Agenda

• Sickle cell disease (SCD) basics
• A tour of sickle cell complications and their radiographic manifestations.
• Patient presentation
  – RH, a 14 year old boy with SCD and RUQ pain
• A closer look at Osteonecrosis and Osteomyelitis
  – Menu of radiographic tests.
  – Can we differentiate these two disease processes?
• Patient presentations
  – WB, a 43 year old man with SCD and L knee pain
  – LF, a 42 year old woman with SCD and L hip pain
• Summary
• References
• Acknowledgements
Sickle Cell Basics

- The rope like polymer of deoxy Hemoglobin S leads to sickling of red blood cells.
- Hypoxia, acidosis, dehydration, and blood flow stasis promote sickling
- Repeated sickling causes rbc dehydration and membrane distortion
- There is increased rbc “stickiness” and adherence to vascular endothelium
- These altered red cells cause the primary pathophysiologic themes in SCD:
  - **Hemolysis and Vaso-occlusion**
- This leads to complications in every organ system...

Courtesy of Orah Platt
Sickle Cell Basics II

- **CNS:** CVA with large and small vessel vaso-occlusion; risk of meningitis.
- **Ocular:** Retinopathy
- **Pulmonary:** Acute chest syndrome, pneumonia; chronic pulmonary disease with fibrosis, restrictive lung disease
- **Cardiac:** Heart failure secondary to fibrosis, MI, cor pulmonale
- **Renal:** Hematuria, papillary necrosis, nephropathy
- **Spleen:** Sequestration crisis with massive splenomegaly; auto-splenectomy
- **Liver/Biliary:** Bilirubin cholelithiasis; cholecystitis
- **Skin:** Leg ulcers
- **Skeletal:** Osteopenia, dactylitis, osteonecrosis, premature OA, growth failure, risk of osteomyelitis
- **Heme:** Chronic anemia with HCT 18-26%; aplastic crisis with Parvovirus B19
- **Immune system:** Functional asplenia, intrinsic defects in immune system.
Neurologic Complications

- CNS: 25% of patients with SCD have neurologic complications:
  - TIA
  - Infarctive stroke
  - Intracerebral hemorrhage
  - Spinal cord infarction or compression
- New role for Doppler ultrasound for prevention of CVA in SCD.
Cardiac Complications

- Anemia need increased cardiac output
  - Chronic chamber enlargement/cardiomegaly
- Increased risk of acute myocardial infarction
  - In absence of atherosclerosis
  - Cardiac muscle has increased demand (high C.O.)
  - Decreased oxygen carrying capacity
  - Microcirculatory disease
- On Chest radiograph look for enlarged cardiac silhouette and upper zone redistribution with high cardiac output state.
Renal Complications

- Occlusion of vasa recta in the medulla
  - Medulla has low oxygen tension, and high osmolality that promote sickling
- Papillary infarcts lead to papillary necrosis and renal failure
- Renal osteodystrophy (with 2° hyperparathyroidism) can contribute to osteoporosis
- Renal disease can also lead to decreased erythropoietin production, exacerbating the anemia

American College of Radiology. Teaching cases: Urogenital case 506.
Pulmonary Complications

* Acute & chronic pulmonary manifestations are the most common cause of death

* Acute Chest Syndrome:
  - Pulmonary vaso-occlusion:
    - In situ infarction
    - Fat embolus
  - Pneumonia
  - Hypoventilation/Atelectasis
    - Abdominal pain
    - Thorax bone pain
  - Pulmonary edema
    - Over-vigorous intravenous fluids
Pulmonary Complications II

- Acute Chest Syndrome
  - Presence of new pulmonary infiltrate
    - Must involve at least ONE lung segment
    - More than simple atelectasis
    - Setting of chest pain, temp > 38.5, tachypnea, cough or wheezing

- Chronic Lung disease from repeated ACS
  - Restrictive lung disease
  - Pulmonary hypertension can cause cor pulmonale
  - Very poor prognosis (most die within 7 years)

Courtesy of Orah Platt
Chest Radiography

• Acute chest syndrome (ACS)
  – On admission, 30% of patients have a normal Chest radiograph
  – Lobar distribution, frequently middle or lower lobes
  – Usually confluent and alveolar in location
  – 25% of patients also get pleural effusions.
  – Pneumonia is more likely in children under 5 y.o. with upper lobe infiltrates.

