Sarcoidosis

Alan J. Kanouff DO, FCCP
Lung Disease Center of Central Pennsylvania

Disclosures

- Speaker for AstraZeneca
  - Symbicort
  - Bevespi
- Speaker for Merck
  - Belsomra
- Speaker for Sunovion
  - Utibron
  - Seebri

Overview

- What I feel you need to know regarding sarcoidosis
- Treatment
- Follow up
- ?Update

What is Sarcoidosis

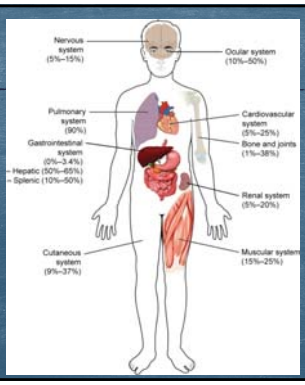
- Inflammatory condition in which the body forms granulomas against itself
- Can occur in any organ
  - Can involve one or more at a time
- Etiology is unknown
  - Genetic predisposition
- More predominant in African Americans

Epidemiology

- 80% of patients are 20-50 years old at diagnosis
- In the US
  - Blacks have a lifetime risk of 2.4%
  - Whites have a risk of 0.85%

Organ Involvement

- Most common is the lung
  - Including mediastinal lymph nodes
- Followed by liver
  - Spleen
  - Eyes
  - Musculoskeletal
  - Peripheral lymph nodes
  - Hematologic
  - Skin
  - Nervous system
  - Cardiac
  - Hypercalcemia
  - Parotid glands



Lungs

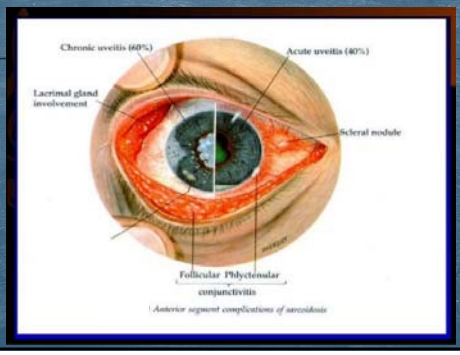
- Most commonly are asymptomatic
  - Bilateral hilar lymphadenopathy on CXR/CT chest
- Symptoms that can be seen are cough, wheezing, shortness of breath
  - Occur in one-third to one-half of all patients
- Airway hyperactivity has been reported in up to 20% of patients
- Can cause pulmonary hypertension and pulmonary fibrosis

Liver

- Also, usually asymptomatic
- Elevation of liver enzymes
- Rarely causes portal hypertension, hepatic failure, or increased mortality related to liver dysfunction

Eyes

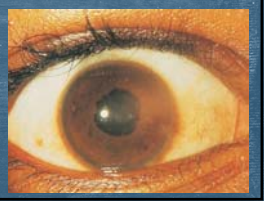
- One of the more concerning issues as can cause blindness
- Uveitis is the most common problem
- Followed by
  - Retinal vascular changes
  - Conjunctival nodules
  - Lacrimal gland enlargement



Anterior segment complications of sarcoidosis

Uveitis

- Acute anterior uveitis usually clears spontaneously or after local therapy with corticosteroids
- Chronic uveitis may lead to adhesions between the iris and the lens (synechia)
  - Glaucoma
  - Cataract
  - Blindness



Musculoskeletal

- Proximal muscle weakness is common
  - Must be distinguished from corticosteroid-induced myopathy
- Myalgias
- Intramuscular nodules
- Evaluate with CK, muscle biopsy if necessary

Hematologic

- Anemia
- Leukopenia
- Usually requires bone marrow biopsy for diagnosis

Skin

- Rash
  - Papules,nodules, plaques
- Erythema nodosum
- Lupus pernio

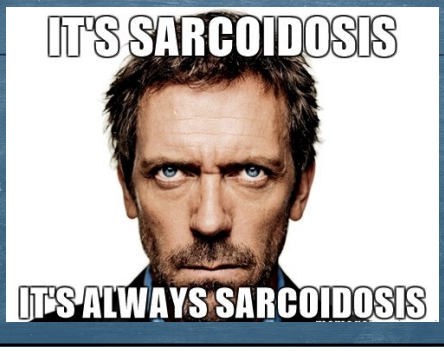
Erythema nodosum

- Most common skin manifestation
- Usually acute, self-limiting process and rarely requires treatment
  - Recurrences are uncommon
  - Can occur in many other diseases
- Typically remits in 6-8 weeks

