RADY 401 Case Presentation

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Ed. John Lilly, MD
Focused patient history and workup

- 4 yo F w/ 1 month history of abdominal pain and pallor presented to outside ED for worsening abdominal pain and fatigue.
- Has also complained of knee/leg pain for 1.5 years
- Vitals unremarkable
- Physical exam remarkable for pallor and hepatosplenomegaly
- Labs: WBC 5.1, ANC 2.7, Hgb 5.1, Plt 120, AST 134, ALT 63, LDH 4026, Uric acid 6.6
- Transferred to UNC for further workup
List of imaging studies

- Abdominal ultrasound
- Chest x-ray (unremarkable)
- CT chest abdomen and pelvis w/ contrast
- MIBG scintigraphy I-123 MIBG (Metaiodobenzylguanidine)
Abdominal Ultrasound

Findings?

Color flow

LUQ Sagittal

LUQ Transverse

Kidney
Findings:
- 7.6 x 7.8 x 9.3 cm left juxtarenal mass, heterogenous in echotexture and vascular
Findings:
- Hyperechogenic masses/mets throughout liver parenchyma
- Enlarged liver (13.8 cm sagittal)
- Normal appearing right kidney
Findings:
- Normal kidneys
- NB: Mean renal length for a patient this age is 7.9 cm +/- 2x 0.5 cm. The right kidney may be under measured due to the adrenal mass.
Findings?
Findings:
- **Enlarged liver** (13 cm) with numerous hypodense mets
- **Large mass in LUQ** with multiple internal calcifications and heterogeneous enhancement
- Note: mass does not arise from the left kidney, but exerts mass effect on left kidney
- **Compression and displacement** of left renal vasculature posteriorly and inferiorly and superior displacement of splenic vessels
- Findings suggestive of metastatic neuroblastoma
Planar Scintigraphy

SPECT/CT
- SPECT= Single photon emission computed tomography

- Heterogenous mass in LUQ → avid radiotracer uptake in periphery, and less avid regions centrally and medially
- Diffuse uptake in liver consistent with metastatic disease involving the liver
- Diffuse osseous uptake involving the pelvis, spine, and appendicular skeleton (most of the femurs and the proximal humeri and tibia).
- No pulmonary nodules.
- MIBG avid left upper quadrant mass and hepatic lesions, with diffuse osseous uptake are consistent with metastatic neuroblastoma
Liver biopsy demonstrated metastatic neuroblastoma with unfavorable histology (The sections show a small round blue cell tumor. In order to further evaluate the tumor a panel of immunohistochemical stains was performed. The tumor is strongly and diffusely positive for synaptophysin. The tumor is negative for CD99, CD45, WT1, and myogenin. The morphology and immunophenotype are consistent with metastatic neuroblastoma)

Bone marrow was biopsied demonstrating involvement by metastatic neuroblastoma, >90% of marrow space bilaterally

Cytogenetics pending

Started on ANBL1531 treatment protocol with cyclophosphamide and topotecan
Can arise anywhere throughout sympathetic nervous system\textsuperscript{1}
Most commonly adrenal gland (40\%), abdominal (25\%)\textsuperscript{1}
Presentation- abdominal mass/pain, bone pain, anemia, back pain, subcutaneous nodules, Horner syndrome, systemic symptoms, etc\textsuperscript{1}
Distant mets at presentation seen in 60-70\% of children with abdominal neuroblastoma—bone marrow, lymph nodes, liver, skin, less commonly lungs and brain\textsuperscript{2}
Ddx: Wilms’ tumor, hepatoblastoma, lymphoma, rhabomyosarcoma

Diagnostic evaluation¹

- Labs: urine vanillylmandelic acid, homovanillic acid (also useful for monitoring)
- Definitive diagnosis: biopsy of 1° tumor or bone marrow biopsy/aspirate
Discussion: What imaging to order first?

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT abdomen with IV contrast</td>
<td>9</td>
<td>Use of intravenous contrast may help better delineate the mass.</td>
<td>****</td>
</tr>
<tr>
<td>MRI abdomen without and with IV contrast</td>
<td>9</td>
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<td>O</td>
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</tr>
<tr>
<td>MRI abdomen without IV contrast</td>
<td>8</td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>US abdomen</td>
<td>7</td>
<td>This procedure may be appropriate as a first imaging examination for certain abdominal masses in adults (eg, superficial). Usually used as the first examination in pediatric and pregnant patients.</td>
<td>O</td>
</tr>
<tr>
<td>CT abdomen without and with IV contrast</td>
<td>6</td>
<td>This procedure, followed by with, contrast may be useful in cases in which enhancement pattern of mass may help differentiate or further characterize the lesion.</td>
<td>****</td>
</tr>
<tr>
<td>X-ray abdomen</td>
<td>5</td>
<td>This procedure is a simple and inexpensive way to evaluate bowel for obstruction or constipation as the cause of the mass.</td>
<td>**</td>
</tr>
</tbody>
</table>
Initial imaging with chest and abdominal radiographs, skeletal films or abdominal ultrasound usually performed to investigate presenting symptoms\(^2\)

Because of variability in origin and metastatic disease, multi-modality imaging is required for staging\(^2\)

- CT or MRI
- \(^{123}\)I-MIBG
Discussion: Imaging Studies

![Figure 13](image-url)

**Mandatory imaging**

- **$^{123}$mIBG scintigraphy** (SPECT or SPECT-CT)*
- MR* or CT of primary tumor compartment (i.v. contrast agent optional for MR, i.v. contrast mandatory for CT)
- Chest X-Ray

**Optional imaging**

- Primary tumor mIBG-negative (or removed)
- Single equivocal skeletal uptake (mIBG or bone scan)
- Primary tumor outside the abdomen
- Pleuro-pulmonary Abnormalities (Clinical examination/Chest-XR)
- Neurological symptoms (other than spinal cord compression) or mIBG/bone scan uptake of skull base or orbits
- Liver imaging (US* or MR* or CT)
- **99m-Tc-MDP Bone scintigraphy** (option: FDG-TEP)
- Plain films of abnormal skeleton regions (+/− MR* or CT)
- Chest CT (+ i.v. contrast recommended)
- Brain imaging (MR* or CT)

*Figure 13: Flowchart of neuroblastoma imaging workup at diagnosis. i.v. = intravenous, XR = radiograph, * = recommended examinations.

