Challenges in Pulmonary and Critical Care: 2018

Sarcoidosis: Update 2018

Faculty

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Disclosures

- Franck Rahaghi, MD, MHS, FCCP serves as a consultant and speaker for Mallinckrod.
Learning Objectives

1. Describe the pathophysiology and the epidemiology of Sarcoidosis.
2. Understand the up-to-date methodology for diagnosis of Sarcoidosis.
3. Review our current understanding of the treatments considered, including steroids, mineralocorticoid receptor agonists and treatments for advanced Sarcoidosis.

PRE-TEST QUESTIONS

Pre-test ARS Question 1

Pre-S1: Please rate your confidence in your ability to manage Sarcoidosis:
1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 2
Pre-S2: All of the below are true about Sarcoidosis, EXCEPT:
1. High prevalence populations include African Americans and the Nordic populations
2. Rare earth metals cause Sarcoidosis
3. Mycobacteria have been implicated in the etiology of Sarcoidosis
4. Sarcoid patients react to Kveim-Siltzbach test

Pre-test ARS Question 3
Pre-S3: Which one is correct regarding the diagnosis of Sarcoidosis?
1. Non-necrotizing granulomas make the diagnosis
2. ACE levels are helpful
3. T-suppressor cells to T-helper cells ratio is increased: CD8 to CD4 (>3.5)
4. Langerhans Giant Cells are at the center of granulomas

Pre-test ARS Question 4
Pre-S4: Regarding treatment of Sarcoidosis all are true EXCEPT:
1. Acute symptomatic Sarcoidosis is treated with steroids
2. Acute asymptomatic lymphadenopathy is not treated
3. A symptomatic patient with Scadding stage III CXR is treated with prednisone which is then tapered to 10mg and continued long term
4. Infliximab and RCI are therapies for advanced Sarcoidosis
Epidemiology

Worldwide: 1.2 million
United States: 150,000

Diverse Features of Sarcoidosis

Etiology

- POSSIBLE ETIOLOGIES — The multicenter NIH-funded ACCESS case-control study of over 700 patients and nearly 30,000 relatives has been completed, and no single etiologic agent or genetic locus was clearly implicated in the pathogenesis of sarcoidosis
- Occupational and environmental exposures: Berylliosis
- Zirconium, barium, other rare earth metals
- World Trade Center (WTC) dust Exposure
**Etiology**

- **Kveim-Siltzbach reagent:** In 1961, Siltzbach noted that approximately 70 percent of patients with early sarcoidosis developed granulomatous inflammation four to six weeks after the intradermal injection of the Kveim-Siltzbach reagent (consisting of homogenates of human sarcoid tissue). However, multiple studies of the components of the Kveim-Siltzbach reagent have failed to identify a responsible antigen.

- **Infectious agents**
  - Numerous microorganisms, most notably mycobacteria and cutibacteria (formerly propionibacteria), have been implicated as possible etiologic agents of sarcoidosis.
  - In addition, the apparent transmission of sarcoidosis following cardiac and bone marrow transplantation has also provided support for an infectious etiologic agent.

**Pathophysiology**

- Accumulation of mononuclear inflammatory cells and T helper lymphocytes
- Formation of granulomas, aggregates of macrophages, epithelioid cells and multinucleated giant cells
Pathophysiology

- Giant cells in the central part of the granuloma.
- The central epithelioid and giant cells are surrounded by a rim of lymphocytes, mostly T-helper cells.
- T-cell lymphocytes are increased in areas of active granulomas.
Pathophysiology

- T-helper cells to T-suppressor cells ratio is increased: CD4 to CD8 (>3.5)
- Exaggerated T-cell activity indicates an altered immune response
- Hyperglobulinemia
- Mass affect of granulomas damages the tissues

What symptoms and clinical findings should prompt a clinician to consider sarcoidosis?

- Common signs and symptoms
  - Cough (usually nonproductive)
  - Fever and weight loss
  - Chest pain (central substernal)
  - Painful ankle swelling
  - Painful red nodules on shins
  - Eye pain or blurred vision
- Lung or thoracic lymph nodes almost always involved
- Lofgren syndrome: common presentation (fever, bilat hilar LAD, ankle swelling, erythema nodosum)
- Uveoparotid fever: hallmark presentation

Chest Radiographic Stages in Sarcoidosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Radiographic Appearance</th>
<th>Stage of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Bilateral hilar lymphadenopathy without infiltration</td>
<td>60%</td>
</tr>
<tr>
<td>II</td>
<td>Bilateral hilar lymphadenopathy with infiltration</td>
<td>25%</td>
</tr>
<tr>
<td>III</td>
<td>Inflammation alone</td>
<td>10%-22%</td>
</tr>
<tr>
<td>IV</td>
<td>Bilateral hilar lymphadenopathy, interlobular, subpleural, and/or pleuroparenchymal infiltration</td>
<td>1% to 5%</td>
</tr>
</tbody>
</table>
Additional Testing

