Mind The Marrow: A Case of Recurrent Bone Pain

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Disclosure of Financial Relationships

- Martha Elster, MD: No relevant disclosures
- Julia Lam, MD: No relevant disclosures
9 year old male

Left Knee Pain
- 4 days ago
- Progressive
- Refusal to walk and weight bear
- No swelling or redness
- No known trauma

Past Medical History
- Unclear etiology
- Extensive outpatient workup
- 2 prior hospitalizations
  Right knee pain, no source
- Surgical Hx:
  I&D R Knee
  Bone Marrow Biopsy

Normocytic Anemia
Thrombocytopenia
Splenomegaly
Knee Pain Encounters

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<th>Event</th>
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<td>TAV</td>
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<td>5/9/2016</td>
<td>Admit</td>
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Additional History

- UTD on vaccines
- Family History:
  - No bleeding disorders, menorrhagia, miscarriages
- Social History:
  - Lives in Oakland, CA with parents, sister (13y), MGF
- Exposures:
  - No travel in past year
  - 3 healthy dogs at home
<table>
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<th>Positive (+)</th>
<th>Negative (-)</th>
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<tbody>
<tr>
<td>GEN:</td>
<td>No fevers, weight loss, chills, night sweats</td>
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<tr>
<td>HEENT: Epistaxis, Seasonal rhinitis</td>
<td>No vision changes, sore throat</td>
</tr>
<tr>
<td>RESP:</td>
<td>No cough, dyspnea, wheezing</td>
</tr>
<tr>
<td>CV:</td>
<td>No chest pain, palpitations</td>
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<tr>
<td>GI: Emesis x2 following epistaxis</td>
<td>No abdominal pain, diarrhea, constipation</td>
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<tr>
<td>GU:</td>
<td>No dysuria, hematuria, change in UOP</td>
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<tr>
<td>MSK: L knee pain</td>
<td>No swelling, redness, warmth</td>
</tr>
<tr>
<td>Heme: Easy bruising, Splenomegaly, Anemia</td>
<td>No petechiae, lumps/bumps</td>
</tr>
<tr>
<td>Neuro:</td>
<td>No headaches, confusion, weakness, numbness</td>
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</table>

**Additional Questions**

- Further thoughts?
- Initial differential diagnosis?
- Exam findings?
Differential Diagnosis

Infectious
- Osteomyelitis
  - Coccidioides, Histoplasmosis
- Septic Joint
- Toxic Synovitis
- Post-Streptococcal

Trauma
- Ligamentous Injury
- Sprain / Strain
- Fracture

Oncologic
- Leukemia, Lymphoma

Hematologic
- Hemarthrosis
- Hemophilia
- Platelet Disorder
  - Von Willebrand

Rheumatologic
- JIA, SLE
- Chronic Recurrent Multifocal
- Osteomyelitis (CRMO)

Metabolic
- Immunologic

Physical Exam

BP 98/62 mmHg | Pulse 108 | Temp 37.2 °C | Resp 21 | Wt 36.4 kg | SpO2 99%

- Pleasant but uncomfortable
- Mild cobblestoning of posterior OP, no epistaxis
- No hepatosplenomegaly but mild TTP in LUQ
- Left Knee
  - Slightly flexed, externally rotated
  - Swelling, no warmth or erythema
  - TTP diffusely, greatest in posterior fossa
- Small palpable effusion in posterior fossa
- Limited extension and flexion secondary to pain
- Refusal to walk or weight bear
- Dime sized scattered bruises on BLE, no petechiae
## Orders

### Infectious:
- Brucella IgM/IgG
- Coccidioides
- Histoplasmosis
- HIV
- ASO titer
- Strep PCR
- Bone biopsy, culture
- **Gamma interferon** (indeterminate)

### Hematologic:
- Bone marrow aspirate
- Von Willebrand Panel
- EKTA
- Factors VIII, IX, XI, XII
- Coagulation studies
- Iron studies
- Lead studies
- **Platelet aggregation** (indeterminate)

### Rheumatologic:
- ANA
- RF
- Coombs
- C3, C4
- **Dilated eye exam**

### Immunologic:
- Neutrophil oxidative burst
- Immunoglobulins A, E, G, M
- Lymphocyte panel (CD8, CD16 low)

### Metabolic:
- Copper
- Ceruloplasmin
- Homocysteine

### Cardiac:
- **Echo**

### Orthopedic:
- Knee XR x2
- LE Doppler x2
- **Abd US x4: Splenomegaly**
- Knee MRI: periosteal fluid collection

### Metabolic:
- Copper
- Ceruloplasmin
- Homocysteine
Labs

- 65% PMNs, 27% lymphs, 6% monos, 1% eos
- Large platelets
- Ristocetin platelet aggregation: **incomplete**

