A Patient’s Journey through Stage IV Melanoma: Radiologic Evaluation and Surveillance

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Outline

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  – ACR Appropriateness Criteria

• Melanoma Overview
  – Characteristics
  – Staging Work-Up

• Image Modalities
  – Modality 1: CT Abdomen/Pelvis
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Our Patient: Clinical Presentation

• A 67 year old woman who noticed a painless lump in her right axilla.
• Review of systems negative.
• Medical history: hyperlipidemia and osteoporosis.
• Cancer screening is up to date.
• Physical Exam: 4x2cm right axillary mass on lateral chest wall that is firm, fixed, non-tender, with no overlying skin changes.
• Labs: Elevated LDH.
ACR Appropriateness Criteria

### Palpable Breast Masses

**Variant 1:** Palpable breast mass; Woman 40 years of age or older, initial evaluation. (See Appendices 1A-1B for additional steps in the workup of these patients.)

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
</tr>
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<tbody>
<tr>
<td>Mammography diagnostic</td>
<td>9</td>
<td>See references [13-15].</td>
<td>🟦🟦</td>
</tr>
<tr>
<td>Digital breast tomosynthesis diagnostic</td>
<td>9</td>
<td>See references [16-18,20,85].</td>
<td>🟦🟦</td>
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<tr>
<td>US breast</td>
<td>4</td>
<td>If she had recent mammogram (i.e., past 6 months), US may be appropriate.</td>
<td>O</td>
</tr>
<tr>
<td>MRI breast without and with IV contrast</td>
<td>2</td>
<td>See references [4,49].</td>
<td>O</td>
</tr>
<tr>
<td>MRI breast without IV contrast</td>
<td>1</td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>FDG-PEM</td>
<td>1</td>
<td></td>
<td>★★★★</td>
</tr>
<tr>
<td>Tc-99m sestamibi MBI</td>
<td>1</td>
<td></td>
<td>★★★</td>
</tr>
<tr>
<td>Image-guided core biopsy breast</td>
<td>1</td>
<td></td>
<td>Varies</td>
</tr>
<tr>
<td>Image-guided fine-needle aspiration breast</td>
<td>1</td>
<td></td>
<td>Varies</td>
</tr>
</tbody>
</table>

**Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

*Relative Radiation Level*
Our Patient

• Received an US and mammogram, which confirmed 6 cm mass.

• Biopsy pathology immunohistochemistry:
  – Stains positive for S100.
  – Weakly positive for MART-1.
  – Weak reactivity with HMB-45.
What is her current diagnosis?
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Melanoma Overview

• Epidemiology:
  – 5th and 6th leading cancer in the U.S.
  – Incidence increasing dramatically worldwide (2.8/100,000 in 2008).

• Clinical features:
  – Varies by type
  – ABCDE criteria
  – Prognosis based on staging and LDH level.

Melanoma Overview

• **Pathophysiology:**
  – Melanocyte growth amplification.
  – BRAF mutations in up to 50% metastatic melanoma cells.
  – MEK and BRAF interact to promote cell growth.
Melanoma Overview: Management of Metastatic Disease

Systemic Therapy

– Surgical metastasectomy

– **Immunotherapy**

– **Targeted therapy**
  - BRAF inhibitor (Dabrafenib)
  - MEK inhibitor (Trametinib)

– **Radiation therapy**

– Cytotoxic Chemotherapy
Melanoma Overview: Management of Metastatic Disease

General approach to the management of patients with metastatic melanoma

- Initial multidisciplinary evaluation
- Is the patient a candidate for metastasectomy?
  - Yes → Metastasectomy
  - No → Recurrent disease
- Systemic therapy
  - Is a targetable driver mutation present (e.g., BRAF, MEK, KIT)?
    - Yes → Checkpoint inhibition immunotherapy or molecularly targeted therapy
    - No → Checkpoint inhibition immunotherapy

From: https://www.uptodate.com/contents/overview-of-the-management-of-advanced-cutaneous-melanoma?source=search_result&search=melanoma%20management&selectedTitle=3~150#H186311262
Melanoma Staging

Seventh TNM stage groupings for cutaneous melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes (N)</th>
<th>Distant metastasis (M)</th>
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<tr>
<td>Stage 0</td>
<td>T0s</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
<td>N1, N2, or N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Staging Work-Up

• Few or no established guidelines.