• Complete blood count: anemia and leukopenia in >20%
• Renal function
• Serum calcium: hypercalcemia up to 10%
• 24-h urine test calcium levels: hypercalciuria up to 30%
• Liver function tests
• Tuberculin skin test
• Total immunoglobulins
• ECG: indicated in all patients
• Neurosarcoidosis evaluation: if unexplained neurologic symptoms or seizures

Elevated ACE

• Asbestosis
• Beryllium disease
• Coccidiodomycosis
• Diabetes mellitus
• Gaucher disease
• Histiocytosis disease
• Hypersensitivity pneumonitis
• Hypothyroidism
• Leprosy
• Lung cancer
• Primary biliary cirrhosis
• Sarcoidosis
• Silicosis
• Tuberculosis

The ACE level is elevated in 75 percent of untreated patients with sarcoidosis. However, serum ACE has limited utility as a diagnostic test, due to poor sensitivity (false negative results) and insufficient specificity (almost a 10 percent rate of false positive results).

Many conditions have elevated ACE Levels

How is sarcoidosis diagnosed? Do all suspected cases require biopsy?

• Diagnosis of exclusion

• Diagnosis generally requires:
  • typical noncaseating granuloma on biopsy PLUS
  • exclusion of other causes of granulomatous inflammation (e.g., tuberculosis)

• Confident diagnosis only at 3-6 months follow-up: if evolves in typical manner
Additional Imaging

- **FDG-PET scan**: Unclear role.
- The use of other tracers may, in the future, improve the utility of PET imaging in diagnosing sarcoid. In a small study (24 sarcoid, 17 lung cancer), the combination of 18F-FDG and fluorine-18-methyltyrosine (18F-FMT) PET scanning was able to differentiate sarcoidosis from malignancy; sarcoid lesions were positive on 18F-FDG PET but negative on 18F-FMT PET (both scans are positive in patients with cancer).
- FDG-PET scanning may also be useful in the evaluation of cardiac sarcoidosis, as a complement to magnetic resonance imaging.
- **Gallium-67** is a radioactive tracer that localizes in inflammatory foci, but is taken up minimally, if at all, by normal lungs. It is not recommended in the routine evaluation of sarcoidosis because a negative scan does not exclude disease and increased uptake in the lungs is not specific for sarcoidosis.

Biopsy

- Biopsy easily accessible sites preferentially:
  - Unexplained skin lesions or peripheral LAD
  - Otherwise: intrathoracic LAD or lung
- Mediastinoscopy bx – 100% yield, but more invasive
- Endobronchial endoscopic US – guided or TBNA options
- Bronchoscopy to Diagnose Sarcoidosis
  - **EBUS** has highest yield for Stage 1 disease
    - Over 80% of cases will be diagnosed
      - Lower yield if no adenopathy seen on chest x-ray
  - Transbronchial biopsy has higher yield when infiltrates are seen on chest CT scan: yield up to 90%
Non Caseating Granulomas: A Differential (and a Pneumonic...)

Sarcoidosis a Systemic Disease

Multicenter obserational study following etiology, socioeconomic status, and clinical course of sarcoidosis patients (1997-1999)
**Prognosis**

**Pulmonary**
- Stage III-IV chest radiograph
- Pulmonary hypertension
- Significant lung function impairment
- Moderate to severe dyspnea on presentation
- BAL neutrophilia at presentation

**Extrapulmonary**
- Cardiac: Age >40 at onset
- Neurologic: (except isolated CN palsy)
- Chronic uveitis
- Lupus pernio
- Splenomegaly
- Hypercalcemia
- Osseous disease

**Other**
- African-American
- Requirement for steroids within 6 months of presentation

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**References:**

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**Ocular:**
- Uveitis
- Pars planitis
- Optic neuritis
- Mutton fat keratic precipitates

**Neurologic:**
- Seizure
- Sixth cranial nerve palsy
- Lymphocytic meningitis
- Gallium enhancing lesion on MIBI

**Thoracic:**
- Bilateral hilar adenopathy
- Bilateral upper lobe infiltrates
- Perilymphatic nodules on HRCT
- Peribronchial thickening on HRCT

**Cardiac:**
- Pulmonary veno-occlusive disease
- Pulmonary hypertension
- Hypertensive myocardial disease

**Liver:**
- Increased alkaline phosphatase
- Hepatosplenomegaly
- Increased 1,25-dihydroxy vitamin D level

**Other:**
- PET enhancement of myocardium
- Gallium enhancement of myocardium
- Ventricular arrhythmias
- Cardiomyopathy

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**Decision to Treat**

[Diagram depicting decision-making process]

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Judson MA, Sarcoidosis Vasc Diffuse Lung Dis 2014; 31:19-27
Most Commonly Treated Manifestations of Sarcoidosis

- Large single-cohort retrospective analysis at the Medical University of South Carolina Multidisciplinary Sarcoidosis Clinic (1999-2010)

- N=1043.


- Cards, Parotid/Salivary Glands, Liver, Bone/Joints, Hypercalcemia, Ear/Nose/Throat, Skin, Neurologic, Muscle

Cause of Death in Sarcoidosis

- Patients With Organ Treatment (%)

Sarcoidosis Treatment Algorithm I

Clinical Phenotype

- Asymptomatic
  - No therapy
- Acute
  - Corticosteroid therapy
- Chronic
  - Cytotoxic and other second line therapies
- Advanced
  - Third line therapy

Steroid Use

As with most sarcoidosis therapies, optimal dose and duration of treatment remain unclear.

