Sarcoidosis
Pulmonary and Extrapulmonary Manifestations

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Sarcoidosis

• A multisystem granulomatous disorder of unknown etiology
• Most frequently involves the lung (90%), skin (25%), and eyes (20%) but extrapulmonary manifestations can also occur
• Organs that are most commonly involved are:
  - Reticuloendothelial system (40%)
  - MSK (15%)
  - Brain (10%)
  - Heart (5%)
  - GI (1%)
• Estimated prevalence 5-50 per 100,000
• Disease prevalence varies geographically and tends to aggregate within families
• Most commonly presents in young adults 10-40 years old (70-90%)
• Men and women affected equally
• In U.S., 8 times more common in African Americans than Caucasians
• African Americans suffer more severe form of the disease
Proposed Pathogenic Mechanism

- Widely thought that there may be multiple causes of sarcoidosis, accounting for the different patterns of disease.
- Presumably, an unknown antigen initiates the disease and activates macrophages and CD4+ T cells in the lung. Cytokines further stimulate humoral and cellular immunity leading to increased Ab production and granuloma formation.
Note that sarcoidosis is an interstitial lung disease that affects the interlobular septae.

On pathologic specimen, most often see a focal, chronic inflammatory reaction formed by the accumulation of epithelial cells, monocytes, lymphocytes, macrophages, and fibroblasts.
Clinical symptoms

- In approximately half of all cases, the disease is discovered incidentally.
- Common presenting symptoms include cough, dyspnea, and chest pain.
- Occasionally, pts present with extrapulmonary symptoms. These include:
  - Skin: plaque-like lesions, subcutaneous nodules
  - Eye: anterior uveitis (iritis), chorioretinitis, keratoconjunctivitis
  - Reticuloendothelial: LAN, hepatomegaly, splenomegaly
  - MSK: joint pain
  - Neurologic: focal neurologic signs
  - Cardiovascular: arrhythmias, pulm HTN, restrictive cardiomyopathy
  - GI: epigastric pain, nausea, and vomiting

- Clinical course can vary from indolent to severe with some patients having a very stable course and others developing permanent lung damage with multiple organ involvement.
- 5% total mortality
Diagnosis

- **Diagnostic criteria:**
  1. Compatible clinical or radiologic findings
  2. Histologic evidence of noncaseating granulomas
  3. Negative bacterial and fungal studies of tissue biopsy, sputum, or other bodily fluids

- **Other useful tests:**
  1. Pulmonary function tests- low FVC with nl FEV1/FVC, decreased DLCO
  2. ACE level- 75% of patients with sarcoidosis have elevated levels
  3. Bronchoalveloar lavage- demonstrates increased number of CD4 T cells, decreased CD8 T cells, and increased immunoglobulins and B cells.
Patient Presentation*

- Ms. B. is a previously healthy 43 year-old white female who presents to the Emergency Room with chief complaint of painful, red eye and blurry vision.

- An ophthalmologic exam done in the ED shows cells in the anterior chamber and small nodules on the surface of the iris (Busacca nodules).

- The DDx of granulomatous iritis (i.e. anterior uveitis)
  - Sarcoidosis
  - Syphilis
  - Vogt-Koyanagi-Harada syndrome
  - Sympathetic ophthalmia
  - Multiple sclerosis
  - Lyme disease

From: http://www.emedicine.com/oph/topic586.htm

* Note: Clinical presentation has been modified to improve the learning value of the case.
Initial Chest X-Ray

- Bilateral hilar adenopathy
- Right paratracheal node involvement
- Enlarged aortopulmonary window nodes
- Parenchyma showed no evidence of infiltrates
- Pt denies all pulmonary symptoms including SOB, cough, wheeze
Differential Diagnosis

- The DDx of mediastinal LAN
  - Sarcoidosis
  - Lymphoma
  - Tuberculosis
  - Metastatic CA

Note: symmetrical LAN distinguishes sarcoid from lymphoma, mets, and other granulomatous infections. Symmetrical LAN occurs in 95% of cases of sarcoidosis.
Based on clinical history and chest X-Ray, pt was given presumed diagnosis of sarcoidosis.
Pt was treated with steroid eye drops and recovered fully.
7 years later, pt came to BIDMC with complaint of increasing abdominal girth with a recent 8 lb weight gain.
Pt denied symptoms of SOB. A repeat chest X-ray was requested.
Abdominal CT was also performed to evaluate source of abdominal discomfort.
Follow up CXR

- Bilateral hilar lymphadenopathy
- Diffuse reticular and nodular interstitial markings in the mid and upper lung zones
Differential Diagnosis

• The DDx of upper lobe predominant reticular nodular radiographic lesions include:
  - 5 S’s
    - Sarcoidosis
    - Pneumoconiosis, esp. Silicosis
    - Ankylosing Spondylitis
    - “Atypical” Pneumocystis carinii pneumonia
    - Histiocytosis
  - Less common:
    - Hypersensitivity pneumonitis, aka “Farmer’s lung”
    - Eosinophilic granuloma
    - Mycobacterial infection
    - Fungal infection
    - Collagen vascular disease
Abdominal CT

- Multiple low attenuation lesions
- Enlarged spleen

DDx splenic lesions
- Granulomatous disease, incl. sarcoidosis
- Abscess (septic emboli)
- Lymphoma
- Metastasis
Patient Presentation (cont.)

