Rheumatic Manifestations of Sarcoidosis
Learning Objectives

• Identify the common and uncommon presentations of sarcoidosis
• Describe the appropriate evaluation for a patient with suspected sarcoidosis
• Discuss the existing treatments for patients with sarcoidosis
Historical Perspective

Sir Jonathan Hutchinson

John W., 1869

In 1899, Dr. Caesar Boeck called this condition “sarkoid” since the skin lesions resembled benign tumors (sarcomas).

From Greek:
- *sarco* = “flesh”
- *eidos* = “like”
- *osis* = “condition”

Dr. Caesar Boeck
Sarcoidosis

• Disease of unknown etiology
• Characterized by noncaseating granulomas in two or more organs
• Other causes of granulomas are excluded

Am J Respir Crit Care Med 160: 736, 1999
The Great Imitator
Case

• LG, 56yo Hispanic male, transferred from OSH for increasing bilateral LE weakness and falling for past 6 months.
• PMH: Dx of progressive multiple sclerosis x 4 yrs with LE> UE weakness and neurogenic bladder. Nonsmoker
• Labs:
  – CBC: Hct 37, WBC 5000, plts 349,000
  – CMP: normal except albumin 3.2
  – TSH, CPK, phos, Mg: normal
  – U/A: + blood, + WBCs, no casts (catheter)
Case

- Labs:
  - ANA: 1:160 neg profile; RF: neg
  - RPR: negative; HIV: negative
  - Vitamin B12: nl, folate: nl
  - 1,25OH Vitamin D: 29 pg/ml (nl 15-75)
  - ACE level: 41 U/L (nl 9-67)
  - SPEP: mild polyclonal gammopathy
  - CSF:
    - Cell count: 104 (88% lymphs, 12% monos). Neg cytology
    - Protein: 426 (nl 15-45); Glucose: 13 (nl 40-80)
    - Immune studies: IgG index: 1.04 (nl 0.28-0.66)
      Q albumin: 63 (nl 0-9)
      Oligoclonal bands: 5
      IgG synthesis rate: 263 (nl 0-8)

- CXR: normal
- Brain MRI: Basilar predominant leptomeningeal enhancement c/w carcinomatous meningitis
Brain MRI

C-spine MRI
Which one of the following would you do now?

A. Ophthalmologic examination
B. CT scan of lung
C. ACE level on cerebrospinal fluid
D. Brain biopsy
E. Bone marrow biopsy
Sarcoidosis: Epidemiology

- **Age**
  - Age 20-40 yrs: 70% of cases
  - Second peak in women > 50 yrs
  - All ages (including children) can be affected

- **Sex**
  - Females more than males (2:1)

- **Familial clustering (genetics):** 5-19%

- **Seasonal clustering (April-June)-infectious causes**

- **Occupational clustering- environmental exposures**

Sarcoidosis: Epidemiology

- Worldwide: prevalence varies by race and ethnicity:
  - <10/100,000: Spain, Portugal, India, China, Brazil
  - 20-40/100,000: Holland, Norway, Germany
  - >50/100,000: Denmark, Sweden

- United States prevalence
  - 10-20/100,000: U.S. Caucasians
  - 20-30/100,000: U.S. Puerto Ricans
  - >30/100,000: U.S. African-Americans

- U.S. incidence 3x higher for AA than whites with lifetime risk 2.4% for AA and 0.85% for whites
  - Onset 10 yrs earlier in AA than white patients

A Case Controlled Etiologic Study of Sarcoidosis (ACCESS)

- NIH-sponsored multicenter (ten clinical centers) trial
  - Patients enrolled between 1996-1999
    - 736 newly diagnosed patients
    - 706 community controls
  - Standard case definition with recent tissue biopsy confirmation
  - Etiology, genetics, clinical characteristics, and short term prognosis

Organ involvement defined early in disease. Only 23% recruit additional organ involvement during the first 2 years of follow-up.

