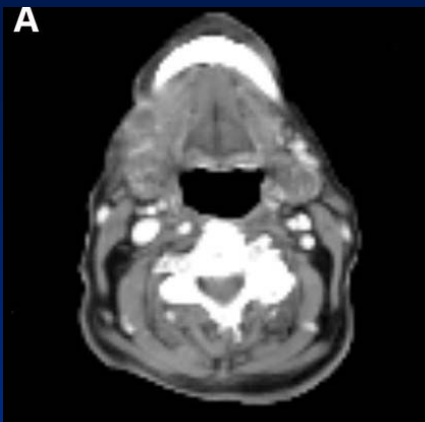
A, CT image does not show any evidence of the primary tumor.

B, PET and,

C, PET/CT images depict the primary tumor (arrow) at the lesser curvature of the stomach. Note additional vertebral metastases.



Companion Patients:



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

Statistics	CT scan	PETscan
Sensitivity(%)	19.0	28.2
PPV* (%)	72.7	64.7

*PPV: positive predictive value



Sensitivity and PPV of PET/CT

Statistics	Gutzeit A et al. N=45	Pelosi E et al. N=68	Ambrosini V et al. N=38
Sensitivity(%)	35.7	35.3	52.6
PPV* (%)	83.3	82.8	95.2

*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

Histology	Suspected primary	Diagnostic procedure
Adenocarcinoma		
Female	Breast Lung Thyroid Colon Gynecological tract	MMG, USG, MRI Chest X ray, Chest CT USG, thyroid scan Colonscopy
Male	Prostate	Abdominal/Pelvis CT PSA, USG

PSA: prostate specific antigen



Algorithm of CUP workup

Histology	Diagnostic procedure
Squamous cell carcinoma Cervical Inguinal	Oto-rhino-laryngeal exam, endoscopy, cervical CT Abdominal CT, cystoscopy and anoscopy
Poor differentiated carcinoma Age < 60 years	Abdominal and thoracic CT

