Chronic Recurrent Multifocal Osteomyelitis

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  - Children’s Miracle Network
  - Peregrine Charities
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  - Care for Kids Research Fund
- All treatment modalities are used off-label
Illustrative Case

• 6 years old developed:
  – Fevers to 104 ~once weekly
  – Knee pain without objective changes
  – WBC 14,000; Plt 495K, ESR 99
  – Poor weight gain

• Work up revealed osteomyelitis in the left distal femur
  – Blood cultures negative
  – Treated for osteomyelitis with prolonged antibiotics without improvement
Illustrative Case

- 1 yr later extensive rash
  - Scalp, ears
- Bilateral knee, wrist, ankle & vertebral osteomyelitis
- No GI work-up, no skin biopsy
- Poor weight gain (22 kg at age 11 yrs)

http://www.lib.uiowa.edu/HARDIN/MD/psoriasispictures.html
Diagnosis = CRMO
Chronic recurrent multifocal osteomyelitis

- Recurrent
- Multifocal
- Involvement long bones and vertebra
- Association with psoriasis

- Atypical = failure to thrive, marked elevation in ESR
- Parents refused GI evaluation
- Rx NSAIDs, methotrexate
CRMO

- Autoinflammatory ds
- Occurs 1° in children
- ~ 2:1 F:M
- Bone pain +/- fever
- Multifocal osteomyelitis
  - 2 to 18 sites
- Recurrent
- X-rays: osteolytic lesions surrounded by sclerosis
- Cultures negative
- No response to Abx
- No validated diagnostic criteria
CRMO vs Growing Pains

- Can mimic growing pains
- Overlapping ages
  - Avg age dx ~9 years CRMO
- Bone pain, worse in the evening
  - Often wakes from sleep
  - Lower extremities
- +/- fever
- Exam can be normal
- Labs can be normal
- X-rays can be normal

- FAMILY HISTORY
  - MRI with STIR of painful site
Variable Severity
Associated Inflammatory Conditions

- Pustulosis palmoplantaris ~ 30%
- Psoriasis: up to 20%
- Intestinal inflammation in ~ 10 %
  - Crohn > ulcerative colitis > celiac
- Pyoderma Gangrenosum
- Sweet syndrome
- Congenital dyserythropoietic anemia
- Generalized pustulosis
- Acne
- Arthritis
- Spondyloarthropathy
- Still disease
- Vasculitis (Takayasu, ANCA positive vasculitis)
- JDM
- Uveitis
Psoriasis

- Plaque
- Flexural
- Seborrheic
- Guttate
- Pustular
- PPP
- Nail psoriasis

Roberson and Bowcock, Trends Genet. 26: 415, 2010
Pustule biopsy: intraepidermal pustule with numerous neutrophilic granulocytes; parakeratotic keratin, and perivascular round cell infiltrate.

Inflammatory Bowel Disease

- Bognar in 1998
- Many reports since that time
- Crohn > UC > celiac

Bazrafshan et al. J Ped Surg 2000
CRMO: w/u

- Normal WBC to mildly ↑ WBC
- Normal or elevated ESR &/or CRP
- Histology
  - PMN or mixed or sclerosis
- Plain films
  - osteolytic or sclerotic
  - Long bones, clavicle, spine, pelvis, mandible, small bones feet/hands
- Whole body imaging
  - MRI [STIR] superior to bone scan
Imaging
Radiographic resolution

Cassidy, Petty, Laxer and Lindsley, Textbook of Pediatric Rheumatology
Corresponding bone scans

2002

2007
Treatment

- **Empiric**
  - No FDA approved medications

- **NSAIDs**

- **DMARDs**
  - Methotrexate, sulfasalazine, both

- **Cytokine blocker**
  - TNF blockers, IL-1 blockers

- **Bisphosphonates**
  - Pamidronate, others
Etiology

- Innate immune system disorder with a genetic basis
  - Sporadic CRMO – locus 18q
    - Reported sibs and parent-sib pairs
    - 1 or 2° relative with psoriasis, IBD in 50%
  - Canine model (HOD)
  - Murine cmo
  - Majeed syndrome
  - Infant onset CRMO with pustulosis
Branches of the immune system

**Innate immunity**
- Oldest branch
- 1\textsuperscript{st} line of defense
- Rapid and blunt
- Recognition of a limited number of molecular patterns
  - PAMPs
  - DAMPs

**Adaptive immunity**
- Sophisticated
- Capable of recognizing highly specific parts of pathogens
- Limitless repertoire
- Adapt to changes that a pathogen might make
- Has a memory
  - \(2\text{nd}\) response is faster
Branches of the immune system

Autoimmunity vs Autoinflammatory

• Autoimmunity
  – T cells, B cells & DC play prominent role
  – Loss of tolerance → reactivity to self antigens
  – Autoantibody production, self reactive T cells

• Autoinflammation
  – Relapsing and remitting bouts of systemic inflammation that is “seemingly unprovoked”
    • Cold, uric acid, silica, necrotic tissue, others
  – Absence of antigen specific T cells and in the absence of high titer autoantibodies
Hypertrophic Osteodystrophy (HOD)

- Large breed dogs
  - *Weimaraners*
  - *Irish Setters*

- Affects juveniles
  - 2 to 11 months of age

- Males > Females

- Clusters in litters and in breeds

- Gene defect unknown
Hypertrophic Osteodystrophy (HOD)