Lupus pernio

- Most characteristic of sarcoidosis
- Typically occurs in the head and neck
  - Nose, cheeks, lips, forehead, and ears
- Occurs typically in black women in their 30s and 40s
- Rarely resolves spontaneously
- Can be cosmetically disfiguring
  - Extensive involvement of the nasal cavity and the maxillary sinuses may lead to nasal obstruction

Lupus Pernio



Nervous System

- Cranial nerve palsies are common
  - Tend to occur early on and respond favorably to treatment
- Optic neuritis
- Hypopituitarism
- Cognitive dysfunction
- Small fiber neuropathy
- Gadolinium-enhanced MRI is the preferred test for evaluating brain parenchyma, meninges, and spinal cord

Cardiac

- Clinical occurrence is 5%
  - Autopsy reports as high as 25%
- Conduction abnormalities
  - Heart block
  - Arrhythmias
    - Ventricular tachycardia and fibrillation
- Congestive heart failure
- Sudden death

Cardiac Diagnostics

- EKG
- Holter monitor
- Echocardiogram
- PET/CT
- Cardiac MRI
- Endomyocardial biopsy
  - May be inconclusive secondary to inhomogeneous distribution of granulomas

Hypercalcemia

- Occurs in about 2–10% of patients with sarcoidosis
- If left untreated can cause
  - Nephrocalcinosis
  - Renal stones
  - Renal failure

Natural History of Sarcoidosis

- Spontaneous remission occurs in 65%
  - 10-30% develop chronic and progressive disease
- Blacks are more likely to have a more symptomatic, severe, and chronic disease than whites
- Lifetime mortality from sarcoidosis is less than 5%

Presentation

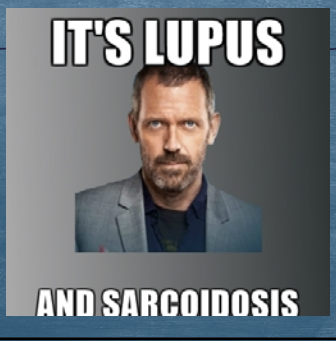
- Cough
- Shortness of breath — 50%
- Constitutional symptoms — 35%
- Many are asymptomatic
  - Bilateral hilar lymphadenopathy on CXR/CT chest

Lofgren's Syndrome

- Acute form of sarcoidosis
  - Bilateral hilar lymphadenopathy
  - Symmetric polyarthralgia or polyarthritis
  - Erythema nodosum
- Typically self limiting

Differential Diagnosis

- Very large and broad
- Most concerning would be lymphoma or other cancer
- Infectious
  - Fungus and mycobacterium cause caseating granulomas
- Inflammatory
  - Hypersensitivity pneumonitis
  - Many ILD
- Most common reason for biopsy



MAJOR PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF SARCOIDOSIS

Lung	Lymph Node	Skin	Liver	Bone Marrow	Other Biopsy Sites
• Tuberculosis • Atypical mycobacteriosis • Cryptococcosis • Aspergillosis • Histoplasmosis • Coccidioidomycosis • Blastomycosis • *Pneumocystis carinii* • *Mycoplasma*, etc. • Hypersensitivity pneumonitis • Pneumoconiosis: beryllium (chronic beryllium disease), titanium, aluminum • Drug reactions • Aspiration of foreign materials • Wegener's granulomatosis (sarcoid-type granulomas are rare) • Chronic interstitial pneumonia, such as usual and lymphocytic interstitial pneumonia • Necrotizing sarcoid granulomatosis (NSG)	• Tuberculosis • Atypical mycobacteriosis • Brucellosis • Toxoplasmosis • Granulomatous histiocytic necrotizing lymphadenitis (Kikuchi's disease) • Cat-scratch disease • Sarcoid reaction in regional lymph nodes to carcinoma • Hodgkin's disease • Non-Hodgkin's lymphomas • Granulomatous lesions of unknown significance (the GLUS syndrome)	• Tuberculosis • Atypical mycobacteriosis • Fungal infection • Reaction to foreign bodies: beryllium zirconium, tattooing, paraffin, etc. • Rheumatoid nodules	• Tuberculosis • Brucellosis • Schistosomiasis • Primary biliary cirrhosis • Crohn's disease • Hodgkin's disease • Non-Hodgkin's lymphomas • GLUS syndrome	• Tuberculosis • Histoplasmosis • Infectious mononucleosis • Cytomegalovirus • Hodgkin's Disease • Non-Hodgkin's lymphomas • Drugs • GLUS syndrome	• Tuberculosis • Brucellosis • Other infections • Crohn's disease • Giant cell myocarditis • GLUS syndrome