• Chronic Lung disease from repeated ACS
  – CT scan: chronic interstitial fibrosis
Abdominal Complications I

• Cholelithiasis
  – Pigmented gallstones from chronic hemolysis
  – Occur as young as 3-4 years of age, 30% by age 18, and eventually in 70% of SCD patients.
  – Most are asymptomatic, but the stones can cause RUQ pain or lead to cholecystitis.

Hyperechoic stones with posterior acoustic shadowing
Abdominal Complications II

- **Splenic sequestration**
  - Cause of acute severe anemia.
  - 10-15% Mortality rate
  - Occurs in young children, before fibrosis of the spleen
    - As high as 30% incidence
    - In 20% of patients this is initial symptom
  - Vaso-occlusion and splenic pooling of red blood cells causes rapidly enlarging spleen
  - Risk of hypovolemic shock
- **Auto-splenectomy**
  - Vaso-occlusion of spleen leads to dysfunction and infarction by 2-4 years of age
  - Spleen tissue undergoes fibrosis.
  - Leads to immunocompromised state

2 year old boy with sequestration

African figurine displaying splenomegaly

Courtesy Orah Platt
Patient Presentation: Mr. RH

• Patient RH is a 14 year old male with SCD
• CC: Pain in both legs, and a cough for 3 days
• PMH: Sickle cell anemia, complicated by:
  – Dactylitis at 7 months of age
  – Multiple admissions for vaso occlusive (pain) crisis
  – History of acute chest syndrome twice in 1995, requiring exchange transfusions
• Admitted for vaso-occlusive crisis
• Plain films of knees were negative.
• On HD#3 developed RUQ pain…
Mr. RH’s RUQ Ultrasound:

- Gallstone in neck of GB
- The common hepatic duct was measured to be 5 mm.
- No GB distension, wall thickening, or pericholecystic fluid
- Duodenum with air and posterior shadowing
- Multiple hyperechoic rounded structures in the GB (moved to dependent side during the study)

These findings are consistent with cholelithiasis. He had a semi-elective laparoscopic cholecystectomy due to prior episodes of RUQ pain. One day later he had dyspnea and rales…
Mr. RH’s Chest Radiograph:

Remember, to diagnose an Acute Chest Syndrome there needs to be a NEW pulmonary infiltrate…

“Can I see his baseline film?”…
Mr. RH’s Chest Radiograph:

Baseline film

Clear Lungs

Normal C:T ratio

Portable AP of the Chest

Poor inspiration

EKG leads

Silhouetted out Left diaphragm, suggesting L basilar atelectasis

This was labeled post-op atelectasis.
The next day he was well enough to have an upright PA and lateral chest radiograph…
Mr. RH, Post op Day #2

RH’s respiratory symptoms resolved over the next 3 days, and he was discharged home on post-op day six.
Skeletal Manifestations

• Bone is affected in various ways by SCD:
  – Marrow Hyperplasia -- a response to the severe chronic anemia
    • Marrow space increases
    • Trabecular and Cortical bone thinning
  – Vaso-occlusion
    • Painful Crisis
    • Dactylitis
    • Osteonecrosis
  – High risk of Osteomyelitis
    • Immunocompromised state
    • Nidus for infection: osteonecrotic areas.
    • Salmonella and S. aureus infection most common
Marrow expansion

• Radiologic findings include: (at least in the literature…)
  – Tower skull
  – **Hair-on-end**, or Crew-cut appearance of skull
  – Forehead bossing
  – Squaring of the metacarpals
  – Diffuse osteopenia
  – course trabecular pattern
    • thicker trabeculae stand out in radiolucent bone
  – **H-shaped** or Cod-vertebrae
    • central cupping of the vertebral endplates
    • Usually involves several contiguous vertebrae
    • 50% of SCD patients

This finding is **VERY RARE**, and is more associated with Thalassemia major than Sickle cell disease!

