Sarcoidosis: Pulmonary Manifestations, Diagnostic Approaches and Treatment

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Learning Objectives
- Have a better understanding of disease characteristics
- How to make the diagnosis of sarcoidosis
- How to monitor patients
- What is the natural history?
- What types of treatments are used?

Sarcoidosis: Disease Characteristics
- Systemic granulomatous disease
- Affects the lungs in up to 90% of patients
- Bimodal onset of disease
  - 2nd and 3rd decades and ~5th decade
- Racial Prevalence
  - African-American triple that of Caucasians in US
- Unknown etiology
  - Gene-environment interaction

Sarcoidosis: Histological Hallmark

Non-necrotizing granulomatous inflammation in any organ

Sarcoidosis: Clinical Presentations

- Acute
  - Löfgren’s Syndrome
    - Fever, bilateral hilar lymphadenopathy, arthritis (ankle) and erythema nodosum
- Chronic
  - Subacute to chronic onset of symptoms
    - Often cough and/or shortness of breath
    - Systemic complaints in 25-50%
      - arthralgias, fatigue, chest pains, muscle pain

How to Make a Diagnosis of Sarcoidosis

- No single diagnostic test!

Diagnosis of Sarcoidosis

- Role of Angiotensin converting enzyme (ACE) level
  - Insensitive
  - Non-specific
    - Elevated in other granulomatous diseases

- High Resolution Chest CT scan
  - UCSF ILD radiologists think HRCT is very specific for the diagnosis if the classical patterns are present

- Non-necrotic granulomas on tissue biopsy of affected organ
  - Important to have an experienced lung pathologist review biopsy, especially if the interpretation is “granulomas with necrosis”
CXR Staging System

**Pulmonary Manifestations: Stage I, Bilateral Hilar Lymphadenopathy (BHL)**

**Pulmonary Manifestations: Stage II, BHL with Parenchymal Nodules**

- Distribution: peri-lymphatic nodules, upper lobe

**Pulmonary Manifestations: Stage III, Parenchymal Nodules Only**

- Nodules can coalesce
Pulmonary Manifestations: Stage IV, Fibrosis, Cystic

Diagnosis of Sarcoidosis

- Exclusion of disease mimics:
  - Mycobacterial or fungal infection
    - Send tissue specimens for culture
    - Travel history (e.g. histoplasmosis, coccidioidosis)
  - Amyloidosis
    - Check SPEP and UPEP patients older than 50 or 60 in whom you are evaluating for sarcoidosis
  - Pneumoconiosis and Berylliosis
    - Take thorough occupational history
  - Lymphoma
    - Clinical history of B symptoms

Tests that I don’t routinely perform
- Gallium scans
  - Unless the patient cannot undergo tissue biopsy
- PET scans
  - Similar reasoning to gallium scans
- ACE levels
  - Can consider if cannot obtain a biopsy
- lysozme levels

Sarcoidosis can be systemic
- Thorough review of systems
- May discover extrathoracic organ involvement
  - E.g. skin, joints, cardiac, central or peripheral nervous system
- Sarcoidosis screening studies

ATS/ERS/WASOG. Am J Respir Crit Care Med. 1999
Sarcoidosis Screening Studies

- Once diagnosis is made, the following screening is recommended:
  - 12 lead ECG and signal averaged ECG
  - Serum Calcium level
  - Precursor and mature forms of Vitamin D
    - 25-hydroxy Vit D and 1, 25-dihydroxy Vit D
  - Ophthalmologic evaluation
  - 24 hr urine collection for calcium excretion
  - Absolute CD4 count

Monitoring Patients with Sarcoidosis

- Pulmonary disease only:
  - Complete pulmonary function tests every 6 months during the first 2 years, and then yearly over the following 3 years unless symptoms dictate for frequently
- Extrathoracic disease:
  - Depends on organ
  - E.g Brain MRI for CNS sarcoidosis
- Monitor symptoms related to organ involvement

Natural History of Sarcoidosis

- ~2/3 of patients have spontaneous resolution or persistent, but non-progressive disease
- ~1/3 have progressive disease
  - ~10% die from sarcoidosis-related organ involvement

