RADY 403 Case Presentation

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July 2020
Focused patient history and workup

March 2016

• 9 y.o. male with PMHx of asthma and salt wasting CAH presents to ED with right knee pain following fall 2 weeks ago
• Meds: hydrocortisone 5 mg tablet TID, fludrocortisone 0.1 mg tablet BID
• Physical exam: circumferential knee pain with full range of motion and no swelling. Patient is weight bearing. No bruising, swelling, erythema, signs of infection, or external signs of trauma
• DDx: patellar fracture vs SCFE (given steroids and elevated BMI)
• Imaging: AP radiograph of hip/pelvis and knee
• Treatment: Tylenol or ibuprofen PRN for pain and discharged
May 2016

- Patient returns to ED with continued right knee pain and unsteady gait/limp for 1 week following fall 2 months ago
- Patient reports the pain awakens him from sleep but denies popping or locking of right knee
- Physical exam: right knee tenderness to palpation over patella and patellar tendon. Negative A/P drawer test and McMurray test. Pain in knee with flexion and extension of right hip joint. No pain on palpation of hip
- Meds: Addition of Motrin PRN for pain
- Imaging: AP radiograph of hip/pelvis and knee
- Plan: consult orthopedic surgery; ordered MR of pelvis, bilateral femurs, and right knee
List of imaging studies

• XR of pelvis and right knee upon initial presentation in ED (March)
  • unremarkable

• Repeat XR of pelvis, bilateral femurs, and right knee (May)
  • Lytic bone lesion in right iliac supra-acetabular region
  • Poorly defined distortion of left proximal femur
  • Normal knee radiograph

• MR of pelvis and right knee (May)
  • Hyperenhancing 2.1 x 2 x 3 cm lesion within the right iliac bone that abuts the acetabular surface
  • Edema in the adjacent soft tissues
  • Normal knee MR

• PET CT (July)
  • Osseous lesions in the right acetabulum and left 4th rib
  • Consistent with LCH
March: XR Pelvis

- No fractures or dislocations
- Joint spaces maintained
- Normal configuration of proximal femurs
- Soft tissue WNL
- Normal hip radiograph
March: XR Knee

**AP knee**

- No fractures or dislocations
- Joint spaces maintained
- Soft tissue WNL

**Lateral knee**

Normal knee radiograph
May: XR Pelvis, Femur, and Knee

Right iliac lytic bone lesion adjacent to right acetabulum with poorly defined borders. 3.58 cm in dimension.

Lytic supra-acetabular bone lesion

Poorly defined lesion in proximal left femur

Right proximal femur normal in appearance

Normal knee radiograph
Hyperenhancing 2.1 x 2 x 3 cm lesion within the right iliac bone, abutting the acetabular surface with edema in the adjacent soft tissues.
July: PET CT

Lytic lesion in left lateral 4th rib with intense FDG activity

Lytic lesion right acetabulum with intense FDG activity
Patient treatment and outcome

- Patient received CT guided bone biopsy to evaluate the right iliac bone lesion
- Pathology: positive for Langerhans cell histiocytosis
- PET scan showed additional lytic lesion in left 4th rib
- Presented a few days later with low energy, intermittent headaches, and excessive urination
  - Initial concern for pituitary invasion and subsequent diabetes insipidus
- Began treatment with vinblastine and prednisone for 12 months
- PET scan 1 year later was normal, but concern for persistent LCH on radiograph
  - Stable appearance of right supra-acetabular lytic lesion
  - Less defined appearance of proximal left femoral diaphyseal lytic lesion
Slight increase in size of right supraacetabular lesion from 3.58 cm

Sclerotic left proximal femur lesion
Lytic left diaphyseal lesion

Sclerotic left 4th rib lesion
Discussion: Langerhans Cell Histiocytosis

- Also called eosinophilic granuloma
- L group of histiocytic disorders
- A histiocytic disorder most characterized by single (monostotic) or multiple (polyostotic) osteolytic bone lesions demonstrating infiltration with histocytes on biopsy
  - Bean-shaped nuclei
- Histiocytes may infiltrate every organ apart from the heart or kidneys
- No staging system
- Named because the morphology and immunophenotype of the cells resembled Langerhans cells
  - LCH derived from myeloid progenitor cells from the bone marrow
  - CD207+ (langerin) histiocytes

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Table 1. The revised classification system of histiocytoses and neoplasms of macrophage-dendritic cell lineages [1]