• Approaches to Stage IV disease:
  – CT of abdomen, pelvis, and chest.
  – MRI of brain.
  – Other imaging studies should be ordered on the basis of symptoms.
  – PET/CT appears to be more sensitive than either PET or CT alone.
Back to Our Patient

Before beginning therapy, a CT abdomen and pelvis with and without IV contrast was performed to stage patient’s disease extent.
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Modality 1: CT Abdomen and Pelvis: Recognizing Normal Anatomy

From: Learning Radiology: Recognizing the Basics, 3rd edition
Modality 1: CT Abdomen/Pelvis

General Considerations

• Radiation dose dependent on several factors.
  – Equipment use
  – Size of patient
  – Energy of X-ray used

• Organ-specific characteristics
  – Liver: usually homogenous in density.
  – Spleen:
    • usually 12 cm long, does not substantially pass 12th rib.
    • same size as kidney.
  – Pancreas:
    • Tail most superior (need successive slices to view)
    • with age, fatty infiltration, giving “feathery appearance”.
There are numerous low density heterogeneous lobulated lesions in the liver and spleen.
Ddx for Low Density Liver Lesions (Post-contrast CT)

- Abscess (pyogenic, amebic, or fungal)
- Cyst (e.g., congenital; epithelial; posttraumatic; hydatid)
- Focal fatty infiltration (focal steatosis)
- Focal nodular hyperplasia
- Hemangioma
- Hydatid disease (Echinococcus granulosus and E. multilocularis)
- Metastasis (esp. from carcinoma of lung, breast, colon, kidney)
- Regenerating nodules

From Reeder and Felson’s Gamuts in Radiology (Gamut G-181)
Ddx for Low Density Splenic Lesions

Common
- Abscess (pyogenic; Candida; Pneumocystis carinii)
- Aneurysm of splenic artery
- Cyst (congenital; epidermoid; dermoid or teratoma; hydatid; posttraumatic)
- Hematoma
- Infarction

UNCOMMON
- Cystic lymphangioma
- Hamartoma
- Hemangioma, cavernous or capillary
- Hemangiosarcoma
- Metastasis
- Peliosis
- Pseudocyst (secondary to pancreatitis)

From Reeder and Felson’s Gamuts in Radiology (Gamut G-206)
Modality 1: CT Abdomen/Pelvis

There appears to be a filling defect concerning for non-occlusive thrombus.
DDx Portal Vein Thrombosis or Obstruction

- Cirrhosis plus portal hypertension
- Hypercoagulable state
- Hepatocellular carcinoma (hepatoma) or cholangiocarcinoma (tumor thrombus or invasion)
- Extrinsic compression or invasion by carcinoma of pancreas or stomach; lymphadenopathy of porta hepatis
- Iatrogenic (e.g., TIPS; umbilical venous catheterization; estrogen therapy; oral contraceptive use)
- Budd Chiari Syndrome
- Pancreatitis
- Postoperative (esp. postsplenectomy)
- Schistosomiasis

From Reeder and Felson’s Gamuts in Radiology (Gamut G-190)
There is a 2.8 x 3.8 cm **nodule** within the medial limb of the adrenal gland.

