Chronic Recurrent Multifocal Osteomyelitis (CRMO)

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Anne Stevens, MD, PhD
12 yo M with left leg pain, normal ESR, CRP, no fever. Bone biopsy showed reactive changes, responded to naproxen.
What is CRMO?

- CRMO is an autoinflammatory, non-infectious bone disease with exacerbation and remission that mainly affects children.
- Diagnosed by excluding malignancy and infection. Often bone biopsy is required.
- Adult equivalent: SAPHO
  - synovitis, acne, pustulosis, hyperostosis, and osteitis
- Other names: CNO, NBO, DSO, Garre’s osteomyelitis

Demographic characteristics of CRMO

• Peak ages: 7 to 12 years
• F: M ratio: 2-4.
• Incidence rate:
  – 0.4 per 100, 000 children annually in Germany (Jansson 2011)
  – Similar rate as infectious osteomyelitis (Schnabel 2016).

Clinical presentations

• Local bone pain associated with warmth and/or swelling
• Insidious onset (+/- acutely worse
• Waxes and wanes
• Any bone of the body
• Most common
  – long bone metaphyses (LE<UE)
  – Clavicle
  – Mandible
  – vertebral bodies
  – pelvis

Kuijpers et al. 2011 Journal of Cranio-maxillo-facial surgery
Clinical presentations

- Symmetrical in 25-40%
- Associated with Palmar plantar psoriasis, psoriasis vulgaris, Sweet syndrome, severe acne, pyoderma gangrenosum, IBD, sclerosing cholangitis, ankylosing spondylitis.
Lab findings

- ESR, CRP and WBC: *most are normal*
- HLA-B27, RF, autoantibodies: *negative*
- ANA: may be positive - *low titer*
- Bacterial cultures, AFB culture, fungal cultures of bone biopsy: routinely negative.
  - Propionibacterium acnes, CONS, Haemophilus parainfluenzae and Actinomyces were seen in SAPHO
- PCR for eubacteria using 16S: negative (12 pts)

MRI versus X ray

MRI on 8-2005

X ray on 9-2005

X ray on 6-2008
MRI versus bone scan
MRI vs. bone scan
Sensitivity of detecting CNO lesions is much higher with MRI

<table>
<thead>
<tr>
<th></th>
<th>Bone scan</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic lesions detected</td>
<td>40/54 (74%)</td>
<td>53/54 (98%) *</td>
</tr>
<tr>
<td>Symmetrical lesions detected</td>
<td>71%</td>
<td>100% *</td>
</tr>
</tbody>
</table>

* P<0.01. N= 32 patients, 14 WB MRIs and 18 focused MRIs

Whole Body MRI
Seattle Children’s
Whole Body MRI Protocol

• Sequences:
  – Coronal STIR from head to toe
  – Sagittal STIR of entire spine
  – Optional: Axial STIR of pelvis and sagittal STIR of foot

• Contrast: not needed

• Duration: 45-60 mins

• Insurance: CPT code 76498
  – Back up option: MRI of total spine and bilateral lower extremity and other known area using separate codes
Bone scan or imaging (Radiographs of painful site(s), Whole-body MRI (T1, STIR, diffusion) looking for additional subclinical lesions +/- localized MRI (pelvic bones, spine...))

Suggestive clinical data
- Recurrent painful sites
- Episodes of mild fever
- Possible joint stiffness
- Possible mucocutaneous lesions

Suggestive biological data
- Normal blood count
- Inflammatory markers (ESR, CRP)

Atypical results
- Solitary lesion
  - Or multifocal atypical lesions → Biopsy

CRMO
- Multifocal lesions
  - Typical sites: metaphysis, physis, spine, pelvic bones, clavicle
  - Therapeutic test and follow-up

In general, a bone biopsy is necessary if there is a concern for cancer, infection or need for initiating immune suppressants.

The presence of typical clinical findings (bone pain +/- localised swelling without significant local or systemic features of inflammation or infection)

AND

The presence of typical radiological findings (plain x-ray: showing combination of lytic areas, sclerosis and new bone formation or preferably STIR MRI: showing bone marrow oedema +/- bone expansion, lytic areas and periosteal reaction)

AND EITHER

**Criterion 1:** more than one bone (or clavicle alone) without significantly raised CRP (CRP < 30 g/L).

OR

**Criterion 2:** if unifocal disease (other than clavicle), or CRP >30 g/L, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis) with no bacterial growth whilst not on antibiotic therapy.
Criteria - Enable Faster Dx?