<table>
<thead>
<tr>
<th>No.</th>
<th>Group of histiocytic disorders</th>
<th>Histiocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L group</td>
<td>LCH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– ECD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed LCH/VECD</td>
</tr>
<tr>
<td>2</td>
<td>C group</td>
<td>Cutaneous non-LCH:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– XG Family: XG, AXG, SRH, BCH, CEN, PNH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Non-XG family: cutaneous RDD, NKG, other not otherwise specified</td>
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<tr>
<td></td>
<td></td>
<td>Cutaneous non-LCH with a major systemic component:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– XG Family – XD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Non-XG family – MRH</td>
</tr>
<tr>
<td>3</td>
<td>A group</td>
<td>Primary MH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary MH (following or associated with another hematologic neoplasia)</td>
</tr>
<tr>
<td>4</td>
<td>R group</td>
<td>Familial RDD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sporadic RDD:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Classical (nodal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Extra-nodal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– RDD with neoplasia or immune disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Other, non-C, non-L, non-M, non-H histiocytes</td>
</tr>
<tr>
<td>5</td>
<td>H group</td>
<td>Primary HLH: Mendelian inherited conditions leading to HLH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary HLH (non-Mendelian HLH)</td>
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<tr>
<td></td>
<td></td>
<td>HLH of unknown/uncertain origin</td>
</tr>
</tbody>
</table>

AKG = adult xanthogranuloma, BCH = benign cathectic histiocytosis, ECD = Erdheim-Chester disease, GEM = generalized eruptive histiocytosis, HLH = hemophagocytic lymphohistiocytosis, ICY = indeterminate cell histiocytosis, JKG = juvenile xanthogranuloma, LCH = Langerhans cell histiocytosis, MH = malignant histiocytes, MRH = multicentric reticulohistiocytosis, NKG = necrobiotic xanthogranuloma, PNH = progressive nodular histiocytosis, RDD = Rosai-Dorfman disease, SRH = solitary reticulohistiocytoma, XD = xanthoma disseminatum, XG = xanthogranuloma.

Discussion: LCH Classification

- Divided into 3 groups based on number of lesions and systems involved:
  - **Unifocal**
    - 70% of cases
    - Limited to a single bone or a few bones
    - May involve the lung
    - Presents at 5-15 years of age
  - **Multifocal unisystem**
    - 20% of cases
    - Multiples bones + reticuloendothelial system
    - Diabetes insipidus when pituitary involved
    - Presents at 1-5 years of age
  - **Multifocal multisystem**
    - 10% of cases
    - Disseminated involvement of RES, anemia, and thrombocytopenia = often fatal
    - Diagnosed in first 2 years of life

<table>
<thead>
<tr>
<th>No.</th>
<th>System involved</th>
<th>Organ involved</th>
<th>Symptomatology</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skeletal</td>
<td>Flat and long bones, spine/skullcap bones, femurs, humeri, spine</td>
<td>Bone pains, lumps</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Orbital cavity</td>
<td>Exophthalmos</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporal bone</td>
<td>Discharge from the middle ear, hearing loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Integumentary</td>
<td>Skin</td>
<td>Seborrhoeic erythematous rash, haemorrhagic rash</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td>Lymphatic</td>
<td>Lymph nodes</td>
<td>Swollen lymph nodes</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Thymus</td>
<td>Widened opacity of the mediastinum</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>Splenomegaly, cytopenias</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Liver</td>
<td>Liver</td>
<td>Hepatomegaly, liver dysfunction</td>
<td>15%</td>
</tr>
<tr>
<td>5</td>
<td>Respiratory</td>
<td>Lungs</td>
<td>Respiratory failure</td>
<td>1–15%</td>
</tr>
<tr>
<td>6</td>
<td>Bone marrow cavity</td>
<td>Bone marrow</td>
<td>Neutropenia, anaemia, thrombocytopenia</td>
<td>15–30%</td>
</tr>
<tr>
<td>7</td>
<td>CNS</td>
<td>Hypothalamic-pituitary disease</td>
<td>Diabetes insipidus, short stature, secondary hydrocephalus, cranial nerve palsies</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
<td>Neurodegenerative disease of the CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Digestive</td>
<td>Gastrointestinal tract</td>
<td>Haemorrhagic diarrhoea, anaemia</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

Table 2. Incidence and symptomatology of systems and organs involvement in Langerhans cell histiocytosis in children [1, 2, 4, 5, 9]

Discussion: LCH Imaging

• Conventional radiographs are primary imaging method to identify and follow LCH lesions
  • In long bones: well-defined, lytic lesion +/- sclerotic margins usually present in the diaphysis or metaphysis
  • Associated soft tissue mass may be present

• LCH lesions are “hot” on radionuclide bone scans. This modality can detect some lesions that are poorly visualized by radiography