**Clinical Manifestations**

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Presenting</th>
<th>Cumulative</th>
<th>ACCESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver/spleen*</td>
<td>4%</td>
<td>5-20%</td>
<td>12/7%</td>
</tr>
<tr>
<td>Neuro</td>
<td>1</td>
<td>5-10</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac*</td>
<td>1</td>
<td>5-10</td>
<td>2</td>
</tr>
<tr>
<td>Muscle*</td>
<td>1</td>
<td>1-5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ENT/Salivary</td>
<td>1</td>
<td>6</td>
<td>3/4</td>
</tr>
<tr>
<td>BM/Calcium</td>
<td>&lt;1</td>
<td>10</td>
<td>4/4</td>
</tr>
<tr>
<td>Renal</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*At autopsy, 20-25% have heart involvement; on biopsy 50-80% have muscle and liver involvement*

Clinical Manifestations

• **Race**
  - Caucasian: Lofgren’s, E. Nodosum, calcium, less severe disease
  - Puerto Rican: Lupus pernio
  - Japanese: cardiac, eye
  - African-American: more severe and widespread disease, increased mortality

• **Sex**
  - Female: Lofgren’s, E. Nodosum, eye, neurologic
  - Male: abnormal calcium metabolism, ankle arthritis

• **Age**
  - Under age 40: adenopathy
  - Over age 40: calcium, constitutional sx (esp>age 70)
Classification and Onset

- Asymptomatic (5%)
- Acute sarcoidosis +/- erythema nodosum (1-20%)
- Subacute/chronic onset (75-90%)
  - Pulmonary sarcoidosis predominant (70%)
    - Intermediate: < 2yrs of pulmonary sx
    - Chronic: > 2 yrs of pulmonary sx
    - At least 50% have or will develop extrapulmonary dz
  - Dominant extrapulmonary sarcoidosis (30%)
    - Overall < 2-5% have only isolated extrathoracic sarcoidosis
Pulmonary Sarcoidosis

- Occurs in over 90% of patients
  - Asymptomatic abnormal CXR: 50%
  - Symptomatic abnormal CXR: 50%
- Symptoms
  - Dyspnea (30%) and dry cough (30%)
    - Endobronchial involvement: stenosis (10%) with wheezing
  - Chest pain (15%)
  - Hemoptysis is rare: cavities with Aspergillomas
- Signs
  - Lung crackles (20%)
  - Clubbing rare
  - Pleural effusions rare
  - Pulmonary HBP (10%): correlates with dyspnea

Pulmonary Evaluation: CXR

- Modified Scadding staging system (stages are not chronologic; poor correlation with sx):
  - **Stage 0**: normal. Can have abnormal HRCT scan
  - **Stage I**: Bilateral hilar adenopathy with rt paratracheal adenopathy
  - **Stage II**: Bilateral hilar adenopathy with reticular opacities (upper > lower lobes)
  - **Stage III**: Reticular opacities
  - **Stage IV**: End-stage pulmonary fibrosis, volume loss, traction bronchiectasis, calcification, cavities/cysts

![Stage 0 CXR](image)
Stage I CXR

Prevalence at Dx 45-65%
Spontaneous resolution 90%

Stage II CXR

Prevalence at Dx 30-40%
Spontaneous resolution 60%
Stage III CXR

Prevalence at Dx 10-15%
Spontaneous resolution 10%

Stage IV CXR

Prevalence at Dx 5%
Spontaneous resolution 0%
Pulmonary Evaluation

- PFTs with $D_L\text{CO}$
  - Restrictive pattern with decreased DLCO
  - Obstructive pattern (15-30%): worse prognosis
  - Poor correlation with degree of dyspnea and HRCT scan
    - 70% have FVC >80% at time of Dx
      - **Severe DOE with normal FVC: R/O pulmonary HBP**, heart
    - Major value of PFTs: assess disease course with sequential measurements
- Bronchoalveolar lavage
  - BAL fluid > 30% lymphs with CD4/CD8 ratio > 3.5 (94% spec, 52% sen)
- Biopsy:
  - Transbronchial
    - Normal CXR : 40% +
    - Abnormal CXR : > 90% +
  - Endoscopic ultrasound guided FNA: 80-93% +
Extrapulmonary Manifestations: Eye

