ZEBRAS AMONG HORSES:
RECOGNIZING MEDICATION ADVERSE REACTION

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Heuristic decision making

"When you hear hoofbeats, think of horses not zebras".

~ Dr. Theodore Woodward, professor at the University of Maryland School of Medicine in 1940s
Overview

- Case Presentation
  - History, Physical & Data
- Build a Differential Diagnosis
- Additional test results and data
- Update our Differential Diagnosis
- Clinical Pearls
Case Presentation

- **Mr. F. D. - 50 y/o man**
- **Setting**
  - PCP office, being transferred to Emergency Department / Hospital admission
- **Chief Complaint**
  - Fever, malaise, fatigue, diffuse body aches and dyspnea for 1 week
Recent History & HPI

- Last 2 years – Swelling of wrist and ankles, tendonopathy and polyarthralgia.
- Imaging studies:
  - MR of the right shoulder, MR left knee, XR pelvis, XR left wrist and XR right ankle – Degenerative arthropathy
  - MR of the left wrist - synovitis
- PCP referred to rheumatologist
  - ANA + (no titer reported) with elevated anti-RNP
  - Negative: HLAB27, RF anti-CCP and normal CRP.
- Patient used ibuprofen 800mg TID PRN with mild symptomatic relief, and was started on sulfasalazine DR 500mg daily, up titrating gradually every 3-5 days to 500mg BID to 1000mg BID for seronegative spondyloarthritis.
History of Present Illness

4 weeks ago
- Sulfasalazine initiated, 500mg – 1000mg/d

3 weeks ago
- Began to experience “flu-like” symptoms, fevers 102, malaise, diffuse body aches, fatigue, dyspnea and occasional chest palpitations.
- Held sulfasalazine for a week with resolution of symptoms.

1 week ago
- Restarted sulfasalazine for a day
- Recurrence of his previous symptoms with increased malaise, myalgias and exertional dyspnea lasting for a week with bed rest the first four days.

Patient then presented to PCP office for evaluation
Other Clinical History

- **Past Medical History**
  - Anxiety, insomnia, migraine, seronegative spondyloarthropathy

- **Past Surgical History**
  - Right rotator cuff surgery, 2 years ago

- **Medications**
  - Buspirone 10mg BID, quetiapine 50mg qHS, sumatriptan 25mg PRN, Ibuprofen PRN and sulfasalazine 500mg.

- **No Known allergies**
Family and Social History

- **FH:**
  - Father - CV disease and stroke

- **SH:**
  - Non smoker
  - Glass of wine with dinner – none in last week
  - No illicit drug use
  - Married, monogamous relationship and owns a bagel store.
  - Exercise ~30min everyday
Physical Exam

- **VS:** 36.8 °C, Pulse 77, BP 113/76, **RR 20** with O2 97%.
- Appears stated age, **mild distress**.
- Lungs were clear to auscultation bilaterally.
- Cardiac examination showed normal rate and regular rhythm **with systolic murmur, grade 2/6, heard lower left sternal border**. No JVD. No edema in extremities.
- Musculoskeletal examination was unremarkable for joint swelling or synovitis.
- Skin examination negative rashes or lesions.
Data

- Na 138, K 4, Cl 102, Bicarb 23, BUN 14, Creatinine 1.02, Glucose 98, Calcium 8.8,
- Albumin 3.3, Bilirubin 0.5, AST 33, ALT 32
- Troponin T 3.93
- Cholesterol 156, TG 77, HDL 34, LDL 107
- PT 36
- ESR 55 and CRP 46.5.
Differential Diagnosis

- ???
Echocardiogram
Management

Medications:
- Aspirin 81mg
- Clopidogrel load 600mg
- Atorvastatin 80mg
- Heparin gtt
Coronary Catheterization

Moderate coronary artery disease involving right coronary artery and proximal left anterior descending artery, coronary artery dissection in circumflex artery and right coronary artery demonstrating signs of healed dissection versus vasculitis changes.
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Cardiac MRI
Cardiac MRI
Cardiac MRI
Cardiac MRI

Microvascular transmural infarction

Epicardial surface at the junction of anteroseptal and inferoseptal segment at basal level, anterior mid-cavity level and anteriorly along with subtle subendocardial enhancement of the anteroseptal segment at the mid cavity level
Cardiac MRI
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Cardiac MRI
Cardiac MRI
Cardiac MRI
Cardiac MRI
Cardiac MRI
Endomyocardial Biopsy
Management

- CT Chest Abdomen Pelvis
  - Bilateral PE and ?Renal infarction
  - Started on warfarin
Hypercoaguable Work Up

- Repeat ANA (-) but RNP (+)
- SPEP - ↑ CRP and alpha-2 zone suggesting a reactive process.
- G20210A mutation in prothrombin gene and Factor V R506Q (Leiden) mutation – (-).
- Mildly high cardiolipin antibody IgM 14.0 (normal ≤12 MPL) with (-) cardiolipin antibody IgG and IgA
Diagnosis

- Sulfasalazine induced myocarditis with coronary vasculitis vs spontaneous coronary artery dissection
Myocarditis

- Inflammation of the myocardium
- 1-10 cases per 100,000
- WHO/ISFC: Diagnosis by established histological (Dallas criteria), immunological, and immunohistochemical criteria
- Most patients do not undergo endomyocardial biopsy
  - Heart failure in combination with acute disease (<2 weeks, class I) or LV dilatation (<3 months, class I).
  - Positive RV biopsy 0-80%
- Cardiac MRI
  - Inflammatory hyperemia and edema, necrosis/scar, contractile dysfunction, and accompanying pericardial effusion
Signs and Symptoms

