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

A case of persistent fevers

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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 ezcema
  - Left wrist pain
- PSH
  - None
- Medications
  - Triamcinolone ointment
  - Hydroxyzine PRN for itching
- Allergies
  - Amoxicillin - rash
- Social History
  - Lives with husband, 3 children. Immigrated in 2009. Works as home health aid. Denies tobacco, alcohol, or illicit drugs

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

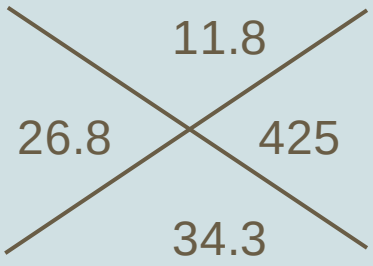
MSK: limited ROM of wrists, knees, elbows, fingers due to pain, no synovitis noted, joints diffusely tender to palpation

Skin: faint sandpaper like rash on forearms and lower legs

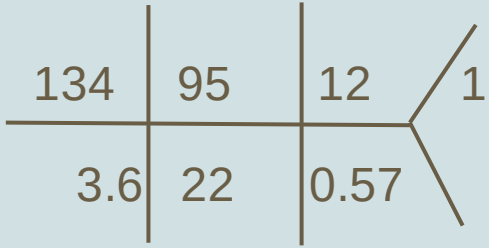
Differential Diagnosis

- Occult bacterial infection: Endocarditis, Abscess
- Acute viral: HIV, hepatitis, parvovirus
- Lymphoma, leukemia
- RA, SLE, polymyositis
- Adult onset Still's disease
- Vasculitis

Case: Labs



PMNs- 88%
Lymph - 8%
Mono - 1%
Eos - 1%
Metamyelos - 2%



Alk Phos - 140
AST - 94
ALT - 109
LDH - 291

ESR - 112

CRP 234.5mg/L

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 - nl
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%

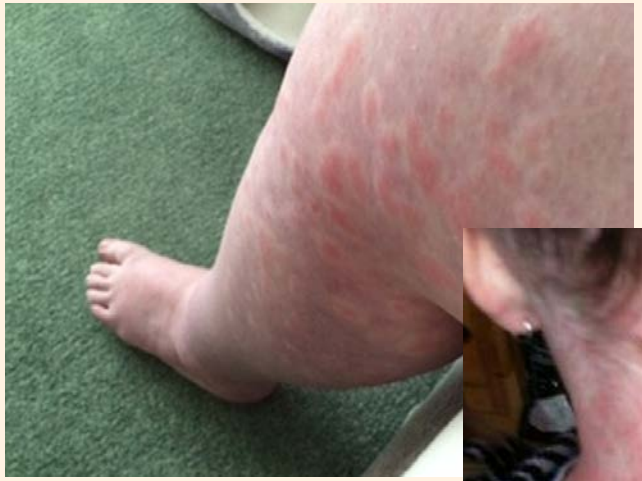
Elevated aminotransferases (65%)
- mild to moderate elev

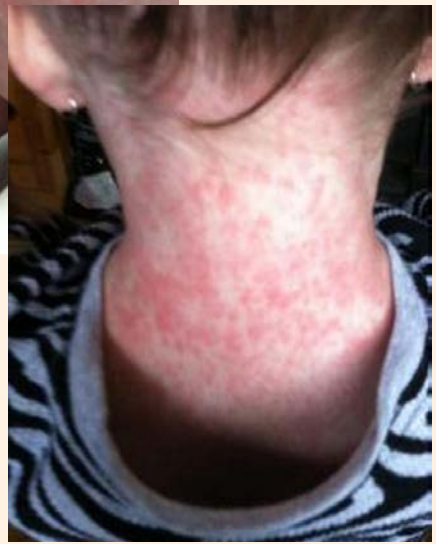
Elevated ESR/CRP (90-100%)

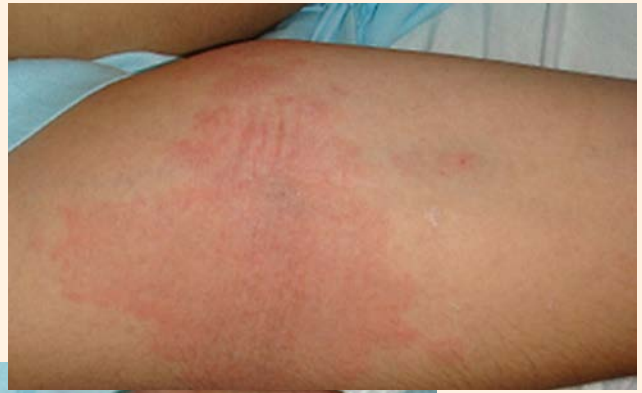
Anemia (50%)