- Ophthalmologic (10-20%)
  - Initial manifestation in 5%.
  - Uveitis: most common, frequently bilateral, and often no sx (33%)
  - Other forms of eye dz: optic nerve, retinal vasculitis, orbital mass, KCS, lacrimal gland enlargement (20%), scleral plaques, conjunctival nodules

Mutton-fat keratic precipitates
## Ophthalmologic Sarcoid

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
<th>Physical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior chamber (iritis)</td>
<td>Pain, redness, blurred vision, asymptomatic</td>
<td>Mutton-fat (KP) precipitates</td>
</tr>
<tr>
<td>Middle chamber (pars planitis)</td>
<td>Floaters</td>
<td>String of pearls, snowballs</td>
</tr>
<tr>
<td>Posterior chamber (chorioretinitis)</td>
<td>Decreased visual acuity</td>
<td>Retinitis, vasculitis, macular dz</td>
</tr>
</tbody>
</table>
Extrapulmonary Manifestations: Skin

• Dermatologic (15-30%)  
  • Specific skin lesions: granulomas on biopsy  
    • Subacute:  
      • Hyperpigmented maculopapular lesions: face, nape of neck, upper back, and sites of trauma (scars, tattoos).  
      • Waxy, pink nodules: face, trunk, and extensor surface of extremities  
    • Chronic: associated with poor prognosis  
      • Lupus pernio: indurated, violaceous lesions on nose, cheeks, ears, lips, and fingers.  
      • Plaque-like  
      • Annular  
  • Nonspecific: Erythema nodosum (10-20%).

Sarcoid skin lesions do not ulcerate!

Specific Skin Lesions: Maculopapular
Sarcoidosis in Tattoos

Courtesy Chris D’Arcy, MD

Courtesy Sally Pullman-Mooar, MD

Courtesy Chris D’Arcy, MD
Specific Skin Lesions:
Lupus pernio
Annular/plaque
Nonspecific Skin Lesions:
Erythema Nodosum

Septal panniculitis
Extrapulmonary Manifestations: Musculoskeletal (4-38%)

- **Joint involvement (25%)**
  - Acute polyarthritis/periartthritis (1-20%)
    - May be migratory, intermittent, or additive
    - Can rarely precede other manifestations by months
    - **Involves ankles** (>90%) and knees most commonly (can mimic gout)
  - Lofgren’s syndrome (70%): poly/periartthritis with bilateral hilar adenopathy (90%), E. nodosum (50-75%), fever (66%), acute uveitis
    - Normal serum ACE level 70-85%
    - Joint pain resolves in weeks to months (avg 3 months): >70%
    - Up to 10-30% have several recurrences or persistent arthritis especially if have elevated ACE level. Synovial bx does not show granulomas. Synovial fluid hard to get.
    - Need to R/O acute histoplasmosis

Lofgren’s Syndrome
Chronic Sarcoid Arthritis

- **Joint involvement**
  - Chronic arthritis (< 5%)
    - Oligoarthritis: nondestructive, nondeforming involving knee, shoulder, wrist, ankle, and/or small joints of hands and feet. Can have dactylitis.
    - Associated with more extensive sarcoidosis, parenchymal lung involvement, and elevated ACE level.
    - Synovial fluid: mildly inflammatory (5000 cells/mm$^3$) with mononuclear predominance
    - Radiographs: STS without destruction
    - Synovial bx: granulomatous inflammation.
  