Work up

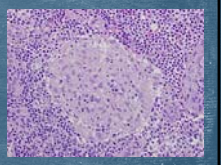
- Mainly based on presentation
- Labwork
  - CBC
  - Serum chemistries
  - LFT's
- CXR
- Pulmonary function test
- EKG
- Routine ophthalmologic exam

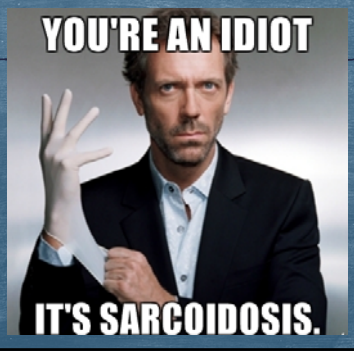
Diagnosis

- Need tissue for confirmation
  - Not always possible
- Most common method is bronchoscopy
  - EBUS (Transbronchial needle aspiration)
  - Transbronchial biopsy
  - Endobronchial biopsy
- EUS
- Mediastinoscopy
- Skin biopsy
- Lymph node biopsy
- Liver and heart biopsy

Non-necrotizing (Non-caseating) Granulomas

- Hallmark of sarcoidosis biopsy
- Should be an absence of current infection
  - Mycobacterium
  - Fungus
    - Especially if necrotizing granulomas are seen

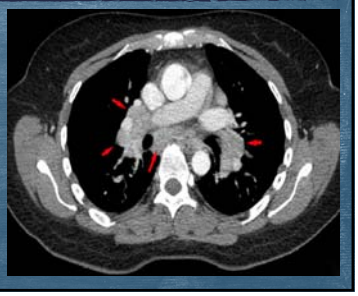




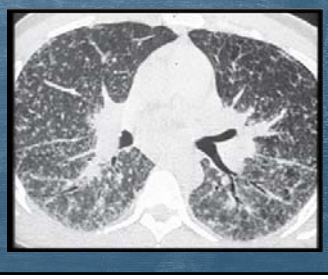
Radiologic Staging

- Based on CXR
- Stage I
  - Bilateral hilar lymphadenopathy
- Stage II
  - Bilateral hilar lymphadenopathy with interstitial lung disease
- Stage III
  - Interstitial lung disease without bilateral hilar lymphadenopathy
- Stage IV
  - End-stage pulmonary fibrosis

Stage I

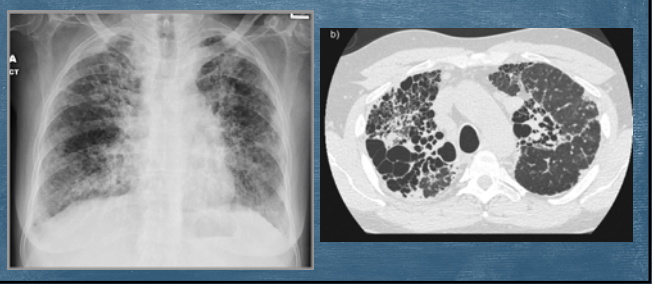


Stage II



Stage III

Stage IV



Stage IV

- Development of pulmonary fibrosis
  - Honeycombing and irreversible damage
- Often accompanied by development of pulmonary hypertension
- Respiratory failure remains the most common cause of death in patients with active sarcoidosis

To Treat or Not to Treat

- Symptomatic stage II or stage III disease
  - SOB, cough, obstruction on spirometry
- Significant extrapulmonary disease
  - Cardiac, liver, uveitis, hypercalcemia
- Not indicated in stage I or asymptomatic stage II
  - Spontaneous resolution is common
  - 55 to 90% of patients with Stage I
  - 40 to 70% of patients with Stage II
- May not be helpful in stage IV
  - Consider lung transplant

Adverse Prognostic Factors

- Lupus pernio
  - Nasal mucosal involvement
- Chronic uveitis
- Age at onset greater than 40 yr
- Chronic hypercalcemia
  - Nephrocalcinosis
- Black race
- Cystic bone lesions
- Neurosarcoidosis
- Myocardial involvement
- Progressive pulmonary sarcoidosis
  - Chronic respiratory insufficiency