Treatment Algorithm for Symptomatic/Organ-Threatening Sarcoidosis
Sarcoidosis Treatment Pearls

- No one should be NOT treated if worsening
- No one should be ONLY on Prednisone if worsening or doing poorly
- Sarcoidosis had medical therapies that Work
- Don’t WATCH patients get worse!

Long Term Steroid Use

- Patients who need corticosteroids for long periods are at risk to toxicity, even if they are receiving a relatively low dose

Medical Therapies
Medical Therapies

There are 2 FDA-approved Therapies for Symptomatic Sarcoidosis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Route of administration</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>Oral</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Subcutaneous or intramuscular</td>
</tr>
</tbody>
</table>

FVC Change in Absolute Percent in Randomized Clinical Trial of Infliximab

References:

Methotrexate vs. Azathioprine

- A two-year, retrospective cohort study of 200 patients with sarcoidosis treated with methotrexate or azathioprine found that the daily prednisone dose decreased a mean of 6.32 mg/year, forced expiratory volume in one second (FEV1) increased 52 mL/year, vital capacity increased 95 mL/year, and diffusing capacity (DLCO) increased 1.23 percent/year.
- No significant differences were noted between the two treatments.
- Higher rate of infection with azathioprine (35 versus 18 percent).

IPF versus Sarcoïdosis Pulmonary Fibrosis

<table>
<thead>
<tr>
<th>Idiopathic Pulmonary Fibrosis</th>
<th>Sarcoïdosis Pulmonary Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most patients die from progressive fibrosis</td>
<td>Only a small percentage have progressive fibrosis.</td>
</tr>
<tr>
<td>Honeycombing in basilar and subpleural regions</td>
<td>Traction bronchiectasis in upper lobes.</td>
</tr>
<tr>
<td>Anti-inflammatory therapy has very limited role</td>
<td>Anti-inflammatory therapy is useful in most patients.</td>
</tr>
<tr>
<td>Acute exacerbations have a high morbidity and mortality</td>
<td>Acute events occur frequently and usually are self limited.</td>
</tr>
</tbody>
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International Delphi: 26 sarcoïdosis experts across the world

- There was consensus that treatment should be started for patients with symptoms and reduced FVC or DLCO, stage 2 or higher chest x-ray, or evidence of pulmonary infiltrates on HRCT.
- For asymptomatic patients, there was consensus not to treat stage 0 or 1 chest x-ray a FVC >80% predicted, or DLCO >70% predicted.
- Patients requiring oxygen supplementation or extra pulmonary disease (cardiac, neuro, or hypercalcemia), should also be considered for therapy.
- Glucocorticoids were the treatment of choice for initial therapy with an initial dose of 20-40 mg a day for prednisone or its equivalent.
International Delphi: 26 sarcoidosis experts across the world

- Prednisone tapering should be based on patient and physician preference.
- There was no consensus about when to begin tapering therapy. However, it was agreed that therapy should be considered ineffective if no response by 3-6 months.
- For patients who experienced toxicity or failed tapering of prednisone, steroid sparing alternatives should be considered.
- The first choice of non biologics was methotrexate. For patients who failed that treatment, infliximab was first choice of biologics.

Delphi Statement on RCI

- There was no agreement regarding the initial RCI dosage (40 vs 80 u sq q72 hours).
- However, it was agreed that an RCI maintenance dose should be used for those who responded and that the dose should be modified to individual response.
- There was also consensus that patients responding to RCI should have their oral corticosteroid dose tapered and withdrawn if possible.
- The group did not agree whether non-biologics such as methotrexate or azathioprine needed to be withdrawn during RCI therapy.
- Consensus was reached on contraindications to treatment including uncontrolled infections such as deep seated fungal infections and herpes simplex ocular infections.
- Strategies for treating edema, anxiety, and diabetes during RCI therapy were identified including dietary modification and RCI dose reduction.
- For patients hospitalized while on RCI, there was agreement that RCI could be continued except in cases of life-threatening infections.

Contraindications to RCI

The following conditions are contraindications to RCI:

- Latent TB
- Hypothyroidism
- Decompensated cirrhosis
- Any cirrhosis
- Uncontrolled osteoporosis
- Any osteoporosis
- Uncontrolled ocular HSV
- Any ocular HSV infection
- Recent surgery
- Uncontrolled hypertension
- Any hypertension
- Scleroderma
- Sensitivity to porcine products
- Patients self-injection

Mean Delphi Score

- For: 4.5
- No: 0.5
- Consensus: 2.5
- Against: 0.5

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Summary

- Etiology remains elusive and is probably different in all cases
- Pulmonary manifestations in most cases
- Combination of symptoms and end-organ damage/threat guide therapy
- No treatment needed if mild and stable
- All advanced or advancing disease deserve therapy
- Start with Steroids, escalate as needed with Cytotoxic Agents, Biologics and Repository Corticotropin

POST-TEST QUESTIONS

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