- **Tenosynovitis (5-13%)**
  - Wrist, ankle, patella, or Achilles tendons

Bone Sarcoid

- Bone involvement (3-13%)
  - F>M (2:1). AA > other races.
  - Associated with lupus pernio, chronic Dz, and poor prognosis.
  - Cystic lesions;
    - Predilection for phalanges of hands and feet.
    - Nasal bone lesions with lupus pernio
  - Calcaneus, skull, vertebrae, ribs, pelvis, sternum, maxilla, and distal ends of long bones rare.
    - Sclerotic lesions of axial skeleton: may mimic cancer.
  - Bone lesions: no periostitis or sequestra
  - MRI, PET, and bone scan more sensitive than xray since over 50% of bony lesions are asymptomatic. 33% of pts have silent bone lesions.

Muscle and Vascular Sarcoid

- Muscle (1-5% symptomatic dz)
  - Up to 80% of random muscle bx in asx pts have granulomas.
  - Chronic myopathy: most common form
  - Poor prognosis
  - Acute myopathy: 20 cases. AA females
  - Muscle nodules: Muscle MRI shows “dark star”

- Vascular
  - Granulomatous inflammation of vessel walls of small and medium sized vessels ANCA neg. CNS vasculitis reported rarely.
  - Large vessel involvement resembling Takayasu’s in AA and Asian children (? Blau’s syndrome)

Extrapulmonary Manifestations: Cardiac

- Symptomatic disease (5%): **can be first or only manifestation**
  - Can affect any part of heart except valves. Poor prognostic sign. **Beware of palpitations, orthopnea, chest pain, near-syncope.**
  - Granulomatous involvement of ventricular septum and conduction system
    - Arrhythmias (V. tach, others) including sudden death
    - Mobitz II or complete heart block
    - Implantable defibrillator if symptoms
  - Other: infiltrative cardiomyopathy with CHF; arrhythmogenic RV cardiomyopathy; papillary muscle causing valve dysfunction
  - Autopsy shows granulomas in 20% of pts in US and 67% of pts in Japan

Cardiac Sarcoid

- Evaluation (baseline EKG repeated annually)
  - EKG abnormal in >50% with cardiac involvement
  - Echocardiogram and Holter on all pts with cardiac sx or abnormal EKG (sen 100%, spec 87% for CS).
  - FDG-PET scan (fasting) and cardiac MRI with late-gadolinium enhancement (sen >90%, spec 78%). Should be done for the following:
    - Unexplained Mobitz II or third degree heart block in pts < 55yo
    - Sustained monomorphic ventricular tachycardia of unknown etiology
    - Arrhythmogenic right ventricular cardiomyopathy
    - Idiopathic heart failure
  - Endomyocardial bx has low yield (5%) unless guided by imaging since granulomas mostly in free wall of left ventricle
Extrapulmonary Manifestations: Neurologic

- CNS involvement occurs in 5%.
  - Initial manifestation of sarcoidosis in 50% of pts that develop neurosarcoidosis
  - No other sarcoid manifestations in 10% with neurosarcoidosis
- Granulomatous basilar meningitis with infiltration and/or compression of adjacent structures causes most CNS manifestations
- Presentations (33% have more than one manifestation)
  - Cranial nerve involvement most common.
    - Seventh nerve (Bell’s palsy) > second nerve most frequent (50%). Bilateral (33%)
    - Heerfordt syndrome: fever, parotid enlargement, arthritis, uveitis, VII CN palsy
  - Perivascular granulomatous inflammation (masses) of brain or spinal cord: seizures, encephalopathy, myelopathy, radiculopathy
  - Lymphocytic meningitis - acute or chronic
  - Hydrocephalus: needs a shunt
  - Central diabetes insipidus or hypothalamic hypopituitarism
  - Peripheral neuropathy: any type. Chronic sensorimotor most common pattern. Small fiber. Less frequent than CNS Dz.
Neurologic Sarcoid