- Present with fever & ostalgia
- Warmth, swelling over site
- Pustulosis or IBD in some
- Osteolytic or sclerotic lesions
- Multifocal sterile osteomyelitis
  - Metaphyses of the long bones, vertebrae, mandible
  - Some lesions asymptomatic
- Treatment NSAIDs or corticosteroids
- Most resolve post-puberty
  - Some have persistent disease
Murine cmo
Murine cmo: autosomal recessive

Adapted from Ferguson et al. Bone 2006
Mutation in pstpip2
Exon 5: c.293T→C, L98P

Leucine to Proline at amino acid 98
Hematopoietic derived cells determine phenotype

Recipient

1100 Rads (split dose)

Irradiated mouse

Outcome at 3 months

Donor

T cell depleted bone marrow

<table>
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<tr>
<th>Donor</th>
<th>Recipient</th>
<th>N</th>
<th>Affected N (%)</th>
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<td>BALB/cByJ</td>
<td>cmo</td>
<td>5</td>
<td>0 (0)</td>
</tr>
</tbody>
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Phenotype independent of adaptive immune system

B6. Rag-/- × cmo
→
F1
→
F1

F2 cmo/cmo Rag -/-
• n = 9, 100% Affected
• Avg 48 days to 1st Sx

F2 cmo/cmo Rag +/-
• n = 9, 100% Affected
• Avg 46 days to 1st Sx
**pstpip2**

- Cytoskeletal associated protein
  - Regulation of actin-based cellular function
  - Important in cytoskeletal function in fission yeast

- Under- or over-expression in vitro
  - Changes in cell motility & phagocytic ability
  - Ability to rearrange the cytoskeleton to form filopodia, ruffles

- Expressed in monocytes, macrophages, Mac1+ granulocytes
Is cmo an IL-1 mediated disorder?
IL-1 receptor is required for disease
cmo mouse – Nlrp3 inflammasome independent disease

Cassel et al., PNAS. 2014
IL-1β driven bone inflammation is mediated via the neutrophil

Cassel et al., PNAS. 2014
cmo mice fed a high fat diet had normal paws and tails

Diet changes microbiome in cmo mouse

Majeed Syndrome

- Autosomal recessive
- Recurrent fevers
- Early onset CRMO
- Congenital dyserythropoietic anemia (CDA)
- Inflammatory dermatosis (Sweet syndrome)

Majeed et al., Eur J Pediatr 160:705
Majeed Syndrome insight into pathogenesis gained at the bedside

- 2 brothers
  - Recurrent fevers
  - pseudoparalysis (CRMO)
    - onset in 1\textsuperscript{st} year of life
  - anemia
- LPIN 2 = 2 bp deletion
- c.1316_1317delCT = p.Ser439Trpfs*15
Treatment with IL-1 inhibitors = marked improvement

- Siblings with Majeed (CRMO, CDA)
  - homozygous c.1312_1313delCT; L438fs+16X
Majeed Syndrome
Response to IL-1 blockade

Majeed Syndrome
IL-1 mediated disorder

- Identification of \textit{LPIN2} as causative gene
- IL-1$\beta$ specific blockade results in resolution of bone lesions and normalization of inflammatory markers
- Unclear of IL-1 blockade changes the dyserythropoiesis
- Can present as isolated CRMO
- Further evidence for the role of IL-1 in sterile osteomyelitis
Generalized pustulosis

- Generalized pustulosis and CRMO
- Early onset CRMO
- This patient with severe growth deformity & recurrent fractures

DIRA

- Neonatal onset
- Pustulosis
- Sterile multifocal osteomyelitis
- Marked acute phase response
- No improvement with antibiotics
- Improves with high dose steroids
- Empiric trial of anakinra → rapid and dramatic improvement
- Led to gene identification – international effort
DIRA : Cutaneous Manifestations
Photos from Raphaela Goldbach-Mansky
Radiographic findings
Genetics

- 6 families identified
- 9 affected children
- All parents are unaffected
- Pedigrees suggest autosomal recessive

Aksentijevich*, Masters*, Ferguson* et al. NEJM 360: 2426, 2009
Mutations in *IL1RN*

Aksentijevich\*, Masters\*, Ferguson\* et al. NEJM 360: 2426, 2009

chr2 (q13)

Break point

113434601 → 113609824
Deficiency of IL-1 Receptor Antagonist (DIRA)

Response to Anakinra (IL-1Ra)

Improved laboratory studies with Rx
Translation of this basic research

- Murine and 2 monogenic human autoinflammatory bone disorders involve dysregulation of IL-1 pathway homeostasis.

- Is there a role for IL-1 inhibitors in the treatment of non-syndromic CRMO?

- Traditional treatment: NSAIDs, DMARD, TNF inhibition, bisphosphonates.
Stills & CRMO: Treatment with anakinra
After treatment failure with Pamidronate

10 months after 100 mg anakinra subcutaneously
[Rash, fever resolved within 24 hours of initiation of treatment]

Summary

• Scientific evidence points to the IL-1 pathway as the therapeutic target of choice for sterile bone inflammation
  – Yet there is limited information about response to IL-1 inhibitors in non-syndromic forms of CRMO

• Diet may play an important role in osteomyelitis
  – Important finding needs to be reproduced
  – Identification of the dietary component responsible for protecting the cmo mice needs to be identified

• Understanding the genetic basis of CRMO will likely shed light on the pathogenesis on its associated disorders (psoriasis, IBD, vasculitis, etc…)
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