• MR scans show the lytic lesion with high T2 and low T1-weighted imaging
  • Use of gadolinium contrast enhances the lesion and soft tissue components

• “Activity” of lesions may be judged by MR or PET
  • PET: most accurate for detecting LCH lesions and response to therapy, except for vertebral lesions (MR most helpful)
Discussion: Radiologic Findings in LCH

<table>
<thead>
<tr>
<th>System</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>“Punched-out” lesion, beveled edge (asymmetric destruction of inner and outer cortices), geographic skull (lesions grow, coalesce, and become maplike)</td>
</tr>
<tr>
<td>Spine</td>
<td>Vertebra plana (symmetric flattening of vertebral body)</td>
</tr>
<tr>
<td>Long bones</td>
<td>More commonly involved in children; diaphyseal or metaphyseal</td>
</tr>
<tr>
<td>Flat bones</td>
<td>“Floating teeth” if enough alveolar destruction; lytic lesion with sclerotic rim and surrounding areas of sclerosis more common in iliac bone</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatomegaly and solid or cystlike lesions</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Most common in neck</td>
</tr>
<tr>
<td>CNS</td>
<td>Diabetes insipidus and neurodegeneration, absent posterior pituitary bright spot, thickening of pituitary stalk</td>
</tr>
<tr>
<td>Lung</td>
<td>Centrilobular nodules or cysts of varying sizes, with mid- to upper-lung distribution and sparing of costophrenic angles</td>
</tr>
</tbody>
</table>

Note.—CNS = central nervous system.

Table 1: Comparison of Imaging Modalities for Lesion Detection and Risk Stratification of Langerhans Cell Histiocytosis

<table>
<thead>
<tr>
<th></th>
<th>True-positive lesions</th>
<th>False-negative lesions</th>
<th>False-positive lesions</th>
<th>Sensitivity (95% confidence interval)</th>
<th>Mean No. of false-positives per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeleton survey</td>
<td>56</td>
<td>43</td>
<td>0</td>
<td>56.6% (46.7–66.0%)</td>
<td>0 (0/38)</td>
</tr>
<tr>
<td>Bone scan</td>
<td>38</td>
<td>61</td>
<td>4</td>
<td>38.4% (29.4–48.3%)</td>
<td>0.11 (4/38)</td>
</tr>
<tr>
<td>WB-MRI</td>
<td>98</td>
<td>1</td>
<td>2</td>
<td>99.0% (93.2–99.9%)</td>
<td>0.05 (2/38)</td>
</tr>
<tr>
<td>Skeletal lesions$^\dagger$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeleton survey</td>
<td>51</td>
<td>30</td>
<td>0</td>
<td>63.0% (52.0–72.7%)</td>
<td>0 (0/33)</td>
</tr>
<tr>
<td>Bone scan</td>
<td>38</td>
<td>43</td>
<td>4</td>
<td>46.9% (36.4–57.8%)</td>
<td>0.12 (4/33)</td>
</tr>
<tr>
<td>WB-MRI</td>
<td>80</td>
<td>1</td>
<td>1</td>
<td>98.8% (91.8–99.8%)</td>
<td>0.03 (1/33)</td>
</tr>
</tbody>
</table>

WB-MRI = whole-body magnetic resonance imaging.

*For all comparisons, P < 0.017.
†For all comparisons, P > 0.017.
$^\dagger$The number of overall lesions: 99 true lesions and 6 false-positive lesions in 38 patients.
$^\dagger$The number of skeletal lesions: 81 true lesions and 5 false-positive lesions in 33 patients.

Discussion: LCH Diagnosis and Treatment

• Histologic confirmation is necessary for diagnosis
  • Clinical and imaging characteristics of LCH mimic other disease processes

• Fine needle aspiration or core needle biopsy and staining for CD1a and/or anti-langerin (CD207)

• Electron microscopy to identify Birbeck granules performed less frequently

• Testing for the BRAF V600E mutation is utilized if the patient needs targeted therapy

• Treatment – depends upon extent of disease and presence of CNS lesions
  • Solitary – no universally accepted protocol
  • High risk lesions – vinblastine and prednisone for 12 months

Wrap Up

• Langerhans cell histiocytosis is a rare condition that presents more often in children
• Infiltrative cells are not Langerhans cells but are myeloid progenitor CD207+ (langerin) histiocytes
• Radiograph is the initial imaging modality of choice as it can reveal the lytic bone lesions
• Bone biopsy + staining for CD1a/CD207 for confirmation
• Treatment depends on extent of lesions and CNS involvement
  • Vinblastine and prednisone for 12 months for severe cases
• PET scans needed to monitor response to chemotherapy except for vertebral lesions