• Evaluation
  • Look for evidence of extraneural sarcoid if initial presentation: eye, chest HRCT scan
  • MRI with gadolinium: meningeal and/or parenchymal enhancement.
  • CSF exam (R/O infection or carcinomatous meningitis)
    • Elevated opening pressure (10%)
    • Mononuclear cell pleocytosis (50%)
    • Elevated protein (70%)
    • Glucose can be normal or low (20%)
    • Elevated IgG index/OCBs (50%) and elevated CSF ACE level (25-50%) are nonspecific
  • Brain Bx: if Dx in doubt
  • EMG/NCV if peripheral neuropathy. Skin Bx for small fiber Dz

Neurosarcoidosis
Other Extrapulmonary Manifestations

• Constitutional (33-70%)
• Reticuloendothelial system
  • Peripheral adenopathy (15-40%): nontender cervical, axillary, inguinal nodes
  • Hepatomegaly (5-20%)
    • Elevated LAEs in 33% (usually alk phos)
    • Noncaseating granulomas in 50-80% with or without hepatomegaly or abnormal LAEs
    • Portal HBP rare
  • Splenomegaly (7-25%)
    • Hypersplenism with anemia, leukopenia, and ↓ platelets can occur rarely

Other Extrapulmonary Manifestations

• Sarcoidosis upper respiratory tract (SURT) (3-10%)
  • Sinus, nasopharynx (saddle nose), larynx (hoarseness), oral
  • Parotid/minor salivary gland enlargement (3-6%)

• Calcium homeostasis (4-10%)
  • Overproduction of 1,25 OH vitamin D by autonomous production of 1α hydroxylase within granulomas (alveolar macrophages) lead to ↑ intestinal calcium absorption and:
    • Hypercalciuria (40-60%), nephrolithiasis (10%), nephrocalcinosis/renal insufficiency (unusual)
    • Hypercalcemia (10%) much less common than hypercalciuria
    • Probably best to avoid calcium/vitD therapy in all sarcoid patients

• Other (<1%)
  • GI tract: ulcer or masses; pancreatic/ peritoneal
  • Renal: granulomatous interstitial nephritis
  • Endocrine: genitals, thyroid, pituitary infiltration, ↑ prolactin

Burke RR, et al. Semin Respir Crit Care Med 31: 474, 2010
Sarcoidosis: Rare Presentations

- FUO
- Single organ involvement: any organ including heart and CNS as initial and/or only manifestation
- Ulcerative skin lesions: must R/O infection
- Necrotizing sarcoid granulomatosis: R/O GPA
  - More common middle-age women
  - Pulmonary nodular lesions +/- infiltrates; other organs
  - Pathology: granulomas with necrosis and vasculitis
  - ANCA negative, ACE negative
  - Good response to prednisone

Sarcoidosis and Coexistent Diseases

• Other autoimmune diseases (RA, SLE, Sjogren’s, etc)
• Case reports with CVID, malignancies/lymphoma, and immune reconstitution syndrome in HIV pts treated with HAART
• Case reports (pulmonary dz) following IL-2, interferon-α, interferon-γ, and anti-TNF-α therapy
Initial Evaluation

- History including environmental, occupational, and medication exposure
- Physical examination
- Chest radiograph or CT scan
- PFTs including $D_L \text{CO}$; six minute walk with oximetry
- Peripheral cell blood counts
- Serum chemistries including Cr, Ca, and LAEs
  - Total immunoglobulins
- 25OH vitamin D and 1,25OH vitamin D
- Creatine kinase
- Urinalysis
- 24 hour urine for calcium and creatinine
- Electrocardiogram with rhythm strip (and echocardiogram)
- Ophthalmologic evaluation including slit-lamp exam
- Tuberculin skin test/ IGRA
- Biopsies of affected organs with special stains and cultures
- Other tests depending on organ system presentation

Am J Respir Crit Care Med 160: 736, 1999
Laboratory Tests

- **CBC**
  - Anemia of chronic disease
  - Leukopenia (5%): R/O bone marrow involvement and hypersplenism
  - Eosinophilia: up to 25%
  - Thrombocytopenia: rare

- **Chemistries**
  - Elevated alk phos/GGT: 33%
  - Hypercalcemia (4-10%)
  - Hypercalciuria (20-40%)

