Thoracic Sarcoidosis and Sarcoid-like Reaction

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Objectives:
- Brief review of clinical history and pathophysiology of sarcoidosis
- Review both common and infrequent thoracic imaging findings associated with sarcoidosis
  - Lung parenchyma
  - Airways
  - Pleura
  - Lymphatics
- Review incidence and proposed etiology for sarcoid-like reaction.

Sarcoidosis:
- Originally described in 1877 by Jonathan Hutchinson.
  - Name derivation: skin lesions which looked like sarcoma.
- Multi-system disease of uncertain etiology.
  - Characterized by non-caseous epithelioid cell granulomas.
  - Lung and lymphatic involvement in 90% of patients, associated with morbidity/mortality.
  - Frequent involvement of skin, eyes.

Clinical Course:
- Self-limited, subclinical → Debilitation, death
  - Stable or remission in 10 years: 67%
    - Recurrence after remission: ~5%
  - Chronic disease leading to fibrosis: 20%
  - Death: ~5%
    - Usually related to lung fibrosis
    - Cardiac, neurologic disease

Epidemiology:
- Typically presents in adults under 40 years of age (peak 20–29 years).
- Variable incidence throughout the world.
  - Differences in environmental exposure, genetics, and surveillance.
  - Higher occurrence in women across ethnic groups.
- Worldwide highest annual incidence:
  - Northern Europe: 5–40 per 100,000
- United States adjusted annual incidence:
  - Three times higher among blacks versus whites: 11.5 vs 10.8 per 100,000.
- Black Americans:
  - More severe and chronic disease
  - Greater extrathoracic disease
- White Americans:
  - More likely asymptomatic at presentation
  - Rare in African and South American black populations.

References:
Mortality:

- 1988-2007:
  - Mortality increased 3% per year.
  - Highest absolute increased death rate among non-Hispanic black males.
  - Greatest increase in mortality: patients 55 years or older (regardless of race or sex).
  - Cause of death in the U.S. among those with sarcoidosis:
    - Sarcoidosis 58.8%
    - COPD 2.3%
    - Lung cancer 1.4%
    - Pneumonia 1.1%

Pathophysiology:
- Etiology remains unclear... Airborne?
  - Frequent involvement of skin, eyes, and lungs.
- Noncaseous epithelioid cell granulomas
  - Product of cell-mediated immunity
  - Activated alveolar macrophages & T cells produce IL-1, growth factors.
  - Recruits more T cells and fibroblasts

N.B.: ACE is product of macrophages, an indicator of granuloma burden.
  - 40% false neg; 10% false pos.

Clinical presentation:
- Asymptomatic in 50%: Incidental CXR findings.
- Most common symptoms: respiratory ailments
  - Cough, dyspnea, reactive airways
- Systemic symptoms: fatigue, night sweats, weight loss, erythema nodosum, arthritis.
- Lofgren syndrome: intrathoracic LAD, erythema nodosum, arthritis.


<table>
<thead>
<tr>
<th>Good prognostic signs</th>
<th>Poor prognostic signs</th>
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<tbody>
<tr>
<td>Bilateral hilar LAD</td>
<td>Age &gt; 40 years</td>
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<tr>
<td>Fever</td>
<td>Stage 2 or 3 at time of diagnosis</td>
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<tr>
<td>Polynythritis</td>
<td>Airways involvement</td>
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<tr>
<td>Erythema nodosum</td>
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</table>

- Pathognomonic:—

Imaging:
- Chest x-ray: bilateral hilar adenopathy is most common finding.
  - Bilateral hilar adenopathy: >95%.
  - Bilateral hilar, right paratracheal
  - Left paratracheal, AP window
  - Anterior mediastinal: <10%
  - Unilateral hilar: 1-3%

- Older at presentation: more likely to have atypical lymph nodes.