- Bone marrow biopsy was performed and showed non-caseating granulomas, consistent with sarcoidosis.
- PPD and tests for other infectious organisms have been negative.
- Pt remains stable from pulmonary perspective and she has been followed with yearly chest X-rays to evaluate for worsening parenchymal disease.
Useful Radiographic Studies in the Evaluation of Sarcoidosis
Pulmonary

- **PA and Lateral Chest X-Ray**
  - Initial study of choice
  - Useful in diagnosis and monitoring progression of disease (Stage I to Stage IV)
- **High Resolution Chest CT**
  - Obtained when chest X-ray is normal but high clinical suspicion of disease
  - More accurate in defining adenopathy, infiltrates, and architectural distortion
  - Can identify areas of reversible vs. irreversible lung damage
- **Gallium 67 Scan**
  - A non-invasive test that can support diagnosis and assess for progression of disease
  - A radioactive compound is injected IV and imaged 1-2 days later
  - Hypothesized that gallium concentrates in lymphocytes and macrophages and identifies foci of inflammation
  - Used less often now since it is not very specific and a negative scan does not exclude disease

Extrapulmonary

- **Studies dictated by extrapulmonary symptoms**
  - MRI/CT- brain involvement
  - Barium studies- GI involvement
  - Echo- cardiac involvement
Stage I

- Bilateral hilar adenopathy
- Right paratracheal adenopathy
- AP window adenopathy

- 75% of patients have spontaneous regression of nodes
Stage II

- Bilateral hilar adenopathy
- Bilateral reticular nodular interstitial infiltrates (usually upper>lower)
- 1/3 will go on to develop progressive disease
Stage III

- Progressive interstitial disease
- Shrinking hilar nodes
Stage IV

- Advanced fibrosis in reticular nodular pattern
- Cystic abnormalities
- Upper lung volume loss
- Relative sparing in lower lobes
High Res CT

- R paratracheal lymph nodes
- Subcarinal lymph nodes 4.5X2.3 cm
- Bulky hilar lymph nodes
High Res CT

- Micronodules
- Ground glass opacities are suggestive of active disease
High Res CT

- Diffuse reticular opacities
- Micronodules
- Conglomerate areas of fibrosis
High Res CT

- Traction bronchiectasis causing architectural distortion
- Ground glass opacities
- Bullous changes at periphery
Gallium Scans

- Radioactive isotope accumulates in inflammatory cells, especially macrophages and lymphocytes
- Thought to correlate with areas of active disease
- “Panda sign” refers to accumulation in the parotid or lacrimal glands
- Note increased uptake in the hilar nodes
- Uptake in liver is normal and not indicative of disease
Radiographic Findings of Extrapulmonary Sarcoidosis
Reticuloendothelial system (40%)

- Diffuse lymphadenopathy
- Splenic enlargement with granulomas
- Hepatomegaly
- Large mass of lymph tissue at the portahepatis

Ddx:
- Lymphoma
Reticuloendothelial System (cont.)

- Multiple hypointense lesions in spleen following Gadolinium administration on MRI

Ddx
- Lymphoma
- Pyogenic abscess
- Other granulomatous infections: MAC, Histoplasmosis, etc.
- Metastasis
Cutaneous Sarcoid (25%)

Subcutaneous nodules
“Erythema nodosum”

Lupus pernio


Eye/Orbit (20%)

- Soft tissue density L orbital lesion extends along the lateral and superior orbit and under the posterior orbital roof
- Extraconal in location and closely associated with the lacrimal gland and extraocular muscles

Ddx:
- Inflammation
- Infection
- Neoplasia- pleomorphic adenoma, lymphoma
Musculoskeletal system (15%)

- Chronic arthritis with trabecular bone resorption
- Note “lacy destruction” of distal and middle phalanx

Ddx:
- Rheumatoid arthritis
- Tuberous sclerosis
- Enchondromas
- Xanthomatosis
- TB
- Fungal infection
- Gout

From: Teaching files of Ferris Hall, MD
CNS disease (10%)

- Multiple small foci of hyperintensity in white matter on MRI, thought to represent vasculitis
- Note that the most common CNS lesions are localized to the meninges

Ddx:
- Chronic ischemia or gliosis
- CNS sarcoid
- SLE
- Lyme disease
GI disease (1%)

- Stomach is most frequently involved
- Narrowing of antrum
- Nodular mucosal irregularities

Ddx:
- Gastric CA, Lymphoma
- Metastatic disease
- Peptic ulcer disease
- Crohn’s disease
- Tuberculosis
- Sarcoidosis
- Syphilis
- Eosinophilic gastritis
- Gastritis- XRT, corrosive
- Amyloidosis

From: Teaching files of Herbert Gramm, MD
Summary

- A multisystem granulomatous disease of unknown etiology
- Most common presentation in young adults with cough, dyspnea, fatigue
- Characteristically affects the lung, but can also affect the eyes, skin, and multiple other organ systems
- Diagnosis depends on:
  - Characteristic clinical symptoms and radiographic findings
  - Ruling out infection, esp. TB
  - Securing histologic evidence of noncaseating granulomas
- Chest X-Rays and Chest CT are most widely used studies for evaluation of disease
- Treatment: Steroids and immunosuppressives for symptomatic or extrapulmonary disease. Lung transplant with immunosuppression for severe lung disease.
Acknowledgements

- Phillip Boiselle, MD
- Steven Weinberger, MD
- Joseph Makris, MD
- Herbert Gramm, MD
- Steve Reddy, MD
- Ferris Hall, MD
- J. Anthony Parker, MD Ph.D.
- Larry Barbaras and Cara Lyn D’amour, our Webmasters
- Gillian Lieberman, MD
- Pamela Lepkowski
References

- King, TE. “Overview of sarcoidosis” on Up to Date 2002.