- **Serologies**
  - Elevated ESR/CRP
  - Hypergammaglobulinemia (30-80%)
  - Low titer RF and/or ANA with speckled pattern but negative specific autoantibodies (up to 40%)
  - ANCA is negative
Supportive Diagnostic Tests

- **Angiotensin converting enzyme (ACE):** secreted by macrophages in granulomas. Levels affected by genetic polymorphisms and extent of organ involvement.
  - Sensitivity 73%
    - Elevated in 60-75% of patients with untreated, active sarcoidosis.
    - Elevated 15-30% of patients with Lofgren’s syndrome
  - Specificity 83%
    - Multiple other causes of elevated ACE levels
    - Mild elevations (<50% above ULN) usually not concerning
    - Causes of ACE > 2x ULN: sarcoidosis, hyperthyroidism, other granulomatous diseases, genetic polymorphism
    - False positive elevations unusual (<5%)

- **Lysozyme:** secreted by monocytes and PMNs. Level affected by extent of organ involvement.
  - Sensitivity 69-79%: may be elevated when serum ACE is normal
  - Specificity 60-76%: multiple other causes of elevated lysozyme

Both tests may normalize with successful therapy but value of following either to assess course of Dz unclear.

Supportive Diagnostic Tests

• Bronchoalveolar lavage fluid
  – CD4/CD8 ratio >4, lymphocyte percentage >16%, and TBBx showing noncaseating granulomas had 100% PPV for sarcoidosis.
  – CD4/CD8 ratio >3.5 with >30% lymphocytes has a 94% specificity and 52% sens for sarcoid

• HRCT scan
  – Can be abnormal with normal CXR

• MRI with gadolinium
  – Superior to other modalities for brain, myocardial, bone, and muscle involvement

• FDG-PET scan superior to gallium scan but expensive
  – May have role in finding sites for possible biopsy in atypical presentations.

Tissue biopsy is gold standard
  - Well circumscribed non-caseating
  - Granulomas of epithelioid type
  - Diagnostic yield
    - Transbronchial lung biopsy
      - Normal CXR: 30-50%
      - Abnormal CXR: >90%
    - Lymph node: >90%
      - Mediastinal/hilar node bx by endobronchial ultrasound-guided FNA (EBUS-FNA): 80-93%
    - Skin(not EN): >90%
    - Parotid/MSG: 93%/36%
    - Synovium with chronic arthropathy: 80%
    - Asymptomatic muscle or liver: 50-80%
    - Lacrimal/conjunctival: 10-55%
  - Kveim-Silzbach skin test is no longer done

Tissue Biopsy: Other Causes of Noncaseating Granulomas (Diff Dx)

- **Lung**
  - Infection: mycobacterial, fungal (cocci, histo), parasitic, brucellosis, tularemia
  - Pneumoconiosis: aluminum, beryllium, cobalt, titanium, zirconium, silica
  - Hypersensitivity pneumonitis
  - Drug effect: MTX, IFN, TNFi, IL-2
  - Malignancy: lymphoma, lung cancer
  - Eosinophilic pneumonia
  - Aspiration pneumonia
  - IV talcosis
  - CTD: RA, SLE, MCTD, Crohn’s
  - Vasculitis: Wegener’s, Churg-Strauss
  - Immunodeficiency: CVID, chronic granulomatous disease
  - Lung transplant

- **Liver**
  - Granulomas in the liver are almost always noncaseating no matter what the cause (PBC, TB, drug reaction)

- **Skin**
  - Foreign body (ie splinter)
  - Treponema, leprosy, tularemia, leishmaniasis
  - Granuloma annulare

- **Synovium**
  - Mycobacterial, fungal, brucellosis, tophi, CPPD, foreign body (plant thorn, suture, sea urchin), Crohn’s, Wegener’s, lymphomatoid granulomatosis, Blau’s syndrome