Lymph nodes:
- Non-calcified:
  - Calcified: related to disease duration.
    - 3% at 5 years.
    - 20% at 10 years.
    - Amorphous, hazy, eggshell.
Chest radiographs:

- Siltzbach staging system, developed 40 years ago; good prognostic value.
- Stage 0: normal 5–10%
- Stage 1: LAD 50%
- Stage 2: LAD & parenchyma 25–30%
- Stage 3: Parenchyma only 15%
- Stage 4: Lung fibrosis 10–20%

The importance of CT:

- Greater sensitivity for subtle or early disease
- High-resolution CT
  - Thin-section axial images (1–1.5mm)
  - Higher spatial resolution
  - Improved detection of subtle nodularity, reticulation, ground-glass opacity
- Expiratory images: small airway involvement

**Asbestos-related disease**
- Nodules
- Ground-glass opacity
- Solid alveolar opacity

**Chronic fibrosis**
- Bronchiectasis
- Architectural distortion
- Cystic changes
Parenchymal disease:
- Alveolitis, interstitial pneumonitis of alveolar walls.
- T-lymphocytes recruit macrophages → epithelioid cells.
- Nodular collections of these cells → interstitial granulomas.

- Congregate within lymph nodes and tissues with rich lymphatic supply.
  - Subpleural
  - Septal
  - Peribronchovascular

Perilymphatic nodules:
- Nodular thickening of fissures, pleural surfaces
- Thickened bronchovascular bundles

Three years later...
CT Imaging:
- Fine nodular pattern
- Reticulonodular pattern
- Coalescent nodules
  - Greater than 1 cm in >50% of pts.
  - May contain air bronchograms.
  - Satellite nodules around mass-like consolidation: "galaxy sign."
  - Ground glass opacity: sometimes surrounding solid opacity
    - Usually extensive interstitial granulomas, may reflect fibrosis.
- Coalescent nodules and masses:
  - Acinar: poorly marginated, small-large nodules.
  - Alveolar: coalescent acinar opacities, with or without air bronchograms.
  - Focal nodule or mass: rare, often requiring tissue sampling.
Lung fibrosis:
- Developing in up to 20% of patients.
- CT findings:
  - Mid-upper lungs
  - Linear opacities (subpleural, septal thickening)
  - Traction bronchiectasis/bronchiolectasis
  - Architectural distortion
  - Fibrocystic changes (bullae, cysts, honeycomb-like cysts)
  - Cavitary
    - Pseudocavitation with dense fibrous lining: <10%
    - Primary cavitary sarcoidosis with confluent granulomatous lining: <1%

Sarcoid-related pulmonary fibrosis:

Abehsera et al:
- CT imaging findings of 80 pts:
  - Bronchial distortion, central: 47% (38/80)
  - Honeycombing: 29% (23/80)
  - Linear opacities: 24% (24/80)
  - Nodular opacities significantly associated with linear opacities (87%) but not with honeycombing (15%).

Airway involvement:

- Airway involvement in nearly 2/3rd pts.
  - Often overlooked; unexplained symptoms.
- Frequency of airway involvement increases as parenchymal disease progresses.
- Associated with increased morbidity and mortality.

Extrinsic compression:

- Enlarged mediastinal and hilar lymph nodes.
- Significant luminal stenosis from adenopathy is uncommon.

Large central airways:

Trachea, mainstem bronchi affected less frequently than lobar and distal airways.

Granuloma formation: wall thickening.

Extrinsic compression is rare.

Medium-sized airways:

- Early stages:
  - Mucosal edema and inflammation
  - Associated with endobronchial granuloma formation
  - Producing mucosal nodularity (waxy yellow nodules)
  - Most profound within lobar/segmental bronchi.
  - Develop within airways and along bronchovascular bundles, near airways.


Bronchoscopy image courtesy of A. Ross Hill, M.D.
Medium-sized airways:

- Early stages:
  - Nodules may result in luminal stenosis or postobstructive atelectasis
  - Stenosis in up to 14% patients, typically minor, asymptomatic.

- Late stages:
  - Fibrotic mucosal changes:
    - Airway narrowing, distortion.
  - Fibrotic parenchymal changes:
    - Traction bronchiectasis, distortion.

