“Fever in the morning; Fever all through the night”

A case of persistent fevers

Allison Buttarazzi, PGY 3
ACP Conference 2015
September 26, 2015
Case: HPI - 47yo Somali female

• HPI: January 20, 2015: Emergency department follow up visit in clinic
  • Fevers, chills, and malaise
    • Worsening for the last 12 days
    • No sick contacts or recent travel
    • Associated nausea and vomiting
    • “Achy joints” - wrists, hands, knees

• ROS:
  • Decreased appetite, but no weight loss
  • No HA, sore throat, nasal congestion, or rhinorrhea
  • No SOB or cough
  • No abdominal pain or diarrhea
  • Intermittent rash
Case: Further History...

- **1/12/15: Clinic visit - CC: Fever**
  4 days of fever, no cough or SOB, diffuse joint aches
  T38, tender LAD, no joint swelling, “reddish flushed forearms”
  Treated for strep throat with azithromycin (culture negative)

- **1/14/15: ED visit - CC: Fever, myalgias**
  6 days of fever, chills, nausea, myalgias, rash
  T39.3, diffuse tenderness, diffuse maculopapular rash
  WBC 15.5, CXR wnl, BCx (negative), flu swab (negative)
  Presumed flu, sent home, encouraged supportive care

- **1/16/15: ED visit - CC: Fever**
  8d fever, rash during febrile episodes, fatigue, myalgias, arthralgias
  T39.3, HR106, cervical adenopathy, mild blanching erythema
  WBC 21.7, elev LFTs, CT Neck wnl, U/A - occ. RBCs, BCx, Anaplasma/babesia, Monospot
  Presumed viral process, sent home, encouraged supportive care
Case: Past History

- **PMH**
  - Dyshydrotic eczema
  - Left wrist pain

- **PSH**
  - None

- **Medications**
  - Triamcinolone ointment
  - Hydroxyzine PRN for itching

- **Allergies**
  - Amoxicillin - rash

- **Social History**
Case: Physical Exam

Vitals: T37.7, HR 91, BP 120/78, RR 20
General: appears uncomfortable, develops rigors during visit
HEENT: TM normal, oropharynx slightly dry but no erythema or exudate
CV: Slightly tachycardic, regular rhythm, no murmurs
Resp: Clear to auscultation bilaterally
Abd: soft, NT, ND
MSK: limited ROM of wrists, knees, elbows, fingers due to pain, no synovitis noted, joints diffusely tender to palpation
Skin: faint sandpaper like rash on forearms and lower legs
Differential Diagnosis

- Occult bacterial infection: Endocarditis, Abscess
- Acute viral: HIV, hepatitis, parvovirus
- Lymphoma, leukemia
- RA, SLE, polymyositis
- Adult onset Still’s disease
- Vasculitis
PMNs - 88%
Lymph - 8%
Mono - 1%
Eos - 1%
Metamyelos - 2%

ESR - 112
CRP 234.5mg/L

134  95  12  128
Alk Phos - 140
AST - 94
ALT - 109
LDH - 291
**Case: Labs**

**HIV - neg**
Parvovirus - +IgG, -IgM
CMV - +IgG, -IgM
EBV - past infxn
HBV - cleared past infxn
HCV - neg
ASO - neg

**RF - neg**
CCP Ab - n1
C3 - 208
C4 - 36.7
ANA - 1:80

**Ferritin 12,950**
Iron - 52
TIBC - 172
Percent sat - 30%

**CT Abd/Pelvis:** Numerous scars in both kidneys consistent most likely with pyelonephritis. There is no current evidence of active pyelonephritis, however, and the bladder and intra and extrarenal portions of the collecting system appear normal. **No CT explanation for fever.**
Case: Follow-up

- Seen by rheum as in-patient, thought AOSD
  4 major, 4 minor Yamaguchi criteria

- Started on weekly actemra (tocilizumab) and steroids

- Currently in remission
  Fevers, rash, joint pain - resolved
  CRP <0.5mg/dL, ESR 2, ferritin 25
  Actemra - weaning dose (4mg/kg), frequency (every other month)
  Prednisone d/c'd
Adult Onset Still’s Disease
Features & Diagnosis
Features of Still’s Disease

**Signs/Symptoms**

Fever (60-100%):
- daily spikes 1-2x/d

Joint complaints (70-100%):
- mild, transient
- wrists, ankles, knees

Evanescent rash (60-80%)
- macular or maculopapular
- associated with fever spikes
- limbs and trunk

Sore throat (70%): early symptom

Other:
- myalgia (45%), LAD (50%), splenomegaly (40%), hepatomegaly (30%), pleurisy (21%), pericarditis (16%), weight loss (27%), abdominal pain (18%)

**Lab Findings**

Neutrophilic leukocytosis (80%)
- >80% PMNs

Elevated ferritin (60-94%)
- 5x normal value suggestive (41-46% spec)
- Decreased glycosylated ferritin, <20%

Elevated aminotransferases (65%)
- mild to moderate elev

Elevated ESR/CRP (90-100%)

Anemia (50%)