- **Other:** lymphoma (esp Hodgkin’s Dz)
Diagnostic Caveats

- Diagnosis of sarcoidosis is combination of clinical findings supported by characteristic histology.
- Acute sarcoidosis (Lofgren’s) does not need histologic confirmation.
- Atypical cases and in patients who are to receive immunosuppressive treatment, histologic confirmation in one organ is essential.
- Clinical criteria for organ involvement without a biopsy can be used only after histologic confirmation of sarcoidosis has been made in at least one other organ.
**Etiology**

- **Infectious**
  - Mycobacterium antigens (mKatG, others)
  - Propionibacterium acnes and P. granulosum
- **Environmental/occupational exposure (ACCESS study)**
  - Occupations
    - Water sources: agricultural settings, water-damaged work environments
    - Metal industry: metalworking fluids contaminated with Mycobacteria
    - Inorganic particulate matter: silicates, etc
    - Insecticides
  - Smoking is protective against developing sarcoidosis
- **Autoimmunity**
  - Serum amyloid A (SAA) misfolding hypothesis
- **Genetics**
  - Increased risk in first degree relatives: Caucasian (RR 18x), AA (RR 2.8x)
  - Monozygotic concordance 10x higher than dizygotic twins (RR 80x vs 7x)
  - HLA-DR/DQ(multiple), ACE polymorphisms, BTN2L2, others

Pathogenesis

Candidate Ags

HLA-DR3/DQ2
Lofgrens

TH1

(TGF-β, PDGF)

TH2

IL-4; IL-13

IL 1; IL 2; IL 15; IL 18; TNF α
γ IFN; RANTES; MCP 1α; MCP1

Chemokines and chemokine receptors

SAA

Antigen presenting cell

Antigen

MHC

HLA-DR11

T-cell Receptor

T cell

Granuloma

Resolution

IL 10; IL 12; IL 18

Chronic disease/fibrosis

Zissel G. Semin Respir Crit Care Med 35: 307, 2014
Natural Hx and Prognosis

- Only 25% develop new organ involvement in first 2 years of follow-up
  - Follow-up q3-6mos: CXR, PFTs, calcium, others as indicated by hx/PE/ROS
  - Follow-up q12mos: eye exam, EKG
- Most patients undergo spontaneous remission (60%) within 3 yrs, additional 10-20% remit with steroids, 10-30% have a chronic course
  - At least 50% have some degree of permanent organ dysfunction
- Chronic sarcoid (10-30%)
  - 50% have chronic progressive lung dz.
  - 50% have involvement of critical organs: eye (20% have visual loss), heart, and/or brain
- **Poor prognostic signs**: >= 3 organ systems involved, AA race, disease onset after age 40, sx lasting > 6 months, stage III-IV chest x-ray, pulmonary HBP, extrapulmonary Dz (cardiac, neuro, lupus pernio, bone, ↑ calcium)
- Mortality
  - Overall mortality is 5% with half dying of pulmonary disease and half dying of cardiac/neurologic disease.
  - Pts with brain or cardiac disease: 10% mortality

Natural Hx and Prognosis

- Pulmonary disease prognosis
  - Stage I
    - Spontaneous remission in 75-80% within 1-3 years. Some (10%) have persistent hilar adenopathy lasting over 10 years.
    - Lofgren’s syndrome has best overall chance for remission (70-90%).
  - Stage II
    - Spontaneous remission in 50-66%. Others have progressive or no change in disease.
  - Stage III
    - Less than 10-20% have remission.
  - Stage IV
    - None have remission
    - Mortality 25-40% with vital capacity less than 1.5 liters

Judson MA. Clin Rev Allergy Immunol 49; 63: 2015
Management: Prednisone

- Patients with good prognostic signs should be observed for first 3-6 months
  - Pts with Stage I pulmonary dz and normal PFTs do not need prednisone
- Meta-analysis of prednisone use in Stage II and III pulmonary disease shows improvement in CXR and $D_L CO$ but only stabilization of FVC.
- No randomized, controlled trials to establish dose and duration of immunosuppressive therapy.
  - Usual starting dose is 40mg or more (up to 1mg/kg/d) of prednisone depending on manifestation
  - No guidelines for what to follow as response to therapy and when to taper therapy
    - Usually try to taper prednisone to 10mg/d by 6 months. Stay on 10mg/d maintenance for another 6 months (total 12 months of prednisone) before trying to taper off.
    - Inhaled steroids of no use unless pt has reactive airways disease (cough)