Medication

- Steroids are mainstay of treatment
  - No good data unfortunately
- Trial of 3 months
  - If no improvement, unlikely to help
- Usually treat for minimum of one year
- Patients with frequent relapses or unable to wean steroids
  - Typically try an immunosuppressive

Immunosuppressive Therapy

- Hydroxychloroquine
- Methotrexate
- Azathioprine
- Leflunomide
- Mycophenolate
- Infliximab
- Adalimumab
- Second line and require close monitoring

Specialist's View

- PFT, CXR and pulse oximetry
- Biopsy
  - EBUS
  - Bronchoscopy with endobronchial/transbronchial biopsy
    - Fungal and AFB cultures
  - Liver biopsy, skin biopsy, lymph node
- Treat based on symptoms and spirometry
  - CXR mainly helpful for staging and can help with response

My Typical Treatment

- Prednisone 40-60 mg daily for 1-3 months
- Re-evaluate symptoms and spirometry
- If no response after 3 months
  - Stop treatment
- If response, typically continue lower dose prednisone
  - 5-10 mg/day
- Re-evaluate every 3 months
  - Symptoms and spirometry
- If symptoms completely resolve and spirometry normalizes
  - Try to stop the prednisone early (6-12 months)

When To Use An Immunosuppressive

- Relapse occurs quickly
  - Or frequent relapses
- Cannot tolerate longer courses of prednisone
- Typically start with methotrexate
  - 7.5 mg and titrate up to 15 mg as needed/tolerated

Monitoring

- Yearly
  - CXR
  - Spirometry
  - Ophthalmalogic exam
  - LFT's
- Based on symptoms
  - EKG
  - Echocardiogram

What's Most Important Regarding Treatment

- Cardiac/neuro issues
- Initial staging
  - Stage IV disease patients do poorly
- Lung standpoint
  - Spirometry
- Lupus pernio
- Uveitis

What's Least Important Regarding Treatment

- Erythema nodosum
- CXR findings alone
- Stage I disease
- Mild hypercalcemia
- Lofgren's Syndrome

Update on Sarcoidosis

- Biomarkers
  - Not sensitive or specific enough
- FDG-PET
- EBUS/EUS

FDG-PET

- Very sensitive method to assess inflammatory activity and extent of disease in sarcoidosis
- Not for screening
- Can help find a suitable area for biopsy
- Useful in detecting cardiac sarcoidosis
  - May also help predict mortality
    - Cardiac MRI has also been useful

Endobronchial and Endoscopic Ultrasound

- Less invasive biopsy
- EBUS
  - Bronchoscopy
  - Anterior mediastinal and hilar lymph nodes
- EUS
  - GI tract
  - Posterior mediastinal and intra abdominal lymph nodes
- Yield is typically 80-90%
- Mediastinoscopy is rarely done

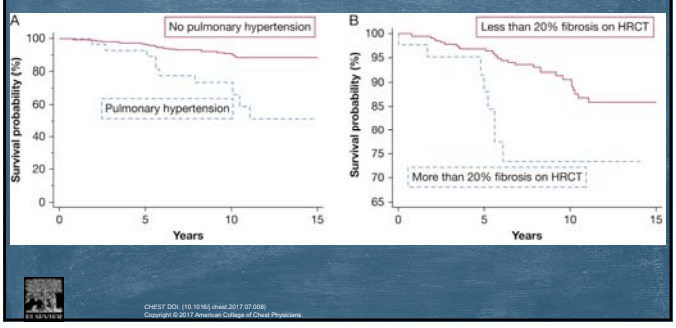
Literature Review

- Many articles
- Mostly review
- Not much from a clinical standpoint

Predictors of Mortality in Pulmonary Sarcoidosis

Gamze Kirkil, MD, Elyse E. Lower, MD, Robert P. Baughman, MD

CHEST
2017



Berylliosis

- Chronic beryllium disease (CBD)
- Formation of granulomas in the lung and other organs
  - Very similar to sarcoidosis
- Occupational exposure to beryllium
  - Aerospace, electronics, nuclear components, high-technology ceramics, dental alloy preparation, and metals extraction
- Positive beryllium lymphocyte proliferation test
  - Blood or bronchoalveolar lavage fluid
- Acute Berylliosis
  - Acute chemical pneumonitis

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