Within the anterior body/neck of the pancreas, there is a 1.4 cm low density, heterogeneous **lesion** noted. Additionally, within the lateral limb of the right adrenal gland, there is a 1.4 x 1.3 cm **lesion**.
Ddx of Adrenal Mass

If small (less than 4 cm)

• Adenoma
• Ganglioneuroma
• Hyperplasia
• Metastasis (esp. lung, breast)
• Pheochromocytoma

From Reeder and Felson’s Gamuts in Radiology (Gamut H-118)
Ddx of Solid Pancreatic Lesion

COMMON
- Adenocarcinoma
- Pancreatitis, focal

UNCOMMON
- Aneurysm, thrombosed
- Annular pancreas; pancreatic divisum
- Hemangioma
- Islet cell tumor (eg, insulinoma; gastrinoma; glucagonoma; somatostatinoma; VIPoma; nonfunctioning)
- Lipoma
- [Lymphadenopathy in celiac axis (eg, metastatic; tuberculous; Castleman disease)]
- Lymphoma
- Metastasis (esp. from carcinoma of breast, lung, stomach, gallbladder, kidney; melanoma)
- Pancreaticoblastoma
- Sarcoma
- Serous cystadenoma (microcystic adenoma)
- Solid and papillary epithelial neoplasm

From Reeder and Felson’s Gamuts in Radiology (Gamut G-213)
Modality 1: CT Abdomen/Pelvis

There is a 1.1 x 0.6 cm soft tissue nodule adjacent to the colon.

An additional soft tissue nodule is seen within the right internal inguinal region.
Modality 1: CT Abdomen/Pelvis

An additional 1.2 x 0.8 cm nodule adjacent to distal colon can be seen.
DDx Retroperitoneal Lymphadenopathy

COMMON
• Lymphoma; leukemia
• Metastatic disease (from carcinoma of breast, lung, colon, pancreas, kidney, bladder, cervix, or testis)

UNCOMMON
• AIDS
• Chronic granulomatous disease (eg, tuberculosis; Mycobacterium avium-intracellular infection; sarcoidosis; histoplasmosis)
• Inflammatory bowel disease (eg, Crohn’s disease)
• Lymphangioleiomyomatosis
• Mesenteritis
• Whipple’s disease

From Reeder and Felson’s Gamuts in Radiology (Gamut H-129)
Back to Our Patient

A CT Chest with and without IV contrast was also performed to stage patient’s disease…
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Image Modality 2: CT Chest: Recognizing Normal Anatomy

- There are six key CT chest levels.
- Starting superiorly...
  1. The **five vessel level** identifies SVC, BC vein, BC artery, common carotid, and left SC artery.
  2. The **aortic arch level** identifies aortic arch, SVC, and azygous vein.
  3. The **aortopulmonary window level** identifies ascending and descending aorta and SVC.
  4. The **main pulmonary artery level** identifies right and left pulmonary arteries, right and left main bronchi, and bronchus intermedius.
  5. The **high cardiac level** identifies LA, RA, and right ventricular outflow tract.
  6. The **low cardiac level** identifies RA, RV, LV pericardium, and interventricular septum.

Images from: Learning Radiology: Recognizing the Basics, 3rd edition
Image Modality 2: CT Chest

Massive conglomerate right axillary lymphadenopathy measures 7.0 x 8.0 x 9.3 cm.
Image Modality 2: CT Chest

A score of pulmonary metastases are identified bilaterally.

The largest 2.2 x 1.9 cm right middle lobe nodule with pleural extension abuts the right atrium.

A right upper lobe nodule measures 1.3 x 1.7 cm is adjacent to the SVC.

A left lower lobe nodule which crosses the major fissure measures 1.9 x 1.8 cm.
### Ddx Small Nodule Distribution on CT – Randomly Distributed Throughout Lung

1. **Miliary tuberculosis**
   - Typically very ill or immunocompromised patient

2. **Pulmonary metastases**
   - Smooth, round, variable size; peripheral and lower lobe predominance; hemorrhagic nodules ill defined

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*From Reeder and Felson’s Gamuts in Radiology (Gamut F-34-2)*
What stage of melanoma does our patient have now?
Back to Our Patient…

• Two months into immunotherapy, she develops right arm pain.