- ESR 88
- CRP 6.3
- Chem, LFTs, coags nml
- Reticulocyte Ct 1.1%

- Abdominal US: **splenomegaly**, slightly increased
- LLE US: Negative for DVT
- Knee XR

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**Abdominal US:** splenomegaly, slightly increased
**LLE US:** Negative for DVT
**Knee XR**

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**Radiograph of the knee region**

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**American Academy of Pediatrics
Dedicated to the Health of All Children**

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**2017 Pediatric Hospital Medicine**

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**Society of Hospital Medicine**

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**Academic Pediatric Association**
Hospital Course

- **Day 1**
  - Pain control (Hycet q6H)
  - Hematology/Oncology consult for knee pain in setting of worsening epistaxis

- **Day 2**
  - Temperature of 101°F
  - Blood culture obtained
  - Clindamycin and ceftriaxone started
  - Orthopedic consult for septic knee concern
  - Rheumatology consult for joint swelling
  - MRI with contrast
Reconsideration

• How does this change the differential?

Differential Diagnosis

Infectious
- **Osteomyelitis**
  - Coccidioides, Histoplasmosis
- Septic Joint
- Toxic Synovitis
- Post-streptococcal

Trauma
- Ligamentous Injury
- Sprain / Strain
- Fracture

Oncologic
- Leukemia, Lymphoma

Hematologic
- **Hemarthrosis**
- Hemophilia
- **Platelet Disorder**
  - Von Willebrand 2B
  - Gray Platelet Syndrome
  - MYH-9 thrombocytopenia

Rheumatologic
- JIA, SLE
- **Chronic Recurrent Multifocal Osteomyelitis (CRMO)**

Metabolic

Immunologic
Clinical Course

Days 3-4
• I&D with purulent collection
• Pain improving

Day 5
• Bone Scan: negative for other lesions
• Infectious Disease consult for possible osteomyelitis
• Genetics consult for possible genetic/metabolic cause
• Bone marrow biopsy

Day 6
• PICC placed
• Cefazolin for total of 6 weeks

Working Diagnosis: Culture Negative Osteomyelitis
### Infectious:
- Brucella IgM/IgG
- Coccidioides
- Histoplasmosis
- HIV
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### Cardiac:
- Echo

### Immunologic:
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### Metabolic:
- Copper
- Ceruloplasmin
- Homocysteine
- Acid Beta-Glucosidase Low
- Two sequence variants in GBA gene

### Orthopedic:
- Knee XR x2
- LE Doppler x2
- Abd US x4: Splenomegaly
- Knee MRI: periosteal fluid collection

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**Gaucher Disease** *(1,2,4)*

- Autosomal recessive lysosomal storage disease
- Lack of beta-glucosidase / beta-glucocerebrosidase
- Sphingolipid catabolism pathway
  - Prevents breakdown of glucocerebroside within scavenger cells
  - Macrophages most affected
- Accumulation of glucocerebroside within cells > “Gaucher cell”
- Deposition of Gaucher cells
  - Liver, spleen, hematologic, skeletal systems
Orthopedic Complications

- Significant osteopenia
- Remodelling difficulties
  - Erlenmeyer Flask deformity
- Pathologic fractures
- Osteonecrosis
- Susceptibility to infection
  - Osteomyelitis
  - Septic arthritis
  - Wound infections
- Bone Crises

Bone Crises

- Nearly indistinguishable from osteomyelitis
- Distal femur / proximal tibia
- Labs, imaging often inconclusive
- Resolve with supportive care alone

Swelling
Tenderness
Fever
Tachycardia
Diaphoresis

10-32% of patients
Discussion

- Include Gaucher disease in the differential diagnosis of a child with multiple episodes of acute bone pain, particularly in the setting of cytopenias and/or hepatosplenomegaly.

- Acute bone crises can be mistaken for acute osteomyelitis and thus early recognition is prudent to potentially prevent unnecessary interventions and prolonged antibiotic treatment.

Discussion

- Enzyme replacement therapy has been shown to reverse and prevent systemic manifestations of Gaucher disease (1,4)

- Prompt identification and initiation of therapy is important for minimizing physical and emotional consequences of delayed diagnosis.
Patient Update

Started enzyme replacement therapy with VPRIV (Velaglucerase alfa) \(^{(1,4)}\)
- overcomes the block in the catabolic pathway
- clears the stored substrate, glucocerebroside
- reverses hematologic and liver/spleen involvement

No further hospitalizations for bone pain

Key References


Thank You!

- Dr. Daniel Egbeyong Baiyee, Kaiser Oakland Pathology
- Dr. Shaun Fitzgerald, Kaiser Oakland Pediatric Hospitalist Medicine