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34 of 41 patients could have avoided biopsy

Another case

- 6 yo M with episodic knee pain and swelling
- Exam: no arthritis
- ESR 85, WBC 3.9, PLT 397, Hct 32.3, CRP 2, ANA negative. X ray normal
- CRP 15.9, ESR 111,
- Blasts 351 at 3rd CBC w/ diff
- Bone marrow---pre B cell ALL
Severe bone pain—Osteosarcoma
Biopsy is important!!
A dietary cause of CRMO

8 year old with joint pain
- Autism
- Eats only white food

Metaphyseal lines, beaks
A dietary cause of CRMO

8 year old with joint pain

MRI
- subperiosteal hematoma
- focal area of metaphyseal marrow edema, hemorrhage
A dietary cause of CRMO

SCURVY

- Developmentally delayed
- MSK symptoms present in 80%
- Radiograph: scurvy line (metaphyseal beaks)
- MRI may show subperiosteal hematoma, focal area of metaphyseal marrow edema d/t hemorrhage
Atypical forms of CRMO

CRMO rarely occurs before the age of 2

–DIRA: neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis
  • Response to anakinra
CRMO rarely occurs before the age of 2. Younger patients should be evaluated for deficiency of interleukin-1 receptor antagonist (DIRA) and Majeed syndrome.

- DIRA: neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis.
- Response to empirical treatment with anakinra
- Majeed syndrome: recurrent multifocal osteomyelitis, neutrophil dermatosis (sweet syndrome), dyserythropoietic anemia, LIPIN2 gene mutation
Imbalance of cytokine production

Scianaro Pediatr Rheumatol Online J. 2014
Imbalance of cytokine production

IL-10

TNF
IL-6

Osteoclast

Scianaro Pediatr Rheumatol Online J. 2014
Treatment Recommendations

NSAIDs (Naproxen)

No/incomplete remission

Corticosteroids + NSAIDs

No/incomplete remission

Corticosteroids + NSAIDs

No/incomplete remission

TNF-α inhibitors
Bisphosphonates
Sulfasalazine
MTX

Remission

Remission

Complicated/severe courses with structural damage

Christian Hedrich et al. 2013 PROJ
Complete Resolution with Naproxen Alone

3 months later
Non-NSAIDs Treatment (Survey of Pediatric Rheumatologists)

- Methotrexate, n = 73
- TNF inhibitor, n = 71
- Pamidronate or other bisphosphonates, n = 50
- Glucocorticoid, n = 32
- Sulfasalazine, n = 23
- Other DMARDs, n = 4
- Other, n = 4

Non-NSAIDs Treatment  
(Survey of Pediatric Rheumatologists)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number (n)</th>
</tr>
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<tbody>
<tr>
<td>Pathological fracture</td>
<td>55</td>
</tr>
<tr>
<td>Growth plate damage</td>
<td>48</td>
</tr>
<tr>
<td>Vertebrae involvement with or without compression fracture</td>
<td>48</td>
</tr>
<tr>
<td>Mandible involvement</td>
<td>28</td>
</tr>
<tr>
<td>Cranial bone involvement</td>
<td>16</td>
</tr>
<tr>
<td>Pelvic bone involvement</td>
<td>10</td>
</tr>
<tr>
<td>Any patient regardless of disease duration or involved bone locations</td>
<td>7</td>
</tr>
<tr>
<td>Clavicle involvement</td>
<td>6</td>
</tr>
<tr>
<td>Long bone involvement with normal growth plate</td>
<td>2</td>
</tr>
</tbody>
</table>

Refractory to NSAIDs treatment, $n = 102$
Treatment goals

• Alleviate pain
  – No pain ≠ no inflammation

• Reduce underlying inflammation
  – Repeat MRI may be necessary

• Prevent permanent skeletal damage
  – Aggressive therapy when sensitive sites are affected
  – Vertebral compression fracture
  – Growth plate damage
Long-term Prognosis

• 17 patients with WB MRI reevaluation 15 years after diagnosis
  – 8 clinically active, 9 inactive

• Twenty lesions in 10 patients were classified as radiologically active

Voit et al. 2015 J Rheum
Take home message

• Not all patients with bone edema on MRI have CRMO
• Bone biopsy under MRI guidance is important to rule out malignancy and infection.
• Whole body scan (bone scan or MRI) is necessary to identify all lesion sites.
• NSAID remains first-line therapy.
• TNF inhibitor and bisphosphonates effective in refractory cases.
• Long-term outcome is unknown.
Questions?

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