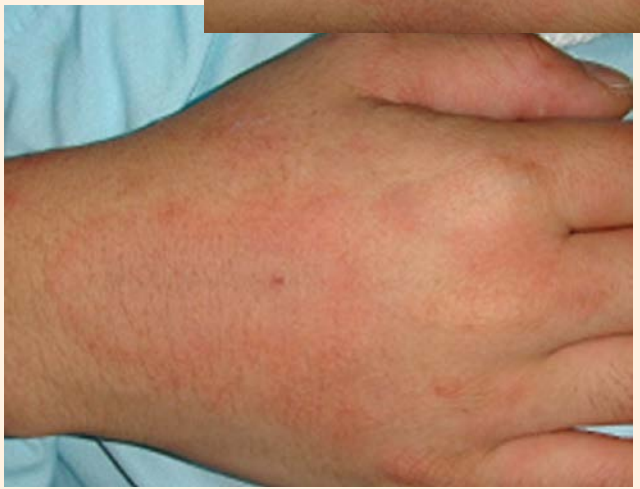
Thrombocytosis (26%)

Rash









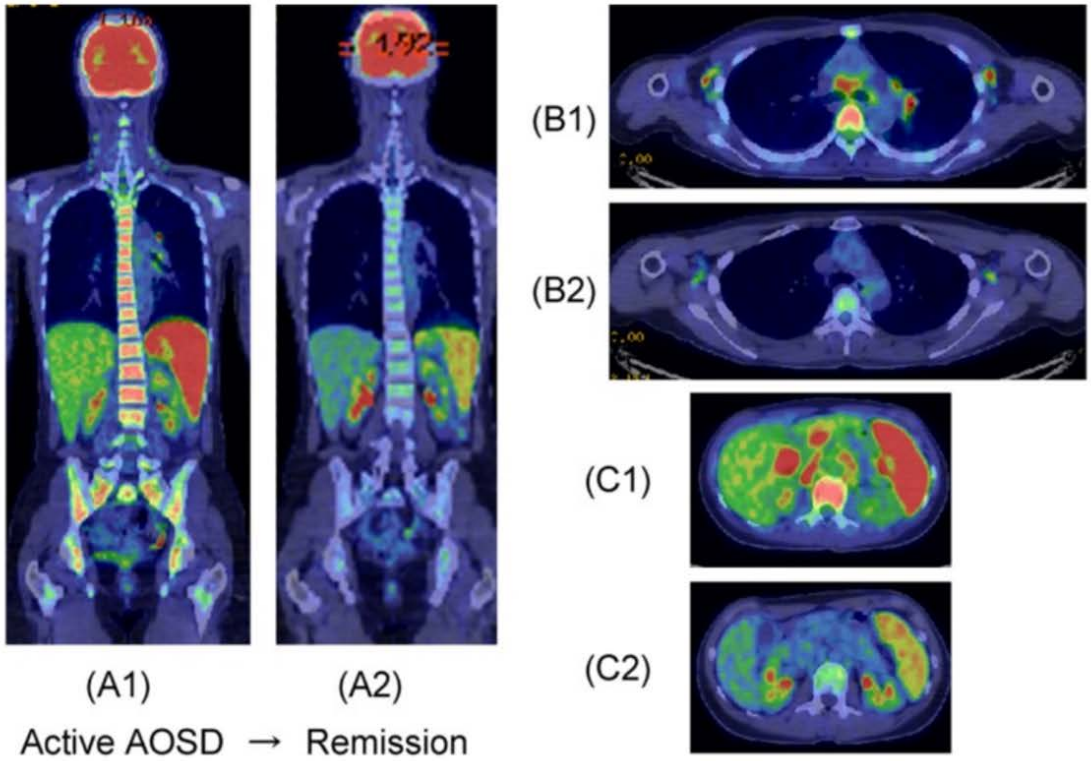


Figure 4 ^{18} **F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) images at diagnosis and after steroid and tocilizumab treatment in a patient with adult-onset Still's disease (AOSD).** (A1, B1, and C1) Marked FDG accumulation was observed in the bone marrow, spleen, and multiple lymph nodes at diagnosis. (A2, B2, and C2) After treatment, FDG uptake decreased in these sites - bone marrow, from $SUV_{max} = 4.02$ (A1) to 2.50 (A2); spleen, from $SUV_{max} = 6.05$ (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/arthritis, 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
- Leukocyotosis > 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