- **Mild symptoms:**
  - Fever, sweats, chills, dyspnea, flu-like illness

- **Other symptoms:**
  - Arthralgia, malaise or pharyngitis, tonsillitis or upper respiratory tract infection
  - Palpitations, syncope, AV block
  - Heart failure & Arrhythmia
    - Rapidly progressive/fatal
Classification of Myocarditis by Etiology

Infection
- Viral
  - (Coxsackie B), erythroviruses (Parvovirus B19), adenoviruses, herpes and HIV
- Bacterial
  - C.diphtheriae, Staph. aureus, Bor. burgdorferi, and Ehrlichia species
- Protozoal
  - Trypanosoma cruzi
- Parasitic
  - Babesia, Schistosomiasis and Larva migrans

Autoimmune
- Churg-Strauss
  - Inflammatory bowel disease
  - Giant cell myocarditis
  - Diabetes mellitus
  - Sarcoidosis
  - Systemic lupus erythematosus
  - Thyrotoxicosis
  - Takayasu’s arteritis
  - Wegener’s granulomatosis

Others
- Toxins
  - Alcohol, radiation, chemicals (hydrocarbons and arsenic).
- Drugs
  - Eg, doxorubicin, cocaine, IL-2
- Hypersensitivity
  - Sulphonamides and penicillins, digoxin, tricyclic antidepressants, dobutamine.
Unique Presentations

- **Acute rheumatic fever**
  - Usually affects heart in 50-90%; associated signs, such as erythema marginatum, polyarthritis, chorea, subcutaneous nodules (Jones criteria)

- **Giant cell myocarditis**
  - Sustained ventricular tachycardia in rapidly progressive heart failure

- **Sarcoid myocarditis**
  - Lymphadenopathy, also with arrhythmias, sarcoid involvement in other organs (up to 70%)

- **Peripartum cardiomyopathy**
  - Heart failure developing in the last month of pregnancy or within 5 months following delivery

- **Hypersensitive/eosinophilic myocarditis**
  - Pruritic maculopapular rash, history of using offending drug
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Eosinophilic myocarditis

- Presence of infiltrates rich in macrophages and eosinophils
- Myocyte necrosis is usually absent, and scattered poorly formed granulomas can be seen.
- Cardiac function may improve or normalize when the offending drug is withheld
Sulfasalazine

- Sulfapyridine
- Mesalazine

- Sulfa drug class
- Combination of salicylate and sulfa antibiotic / sulfonamide by Azole bond
Sulfasalazine

Arachidonic acid metabolites

IL-1 TNF

NFκB

Leukocyte chemotaxis

SASP/5-ASA

Apoptosis induction

Activation of PPAR-γ and its expression

Reactive oxygen scavenger
Sulfasalazine

- Rheumatoid arthritis 70s years ago
- Juvenile idiopathic arthritis
- Ankylosing spondylitis
- Psoriatic arthritis
- Ulcerative colitis
Sulfasalazine –
Common Side Effects

- Nausea
- Abdominal discomfort (improve over time)
- Mouth sores, itching, liver function abn, pulmonary problems
  - Folate supplementation recommended
- Photosensitivity
- Rare: agranulocytosis, hypospermia, case reports - myocarditis
Sulfasalazine/Mesalamine induced Myocarditis & Coronary Vasculitis

- Literature Review 1980: Mesalamine and its prodrug (Sulfasalazine and Balsalazide)
- Indication
  - UC, seronegative and seropositive spondyloarthritis
- ~20 cases of mesalamine cardiac toxicity reported in Pubmed
- ~30 adverse events reported to FDA (FAERS)
Cardiotoxicity Mechanism

- Unclear
- Hypersensitivity reaction rather than a cytotoxic effect.
- Humoral-mediated hypersensitivity in which antibodies formed against mesalamine cross-react with cardiac tissue causing inflammation.
- Most cases of mesalamine-induced cardiovascular toxicity occur 2–4 weeks after the initial exposure to the drug, although presentation may be delayed in the setting of concomitant steroid administration.
- Resolution of symptoms generally occurs within one week of drug discontinuation.
Drug induced myocarditis - Prognosis

- Varied presentation
  - Improvement post discontinuation of drug
  - Gradual progression to heart failure
  - Fulminant heart failure
Spontaneous Coronary Artery Dissection

- Younger, Peripartum woman
- Connective tissue disorders
- Vasculitidies
- Exercise
An Unfinished Story...

- 1.5 months later
  - Normal echocardiogram, no wall motion abnormalities and normal EF
- 2 months later
  - Exercise stress test 12mins, normal
- 4.5 months later
  - Warfarin discontinued (Indication: PE)
- 5 months later
  - Dyspnea, Chest discomfort, repeat echo with global hypokinesis and mobile apical thrombus
  - Repeat diagnostic cath with mild-mod non obstructive CAD, no dissection noted
An Unfinished Story...

- 5 months later
  - Restarted warfarin therapy
- 8 months later
  - Echocardiogram - Normal LV function, Inferior wall hypokinesis, No clot in LA
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References

Cardiac Magnetic Resonance Assessment of Myocarditis. http://circimaging.ahajournals.org/content/6/5/833.full#T1
Summary Points & Questions

- Sulfasalazine, mesalamine-derivative, associated with rare cardiac adverse effect – myocarditis, vasculitis.