• On physical exam:
  – Tenderness to palpation on right proximal humerus
  – Decreased range of motion secondary to pain.
  – Normal sensation and peripheral pulses.
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Image Modality 3 - Radiograph of Humerus: General Considerations

- Characteristics of Acute Fracture
  - Abrupt disruption of the cortex.
  - Acute changes in the smooth contour of normal bone.
  - Fracture lines sharply angulated.
  - Fracture fragments are jagged and rough

- How fractures are described:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Term Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of fracture fragments</td>
<td>Simple, comminuted</td>
</tr>
<tr>
<td>Direction of fracture line</td>
<td>Transverse, oblique, spiral</td>
</tr>
<tr>
<td>Relationship of fragments</td>
<td>Displaced, angulated, shortened, rotated</td>
</tr>
<tr>
<td>Open to atmosphere</td>
<td>Closed or open (compound)</td>
</tr>
</tbody>
</table>
There is a permeative lesion spanning 9-cm of the mid-diaphysis of the left humerus with adjacent cortical thinning.
There is an associated non-displaced, closed, simple, oblique, pathologic fracture. There is also increased lucency of the left lateral epicondyl-condylar region, which may represent another area of metastatic disease.
There is a 4.6-mm round opacity that appears to be in the left lung.
Back to Our Patient

• Patient took oxycodone and received radiation therapy on her humerus (800cGy) from radiation oncology.
• She is on a sling with planned rod placement from orthopedic surgery.
• Orthopedic surgery is worried about metastases to other bones…
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• **Indications:**
  – Unexplained bone pain.
  – Evaluation for avascular necrosis or bone infarction.
  – Evaluate neoplastic disease.

• **Limitations:**
  – Sensitive, but not specific.
  – Correlation with history and physical required.
  – Limited scintigraphy may miss significant findings.
The images show multiple foci of increased uptake. Areas include lower thoracic spine (approximately T10), and L-spine. Areas include head, mandible, and proximal and distal femur.
Image Modality 3: Bone Scan

The images show multiple foci of increased uptake.

Areas include manubrium and sternum.

Areas include bilateral sacrum and iliac crest.
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Patient’s staging brain MRI was normal, but what if it was not?
There is 1 millimeter focus of T1 hyperintense signal of the left occipital lobe, likely represents melanin.
Axial T1 Post Contrast Study

This corresponds to a 9 mm enhancing lesion on post contrast sequence.
Companion Patients– Modality 6: MRI

Normal GRE lowers concern for hemorrhage and increases concern for metastatic melanoma.

BIDMC PACS, courtesy of Dr. Yu-Ming Chang
Here is what patient’s ultrasound and mammogram may have looked like.
Companion Patients: Modality 7 – Ultrasound/Mammogram

Rounded hypoechoic **lymph nodes** without fatty hilum.

For comparison: Normal axillary **lymph node** reniform shape with fatty hilum.

There is a dense, round **node** with irregular margins.


From: http://media.rsna.org/media/journals/rg/presentations/2014/34.7.Net/index.html
Keep your differential for abnormal axillary lymph nodes broad..
There are multiple enlarged left axillary lymph nodes.

Lesion with “snowstorm” echotexture. This is a silicone granuloma in a patient with breast implants.
Index Case Conclusion

- Patient showed **disease progression** with immunotherapy (increased metastasis size/number).
- She was found to have a BRAF mutation, so she discontinued immunotherapy and began **targeted therapy** (BRAF/MEK inhibition).
- Patient was a **complete responder** to targeted therapy, now 2 years with minimal and stable disease.
- Unfortunately, stage IV melanoma has a **poor prognosis**.
- **No optimal follow up** algorithm has been established.
Take-Home Points

• Melanoma metastasis can affect many visceral and non visceral organs.

• Staging work-up for melanoma can be extensive, with no established guidelines.

• Staging should be tailored to patient symptomatology and physical exam.

• With the advent of more effective systemic therapies, imaging may play a more important role in the follow-up of patients with melanoma.
References

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