## Indications for Prednisone

<table>
<thead>
<tr>
<th>ABSOLUTE</th>
<th>RELATIVE</th>
</tr>
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<tbody>
<tr>
<td>Neurologic</td>
<td>Progressive Stage II/III pulmonary Dz</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Dec FVC&gt;15%</td>
</tr>
<tr>
<td>Severe hypercalcemia</td>
<td>Dec TLC&gt;10%</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>Dec D_LCO&gt;20%</td>
</tr>
<tr>
<td>Ocular</td>
<td>Inc CXR changes</td>
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<tr>
<td>When topical therapy fails</td>
<td></td>
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<tr>
<td>Organ-threatening Dz</td>
<td>Arthritis</td>
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<tr>
<td>Severe skin</td>
<td>Hepatic</td>
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<td></td>
<td>Systemic Sxs</td>
</tr>
</tbody>
</table>

Indications for Additional Immunosuppressive Rx

- Failure to taper high dose prednisone to 10mg/day by 6 months should prompt addition of a second agent.
- Severe disease (cardiac, neuro, other): start at same time as prednisone
  - Cyclophosphamide (3-6 months) followed by methotrexate, azathioprine, or mycophenolate mofetil (MMF)
- Moderate disease
  - Methotrexate has been studied the most.
- Hydroxychloroquine should be added to other DMARDs especially for skin, arthritis, hypercalcemia, and neurologic dz.

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Cytotoxic agents</th>
<th>Immunomodulators</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Methotrexate</td>
<td>Chloroquine/hydroxychloroquine</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Azathioprine</td>
<td>Pentoxifylline</td>
<td>Clofazimine</td>
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<tr>
<td>Acthar gel</td>
<td>Cyclophosphamide</td>
<td>Thalidomide</td>
<td></td>
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<tr>
<td></td>
<td>MMF, leflunomide</td>
<td>Infliximab, Rituximab</td>
<td></td>
</tr>
</tbody>
</table>

Management

• Other therapies
  • Pneumocystis jiroveci prophylaxis
  • Osteoporosis therapy
  • Immunizations
  • Fatigue (50-70%): R/O sleep apnea, hypothyroidism, hypoxemia
  • R/O depression (40-60%)
  • Diffuse pain: R/O small fiber neuropathy

• Pulmonary hypertension
  • Sildenafil, bosentan, epoprostenol

• Lung transplant
  • Patients with FVC <50%, hypercarbia, NYHA functional class III-IV, or pulmonary HBP should be referred to lung transplantation center.
  • Rate of recurrence of sarcoid is 50% in transplanted lung

Lazar CA, Culver DA. Semin Respir Crit Care Med 31: 501, 2010
Which one of the following would you do now?

A. Ophthalmologic examination
B. CT scan of lung
C. ACE level on cerebrospinal fluid
D. Brain biopsy
E. Bone marrow biopsy
Additional evaluation:
- Transbronchial bx and EBUS-FNA: noncaseating granulomas
- Ophthalmologic exam: negative
- CSF ACE level: 10.5 U/L (nl < 2.5)
Summary

- Sarcoidosis is common with protean presentations and manifestations. **The Great Imitator**
- Evaluation for extrapulmonary organ involvement is a critical part of the assessment.
  - Supports the diagnosis
  - Identifies reasons for therapy
  - Provides prognostic information
- Therapy for sarcoidosis is directed for both acute and chronic disease
  - Chronic disease may benefit from steroid-sparing agents
- More research is needed
  - https://www.stopsarcoidosis.org