Sarcoid-related pulmonary fibrosis:

Abehsera et al. CT imaging findings of 80 pts:
- Bronchial distortion, central: 47% (38/80)
- Honeycombing: 29% (23/80)
- Linear opacities: 24% (24/80)
- Nodular opacities significantly associated with linear opacities (57%) but not with honeycombing (15%).

Small-airway disease:

- Involvement of bronchioles: air-trapping.
- Can occur in early disease, with/without parenchymal involvement.
- Expiratory images

Hemoptysis:
- Typically result from complication such as Aspergilloma.
- Rarely caused by traction bronchiectasis (only handful of reported cases).

Smoking effects:

- ACCESS study:
  - The odds risk of sarcoidosis in patients who have ever smoked is significantly lower than lifelong non-smokers. (OR 0.65, CI 0.51–0.82, P < .001)

Sarcoidosis and Aspergillus:
- Pena et al studied incidence of aspergillus-related lung disease in sarcoidosis:
  + Approximately 2% (10 of 437 patients)
  + Incidence higher than compared to other chronic lung diseases.
  + All affected patients had fibrotic lung disease.
    - 4 had bilateral aspergillus disease.
    - 3 died: 2 from hemoptysis, 1 from surgery complications.


Smoking effects:

- Smokers had decreased frequency of bronchovascular bundle thickening (BVBT) than non-smokers on CT (11/38 (29%) vs 50/86 (58%), P = .003).
- BVBT less likely among ever-smokers (11/61 (18%) vs 27/63 (43%), P = .003) and current smokers (4/61 (7%) vs 15/63 (24%), P = .008).
- BVBT strongly associated with airway obstruction (25/37 (68%) vs 36/87 (41%), P = .008).
Smoking effects:


- Air trapping on expiration seen among 98% (45/46).
- No significant differences between smokers and nonsmokers:
  - Air trapping, consolidation, small nodules, reticulation.

Sarcoidosis and malignancy

- Controversial relationship between sarcoidosis and malignancy
- Higher incidence of lung cancer
- 5x increased likelihood of hematologic malignancy
- “Sarcoid-like reaction” described in small series and case reports
- Associated with several solid-organ malignancies

Sarcoid–like reaction:

- 2048 FDG PET/CT exams, malignancy patients
  - 23/2048 (1.1%): Sarcoid-like reaction suspected
  - 13/2048 (0.6%): Confirmed by path or clinico-radiological follow-up
- Restaging for suspected recurrence 10/13 (77%) vs primary staging 3/13 (23%) (p=0.05).

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<th>Manifestation (n, %)</th>
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<tr>
<td>Mediastinal nodal (11/13, 85)</td>
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<tr>
<td>Bilateral hilar (11/13, 85)</td>
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<tr>
<td>Pulmonary CT abnormality (9/13, 69)</td>
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<tr>
<td>Subpleural nodule (n=5)</td>
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<tr>
<td>Nodular infiltrate (n=2)</td>
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<tr>
<td>Ground-glass airspace opacity (n=2)</td>
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<tr>
<td>Pulmonary FDG abnormality (7/13, 54)</td>
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<tr>
<td>Extrathoracic FDG abnormality (6/13, 62)</td>
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Smoking effects:


- Smoking decreases inflammatory cytokines, TNF-alpha production by alveolar macrophages:
  - Products which contribute to granuloma formation.
- Smoking inhibits immune response responsible for granuloma formation.
- BVBT may be surrogate marker for assessment of disease burden or airway obstruction.
Sarcoid–like reaction:

- Pathogenesis remains unclear
- Tumor necrosis: TNF
- Cytokine responsible for activation of T cell-mediated factors: IFN, IL
- Recruitment and activation of macrophages
- Noncaseating granulomas
- Degenerating tumor... Sarcoid-like reaction?

Pleural involvement:

- Affects 5–10% of patients.
- Small-moderate effusions, clearing within 2–3 months.
- Chylothorax: Rare, several case reports.
  - Obstruction of thoracic duct.
Don’t forget:

- Nuclear medicine:
  - Gallium-67 citrate scintigraphy
  - Presence of active disease
  - Differentiating reversible (active) from irreversible (fibrotic) disease
  - Response to treatment
  - Extrathoracic disease

References:


Thank you!