H-shaped vertebrae

- Characteristic feature of sickle cell disease, best seen on lateral chest radiograph.
- Can also be seen in Gaucher’s disease, Thalassemia major, and Homocystinuria

Mechanism:

Recurrent vaso-occlusion and ischemia of the end-arterioles serving the central portion of the growth plate impairs endochondral bone formation.

There is gradual development of a flat, central end plate depression of both the superior and inferior end plates.

Osteonecrosis

• Patients present with pain and swelling at the area of bone infarction
• Femoral and Humeral heads most common area
• Proximal tibia, vertebrae, and small bones of hand and feet also at risk (dactylitis)
• Complications:
  – Fat and bone marrow embolism
  – Osteomyelitis (secondary seeding of dead bone)
  – Premature osteoarthritis
Dactylitis

- The most common initial symptom in Sickle cell disease

Swelling of the hands…

...and the feet.

from vascular necrosis of the metacarpal and metatarsal bones

Courtesy of Orah Platt
Dactylitis

- Typical between 6 to 18 months of age, while red cells with HbSS replace those with HbF in the bone marrow in the hands and feet.

- Example: Ischemic dactylitis in 10 month old boy:

Osteomyelitis

• An infection of the bone and bone marrow.
• Typical symptoms:
  – Pain with passive motion, tenderness, warmth, pseudoparalysis
• Can be acute, subacute, or chronic.
• Incidence in SCD: 0.36% per year
• Humerus, femur, and tibia most commonly affected
• In most children osteomyelitis affects the metaphysis; in SCD patients, it often affects the diaphysis.
• Very difficult to differentiate from osteonecrosis in SCD.
• Radiology plays central role in evaluation…
  – Imaging findings of osteomyelitis are the same as those found in children without SCD.
  – Suspect osteomyelitis when the symptoms of acute vaso-occlusive crisis persists despite medical management, or with new onset unifocal bone pain.
Musculoskeletal imaging: Menu of Tests

- **Plain film**
  - Always first step; may provide clues for other disease processes
  - 30-50% of bone calcium must be lost before density change is seen
- **Sonography**
  - Quick look at soft tissues, guides aspiration
- **Scintigraphy**
  - Great for initial assessment of osteonecrosis and osteomyelitis
  - Total body scan: detect multiple areas of involvement
- **CT**
  - See bone changes well (destruction, periosteal reaction, sequestrum or involucrum)
- **MRI**
  - See full extent of local disease process (bone, muscle and soft tissue)
Plain Films

• Osteonecrosis:
  – During a Pain crisis:
    • Soft tissue swelling
    • Evidence of old infarcts
  – At 10-21 days:
    • Osteopenia in a permeative pattern, as osteoclasts dissolve dead bone
    • Periosteal new bone formation
  – Later: cortical thickening, sclerotic areas
  – The Crescent sign (subchondral lucency) is pathognomonic

• Osteomyelitis:
  – 2-3 weeks required for bony changes to appear
  – Order of plain film manifestations: soft tissue swelling, demineralization, periosteal reaction, and cortical disruption

Osteonecrosis of the Femoral head

Lucent regions with associated sclerotic rims

After many insults, the weight-bearing femoral heads can collapse, or secondary osteoarthritis may lead to a need for hip replacement.