Discussion: Imaging Findings

- Ultrasound$^2$
  - Heterogenous solid lesions, mostly echogenic
  - Calcifications are common - coarse or fine
  - Anterior displacement of aorta and IVC

CT²

- Large, heterogenous, lobulated soft-tissue masses that show heterogenous or little enhancement
- Calcifications seen in 85% of abdominal and 50% of thoracic cases
- Diffuse infiltration or focal hypodensities seen with liver involvement
- Can show displacement of organs and vasculature

MRI²

- Heterogenous with variable enhancement pattern, prolonged T₁ and T₂ relaxation times with low signal intensity on T₁W and high signal intensity on T₂W.
- Can identify cystic and hemorrhagic areas, but not calcifications

MIBG

- Analogue of catecholamine precursors, concentrated in neuroblastic cells and sympathetic tissue
- High sensitivity (88%) and specificity (99%) in detecting 1° tumor and metastatic involvement in >90% of patients

**Discussion: Staging**

### Table 1. Image-Defined Risk Factors in Neuroblastic Tumors

- Ipsilateral tumor extension within two body compartments (Neck-chest, chest-abdomen, abdomen-pelvis)
- Neck
  - Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
  - Tumor extending to base of skull
  - Tumor compressing the trachea
- Cervico-thoracic junction
  - Tumor encasing brachial plexus roots
  - Tumor encasing subclavian vessels and/or vertebral artery and/or carotid artery
  - Tumor compressing the trachea
- Thorax
  - Tumor encasing the aorta and/or major branches
  - Tumor compressing the trachea and/or principal bronchi
  - Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
- Thoroaco-abdominal
  - Tumor encasing the aorta and/or vena cava
  - Abdomen/pelvis
    - Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
    - Tumor encasing branches of the superior mesenteric artery at the mesenteric root
    - Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
    - Tumor invading one or both renal pedicles
    - Tumor encasing the aorta and/or vena cava
    - Tumor encasing the iliac vessels
    - Pelvic tumor crossing the sacrotuberous notch
- Intraspinal extension whatever the location provided that:
  - More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
  - Infiltration of adjacent organs/structures
    - Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentry
  - Conditions to be recorded, but not considered IDRFs
    - Multifocal primary tumors
    - Pleural effusion, with or without malignant cells
    - Aneurysms, with or without malignant cells

**Abbreviation:** IDRFs, image-defined risk factors.

### Table 2. International Neuroblastoma Risk Group Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment</td>
</tr>
<tr>
<td>L2</td>
<td>Locoregional tumor with presence of one or more image-defined risk factors</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastatic disease (except stage MS)</td>
</tr>
<tr>
<td>MS</td>
<td>Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow</td>
</tr>
</tbody>
</table>

### Descriptions of Original INSS Tumor Stages

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically. Nodes attached to and removed with the primary tumor may be positive.</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross excision, representative ipsilateral nonanatomic lymph nodes negative for tumor microscopically.</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without complete gross excision, with bilateral anatomic lymph nodes positive for tumor microscopically.</td>
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<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline (beyond the opposite side of the vertebrocostal column) with or without regional lymph nodes involvement, or midline tumor with bilateral extension via infiltration (unresectable) or lymph node involvement.</td>
</tr>
<tr>
<td>4A</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S disease).</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A, or 2B disease) with dissemination limited to skin, liver, and/or bone marrow (limited to infants younger than 1 year; marrow involvement of less than 10% of total nucleated cells, and MIBG scan findings negative in the marrow).</td>
</tr>
</tbody>
</table>

**References:**
- J Clin Oncol. 2009 Jan 10;27(2):298-303
- INRGSS: pre-op staging
- INSS: post-op staging + prognosis
## Cost and Radiation Dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Cost</th>
<th>Effective Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Radiography</td>
<td>$29 - $472</td>
<td>0.1 mSv</td>
</tr>
<tr>
<td>Abdominal Ultrasound (duplex)</td>
<td>$436 - $1,404</td>
<td>0 mSv</td>
</tr>
<tr>
<td>CT Chest (w/ contrast)</td>
<td>$440 - $2,464</td>
<td>7 mSv</td>
</tr>
<tr>
<td>CT Abdomen and Pelvis (w/ contrast)</td>
<td>$512 - $5,055</td>
<td>10 mSv</td>
</tr>
<tr>
<td>MRI Abdomen</td>
<td>$935 - $4,136</td>
<td>0 mSv</td>
</tr>
<tr>
<td>MIBG Scintigraphy</td>
<td>$1,454 - $5,241</td>
<td>3.5 mSv^2^</td>
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</tbody>
</table>
Neuroblastoma: Summary

- Can arise anywhere from sympathetic nervous system, but most commonly from adrenal gland.
- Abdominal US first-line imaging for palpable abdominal mass
- Required imaging: CXR, CT/MRI of primary tumor compartment, MIBG scintigraphy
- Imaging is important for staging and treatment planning
References

1. Shohet DI, Nuchtern JG. Clinical presentation, diagnosis, and staging of neuroblastoma. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2018.