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

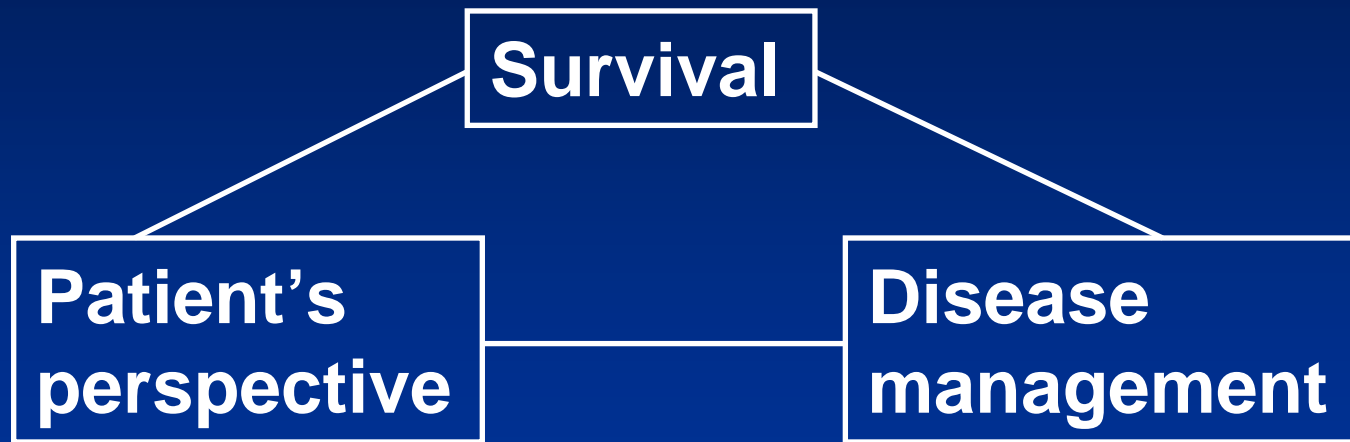


Diagnostic Persistence in workup of CUP

- 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



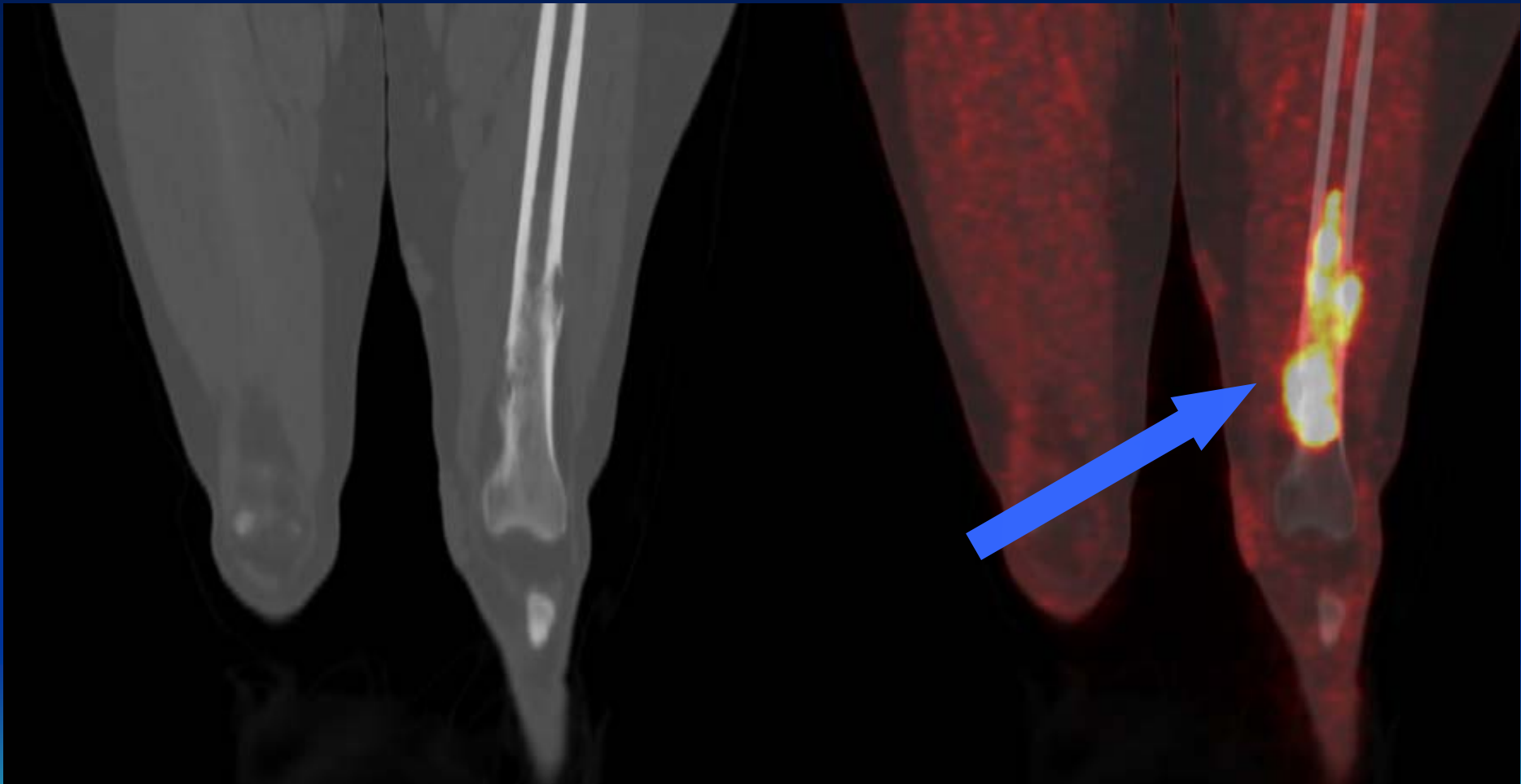
- We should judiciously balance between the expected survival and patient's idea and concern and the impact of known primary on disease management before extensive workup.