Scintigraphy

- High sensitivity, low specificity
- Three phase bone scan
  - Tc-99m bound to methylene diphosphonate accumulates in areas of increased osteoblast activity
    - Immediate blood flow
    - Blood pool imaging
    - Delayed bone imaging
      - 1.5-2 hours after initial injection
  - Bone Marrow scan
    - 99-Tc labeled sulfur colloid goes to RE system -- bone marrow, liver, and spleen
  - WBC labeled with Tc 99m or indium go to inflamed areas.
  - Gallium 67 also goes to inflamed areas (binds to degranulated WBC lactoferrin).
- Dual tracer scans compare images from:
  1. Physiologic/Anatomic tracer scan: Tc99-MDP or Tc99-colloid
  2. Inflammation tracer scan: WBC-Tc99 or gallium 67

Increased uptake in osteomyelitis
# Osteonecrosis vs. Osteomyelitis in Sickle cell disease

<table>
<thead>
<tr>
<th></th>
<th>Bone scan (Tc-99 MDP)</th>
<th>Bone Marrow (Tc-99 - colloid)</th>
<th>Bone scan with Gallium 67</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteonecrosis</strong></td>
<td>Doughnut sign: Increased turnover around cold spot</td>
<td>Decreased uptake (cold spot)</td>
<td>Early: decreased uptake With repair: Increased uptake around cold spot</td>
</tr>
<tr>
<td><strong>Osteomyelitis</strong></td>
<td>Three phase: Increased uptake on ALL 3 phases</td>
<td>Not increased or decreased uptake</td>
<td>Very increased uptake (more than marrow or bone scan)</td>
</tr>
</tbody>
</table>

Osteonecrosis is 50x more common than osteomyelitis in Sickle cell disease.
Scintigraphy for acute osteomyelitis

The scans demonstrate increased uptake in the distal metaphysis of the right tibia. The blood pool and delayed bone scans suggest osteomyelitis; the gallium shows a large, associated area of inflammation -- evidence that this is not just bone repair.

Plain radiographs were negative.

Osteomyelitis: Bone Scan and Plain Film

*Salmonella* osteomyelitis of the right fifth proximal phalanx in a 4-year-old girl.

**Initial Gallium scan: 24 hours after symptoms started**

**Follow-up radiograph, 5 weeks following antibiotic therapy.**

Ultrasound

- Convenient, practical, and cost-effective
- No need for sedation in children
- Increasing use for pediatric MSK evaluation
- Cartilage, bone, and soft tissue distinguished
- Cons: Very operator dependent
- Osteomyelitis:
  - Soft tissue disturbance
  - Subperiosteal abscess: thin layer of fluid contiguous with the bone
  - Doppler: for monitoring the course of the disease
    - Prolonged increased Doppler signal may indicate need for surgery
  - Useful for guiding needle aspiration
MRI for Osteonecrosis and Osteomyelitis

• Most sensitive, most specific
  – Shows changes early in course of disease when plain films and bone scans are negative
  – **Cons:** high cost, lower availability, and need for sedation in young children

• Osteonecrosis:
  – Pathognomonic double line:
    • Early: T-1 images show single density line
    • T-2: second high intensity line
      – Represents hypervascular granulation

• Osteomyelitis:
  – Clearly demonstrates extent of soft tissue changes and medullary edema before cortical destruction occurs.
  – Especially good for vertebrae and feet
  – Can distinguish acute from chronic infections.
Osteonecrosis on MRI

Double Line Sign:
Concentric high and low signal at the periphery

Fat suppression MRI sequence:
Serpentine intramedially pattern of decreased signal intensity

# Comparison of Studies for Osteomyelitis

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plain film</strong> (at 7-10 days after onset of symptoms)</td>
<td>43-75%</td>
<td>75-83%</td>
</tr>
<tr>
<td><strong>Three-phase bone scan</strong>, 24-48 hours after onset of symptoms</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td><strong>MRI with T1, T2, and Fat suppression images</strong></td>
<td>86%</td>
<td>95-100%</td>
</tr>
</tbody>
</table>
Patient II: Mr. WB

- Patient WB is a 43 year old male with SCD
- CC: Left knee pain for several months
- PMH: Sickle cell anemia, complicated by:
  - Chronic Pain
  - Renal failure with papillary necrosis in 1985
  - Retinopathy
- Family Hx: He has 13 siblings, 3 of whom have SCD.
Mr. WB’s plain films of the knee

Four areas of increased density…

… These ill defined sclerotic lesions are most likely infarcts, but MRI is recommended

Sclerotic area, measuring 6.7 by 2.1 cm
Mr. WB’s knee: Plain Film and MRI Comparison:

- Joint space is preserved
- Sclerotic bone in old osteonecrotic sites
- New infarct with edema and high MR signal
Mr. WB’s MRI of the knee

Mr. WB continues to have pain in his L knee. Fortunately there is minimal medial articular damage, and no evidence for osteomyelitis. He may consult orthopedics in the future.
Patient III: Ms. LF

- Patient LF is a 42 year old female with SCD
- CC: Bilateral hip pain, L>R
- PMH: Sickle cell anemia, complicated by:
  - Severe osteonecrosis and OA of L hip, requiring total hip replacement in 1991
  - Moderate, stable osteonecrotic change in R hip
  - Chronic lung changes from multiple episodes of acute chest syndrome
  - Cardiomegaly
  - S/p cholecystectomy in 1984
- Hospital course: L total hip revision.
Patient II: Ms. LF

- Prominent Pulmonary markings
- Heart is enlarged
- s/p cholecystectomy
Ms. LF’s AP of the pelvis

Ms. LF has stable OA and evidence of multiple episodes of osteonecrosis in her R hip and may need a R hip replacement in the future.
Three patients... many morbidities:

Patients RH, WB, and LF have had these SCD related illnesses:

- CNS: CVA with large and small vessel vaso-occlusion; risk of meningitis.
- Ocular: Retinopathy
- Pulmonary: Acute chest syndrome, pneumonia; chronic pulmonary disease with fibrosis, restrictive lung disease
- Cardiac: Heart failure secondary to fibrosis, MI, cor pulmonale
- Renal: Hematuria, papillary necrosis, nephropathy
- Spleen: Sequestration crisis with massive splenomegaly; auto-splenectomy
- Liver/Biliary: Bilirubin cholelithiasis; cholecystitis
- Skin: Leg ulcers
- Skeletal: Osteopenia, dactylitis, osteonecrosis, premature OA, growth failure, risk of osteomyelitis
- Heme: Chronic anemia with HCT 18-26%; aplastic crisis with Parvovirus B19
- Immune system: Functional asplenia, intrinsic defects in immune system.
Summary

• Reviewed Sickle Cell basics and organ system complications
• We met Mr. RH who had cholelithiasis and acute chest syndrome
• Menu of tests in musculoskeletal imaging, emphasizing osteonecrosis versus osteomyelitis
• We met two patients, WB and LF, with osteonecrosis due to sickle cell disease, in different stages of joint involvement
References

American College of Radiology. Teaching cases: Urogenital case 506.

BIDMC PACS


Children’s Hospital of Boston: Radiology film library (for Patient RH).

Diggs LW, Pulliam HN, King JC: The bone changes in sickle *AJR Am J Roentology* 1979 Mar; 132 (3): 373-7

Donohue, JP Osteonecrosis. 2002 *UpToDate. (www.uptodate.com).*

Embury SH, Vichinsky EP. Overview of the clinical manifestations of sickle cell disease. 2002 *UpToDate* (www.uptodate.com)


Ghiorzi T, Mackowiak P. Diagnosis of osteomyelitis. 2002 *UpToDate (www.uptodate.com)*

Hammerman SI, Farber HW. Pulmonary complications of sickle cell disease. 2002 *UpToDate* (www.uptodate.com)


Orah,P. “Sickle cell disease” Module I lecture slides, with permission.


Quinn CT, Buchanan GR. Medical Progress: The acute chest syndrome of sickle cell disease. *J of Pediatrics* 135(4).


Acknowledgements

- My patients, RH, WB, and LF
- Orah Platt, for her generosity in sharing her Module II lecture slides
- Dr. Hall, Dr. Donohoe, Dr. Saurborne, and Dr. Cornfield for their editorial guidance.
- Gillian Lieberman, MD
- Pamela Lepkowski, for her superb teaching of the PowerPoint program
- Michael Larson for Trouble shooting in the Media Lab
- My classmates in RD500M.1
- Larry Barbaras and Cara Lyn D’amour our Webmasters