Radiographic Staging: Predictor of Spontaneous Resolution

<table>
<thead>
<tr>
<th>Stage</th>
<th>Chest Xray Finding</th>
<th>Spontaneous Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>BHA</td>
<td>55-80%</td>
</tr>
<tr>
<td>II</td>
<td>BHA, reticular infiltrates</td>
<td>40-60%</td>
</tr>
<tr>
<td>III</td>
<td>Reticular infiltrates only</td>
<td>10-20%</td>
</tr>
<tr>
<td>IV</td>
<td>Fibrosis, volume loss</td>
<td>0%</td>
</tr>
</tbody>
</table>
Markers of Disease Activity

- No clinically proven biomarkers of disease activity or progression
- ACE Level: should it be used to monitor disease course?
  - Not enough data to recommend routine use
  - Some clinicians use ACE levels to assess disease activity
    - In patients who present with very elevated levels, it may reflect disease activity

Treatment Recommendations

First Assess the need for therapy

Absolute indication for corticosteroids:
- Cardiac*
- Neurologic*
- Ophthalmologic
- Hypercalcemia

*Often high dose (60-80 mg/day) for first several weeks/months

Treatment Recommendations

- Non-life Threatening Disease or Severe Organ Dysfunction
  - Expert opinion/Controversial topic
  - High rate of spontaneous remission and low mortality rate from pulmonary disease
  - Stage I pts (BHA) should be observed for 6 months and not treated
  - Early treatment of Stage II disease (BHA + infiltrates) may improve lung function
  - No data for disease-modification long term

Treatment for Pulmonary Disease

Progressive worsening of symptoms or PFTs
- ~ 40 mg prednisone for 3-6 wks, and if improved symptoms, taper by 5-10 mg increments every 4-8 wks
- Relapse rate can be up to 60%, so maintenance continued for 6-8 mos, resulting in at least a year of treatment.
- Second-line agents added for steroid-dependent, progressive disease or steroid intolerance
Second-Line/Alternative Therapies

- Methotrexate: (up to 15mg/week)

- Azathioprine (up to 200mg/day)
  - open-label series studied azathioprine (2 mg/kg per day) combined with glucocorticoids in 11 patients with chronic or relapsing pulmonary sarcoidosis: Eur Respir J. 1999;14(5):1117
  - Check serum thiopurine-S-methyltransferase (TPMT) to avoid severe pancytopenia

TNFα-blockers

- Infliximab (Remicade): chimeric, humanized monoclonal antibody
  - RCT: 138 patients with chronic pulmonary and extrapulmonary sarcoidosis refractory to glucocorticoid therapy (placebo, low-dose (3 mg/kg), higher-dose (5 mg/kg) at baseline and weeks 2, 6, 12, 18, and 24)
  - Minimal improvement in FVC

- Adalimumab (Humira): fully human anti-TNFα antibody
  - Case reports and small case series suggest benefit

- Etanercept (Enbrel): soluble TNFα receptor fusion protein
  - Not effective in pulmonary sarcoidosis

Novel Therapies

- IL-12 Antagonism (ustekinumab)
  - Unpublished
  - All outcome measures negative
    - PRO
    - Skin
    - Lung

Take Home Points

- Sarcoidosis has a variable clinical course
  - Treatment often tailored to individual patient

- Spontaneous remissions are common

- Difficult to predict progression, response to treatment, or relapse

- No single test to indicate “active” disease

- Treatment does not “cure” sarcoidosis
**Take Home Points: Treatment of Pulmonary Disease**

- No evidence that any treatment is disease modifying
- ICS may be beneficial for cough without significant radiographic disease
- Methotrexate good for steroid-dependent and refractory disease
  - Azathioprine good as second line after methotrexate intolerance or treatment failure
- Modest improvement with TNF-α inhibitors and very expensive

**GRADS: Genomics Research in Alpha-1 Antitrypsin disease and Sarcoidosis**

- NIH funded, multicenter
- UCSF -- only West Coast center
- Study design: obtain clinical data, CT scans, blood, and BAL specimens for genomic, genetic and microbiomic analyses
- Goal: Identify markers for disease progression and determine the role of microorganisms in disease etiology and progression
- Enrollment: **NOW**

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Thank you for your attention!