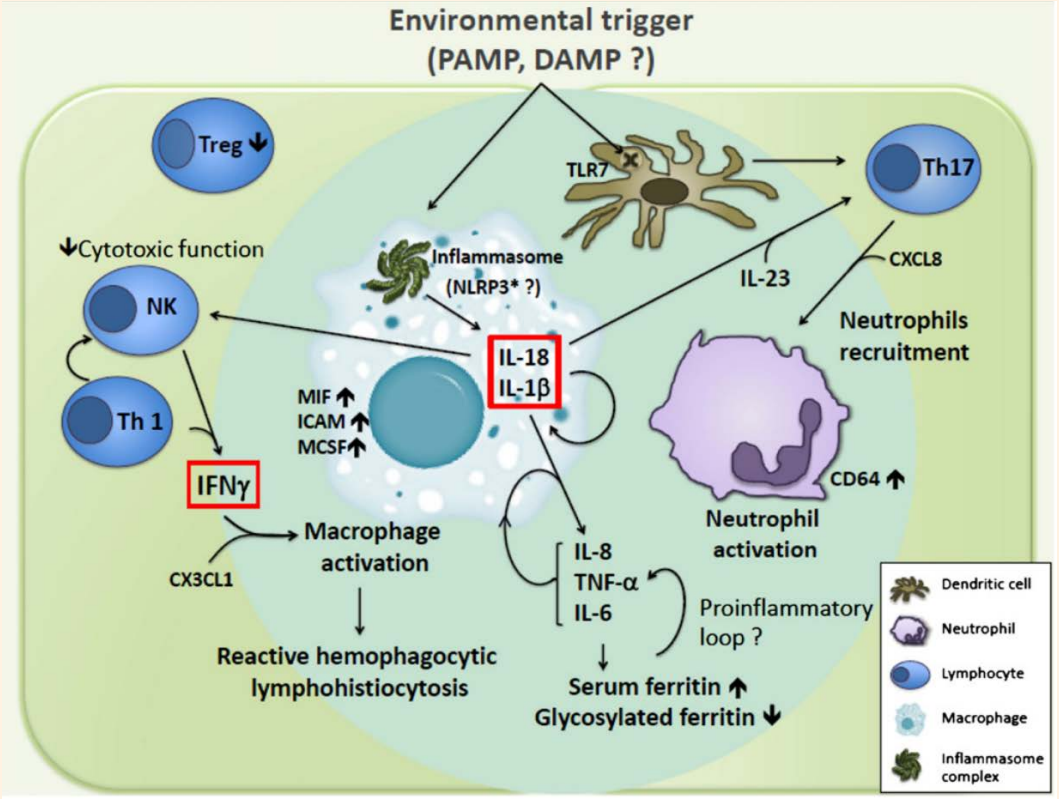
Macrophage activation

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

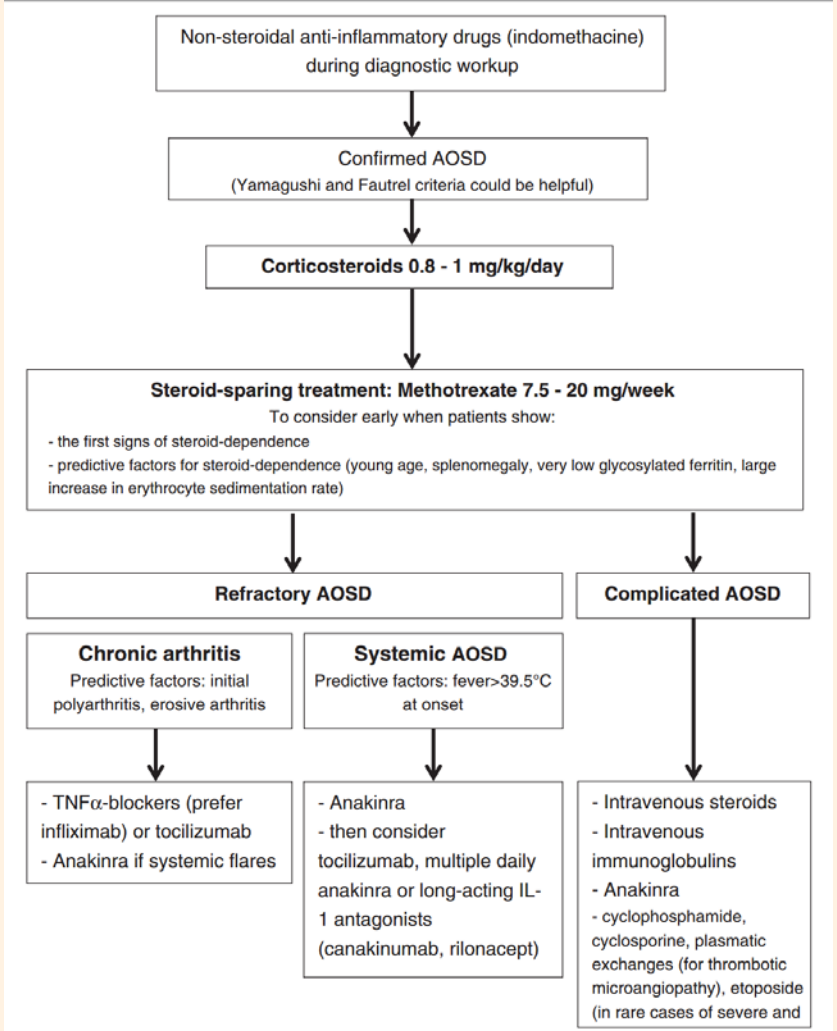


Fig. 2. Proposal for a therapeutic strategy in adult-onset Still's disease.

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

References

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