Thrombocytosis (26%)
Rash
Figure 4 $^{18}$F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) images at diagnosis and after steroid and tocilizumab treatment in a patient with adult-onset Still's disease (AOSD). (A1, B1, and C1) Marked FDG accumulation was observed in the bone marrow, spleen, and multiple lymph nodes at diagnosis. (A2, B2, and C2) After treatment, FDG uptake decreased in these sites - bone marrow, from $\text{SUV}_{\text{max}} = 4.02$ (A1) to 2.50 (A2); spleen, from $\text{SUV}_{\text{max}} = 6.05$ (A1 and C1) to 4.38 (A2 and C2) - as well as in multiple lymph nodes, including in the axilla, mediastinum, hilar region of the lung, hilar region of the liver, and para-aortic region (B1/C1 → B2/C2). SUV, standardized uptake value.
**Phenotypes**

- **Systemic**
  - Highly symptomatic
  - Fevers
  - Systemic
  - Cyclic
  - Mono: single, self limited episode
  - Poly: multiple flares
  - Remissions 2wks to 2 years

- **Indolent**
  - Arthritis
  - Less systemic
  - Persistently active
Diagnostic Criteria

Yamaguchi (sens 78.6%)
>= 5 criteria, 2+ major

Major
- Fever >39 for 1 week or longer
- Arthralgia/arthritus, 2 wks or longer
- Rash
- Leukocytosis >10,000, >80%PMNs

Minor
- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Elevated LFTs
- Negative ANA and RF

Fautrel's (sens 80.6%, 98.5% spec)
>= 4 major OR 3 major and 2 minor

Major
- Spiking fever >39
- Arthralgia
- Transient erythema
- Pharyngitis
- PMN > 80%
- Glycosylated ferritin < 20%

Minor
- Maculopapular rash
- Leukocytosis > 10,000
Natural History

Etiology unclear

Infection as trigger

Malignancy (recent study described 28 cases of AOSD like disease associated with malignancy)

Median age: 36 years

Duration to diagnosis - variable

Mean: 21 months (Colina)

Median: 3 months (range: 0.5 to 84 months) (Pay)

Median: 4 months (range: 0 to 312 months) (Gerfaud-Valentin)
Pathophysiology & Management
Pathophysiology

IL-18 and IL-1β

Dysregulation of NK cells

Macrophage activation

Macrophage & neutrophil activation

“Hallmark” of AOSD

IL-6

cause fever and rash
Management

NSAIDs: high dose, poor control of sx

Glucocorticoids: 0.5-1mg/kg/day, quick response, good control of sx

DMARDs (MTX, etc)

IVIG

Biologics

TNFα blockers - useful in chronic, indolent phenotype, remission 25%

Etanercept

Infliximab
Non-steroidal anti-inflammatory drugs (indomethacin) during diagnostic workup

Confirmed AOSD (Yamagushi and Fautrel criteria could be helpful)

Corticosteroids 0.8 - 1 mg/kg/day

Steroid-sparing treatment: Methotrexate 7.5 - 20 mg/week
To consider early when patients show:
- the first signs of steroid-dependence
- predictive factors for steroid-dependence (young age, splenomegaly, very low glycosylated ferritin, large increase in erythrocyte sedimentation rate)

Refractory AOSD

Chronic arthritis
Predictive factors: initial polyarthritis, erosive arthritis
- TNFα-blockers (prefer infliximab) or tocilizumab
- Anakinra if systemic flares

Systemic AOSD
Predictive factors: fever>39.5°C at onset
- Anakinra
- then consider tocilizumab, multiple daily anakinra or long-acting IL-1 antagonists (zanakinumab, rilonacept)

Complicated AOSD
- Intravenous steroids
- Intravenous immunoglobulins
- Anakinra
- cyclophosphamide, cyclosporine, plasmatic exchanges (for thrombotic microangiopathy), etoposide (in rare cases of severe and

Fig. 2. Proposal for a therapeutic strategy in adult-onset Still’s disease.
Complications

Reactive hemophagocytic lymphohistiocystosis (macrophage activation syndrome)

- pancytopenia, liver insufficiency, coagulopathy - DIC, CNS dysfunction

Myocarditis, tamponade, constrictive pericarditis, endocarditis

Shock, multiorgan failure

ARDS, intraalveolar hemorrhage

DIC, thrombotic microangiopathy

Fulminant hepatitis
Hyperferritinemia

Increased metabolism, tissue damage

- infection, inflammation, neoplasm

“Hyperferritinemic Syndrome”

- Adult onset Still’s, RHL, Antiphospholipid syndrome, and septic shock
- Similar signs and symptoms, lab findings, very elevated ferritin
- Very elevated ferritin → cytokine storm

Acute phase reactant - ?causative role in inflammation

- Removal of ferritin → improvement of condition?
Summary

Features:

Fevers, joint pains, rash
Leukocytosis, elevated LFTs, very elevated ferritin

Diagnosis:

Yamaguchi or Fautrel diagnostic criteria
Rule out alternative diagnoses

Pathophysiology

Upregulation of IL-18 and IL-1β, secretion of IL-6