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Our Patient: PET/CT Scan

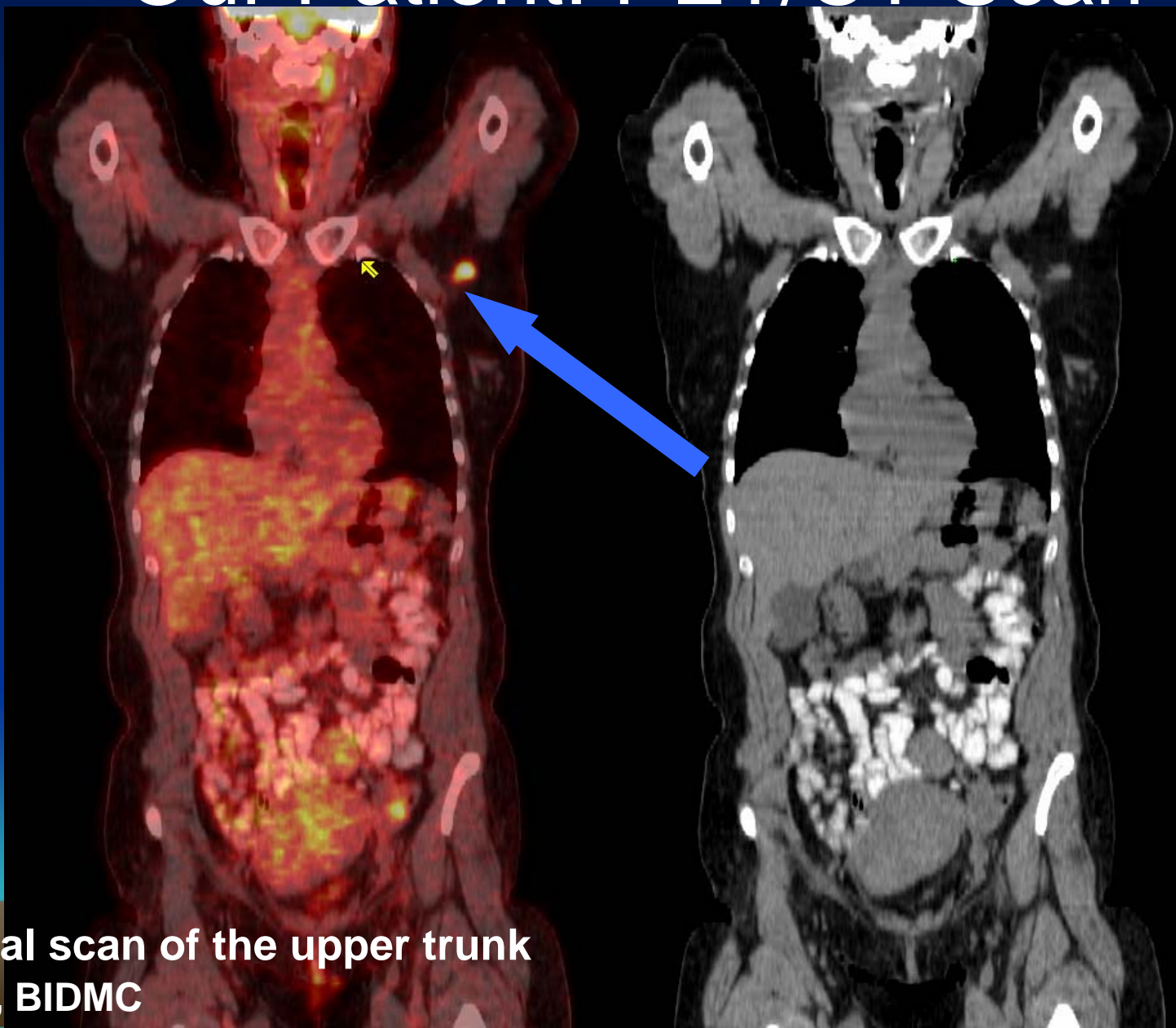


Coronal scan of the lower limbs

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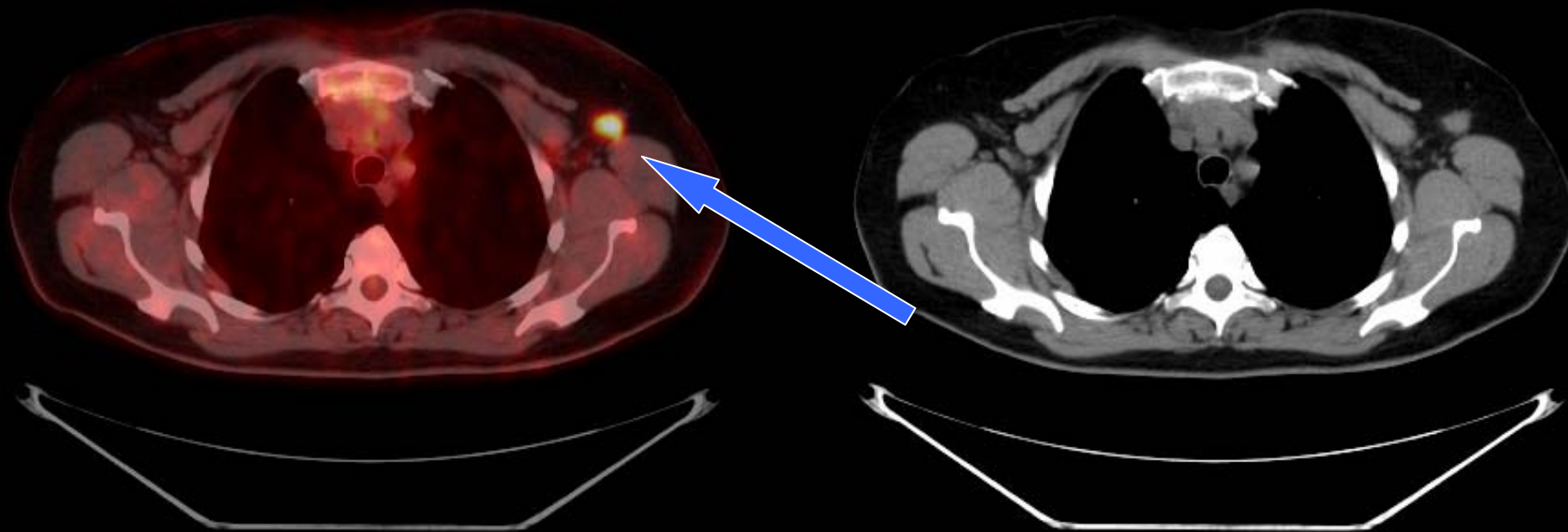
Our Patient: PET/CT Scan



Coronal scan of the upper trunk
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Our Patient: PET/CT Scan



Axial scan of the axillary lymph node

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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.



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