SARCOIDOSIS

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Definition

• Sarcoidosis is a multisystem disorder of unknown etiology characterized by noncaseating granulomas in more than one organ or tissue.

• Occurs world-wide with high prevalence in Scandinavia, the United States, and Japan
Epidemiology

• **Race**- More common in blacks (40 per 100,000 blacks vs. 5 per 100,000 whites in U.S.

• **Age**- Usually manifest between ages of 20 to 40 years; rarely in children or the elderly

• **Sex**- Females equal to males worldwide
Etiology- Theories

1. A defect in the immune system  
2. An unidentified toxic substance  
3. An unknown environmental cause  
4. An inherited or genetic cause  
5. A viral or bacterial infection
Infectious agents → Organic particles → Inorganic agents

T cell → HLA/BTNL2 → Antigens

TNF-α, interleukin-12, -15, -18, GM-CSF, MIP, MCP-1

CD4+ T cell → Th1 cells, Interleukin-2, interferon-γ

Granuloma

Th2 cells, Interleukin-4, -5, -6, -10

Resolution → Fibrosis
Pathology

Characteristic lesion is the sarcoid GRANULOMA

Sarcoid granulomas are of noncaseating type, containing macrophages, epithelioid cells (modified macrophages), multinucleated giant cells, and lymphocytes.
Granulomas are shown in nasal mucosal tissue (Panel A), synovial tissue (Panel B), a scar on the skin (Panel C), the lung (Panel D, arrow points to
• 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
• Histologic studies of pulmonary sarcoidosis suggest a sequential course from alveolitis and granuloma formation to fibrosis
CYTOPLASMIC INCLUSION BODY
Schaumann body (arrow) is common in sarcoidosis but is nonspecific.
Organ Involvement

Sarcoid granulomas can be found anywhere in the body. Autopsy series indicate the following distribution:

- **Lungs**: 90%
- **Lymph nodes**: 50-78%
- **Spleen**: 54%
- **Liver**: 33-50%
- **Skin**: 13-20%
- **Bone Marrow**: 10%
- **Heart**: 5-25%

These percentages do not necessarily mean organ dysfunction.
Natural history of the sarcoid granuloma

Most resolve spontaneously

If they do not resolve, they are converted into avascular, acellular connective tissue

Granulomas persisting longer than a year or 2 show fibrosis

In late stages, this fibrosis extends beyond the granuloma into the surrounding tissue

It is the fibrosis associated with non-resolving granulomas that causes organ dysfunction in sarcoidosis
Clinical Presentation

3 types of clinical presentation:

1. CXR or lab abnormalities in asymptomatic patient (40-50% of all recognized cases)
2. Pulmonary symptoms
3. Systemic symptoms or extrapulmonary disease
Symptoms (Specific/Non-specific)

• Nonspecific
  – Fever, sweating
  – Weakness,
  – Weight loss
  – Aches and pains

• Organ specific symptoms
Sarcoidosis in thorax

- Lymph nodes
- Pulmonary (parenchymal, interstitial)
- Endo-bronchial
- Pleural effusion, thickening, nodule
- Pneumothorax
- Necrotizing sarcoid granulomatosis
Pulmonary manifestations

- Normal
- Mediastinal and hilar lymphadenopathy (paratracheal, hilar, aorto-pulmonary window)
- Reticular, nodular, ground glass involvement of upper and middle lung zones
- **Perilymphatic nodules (2-10mm)** around the broncho-vascular bundles, pleural and fissures
Interval development of multiple, bilateral pulmonary nodules throughout both lung fields + a fullness in the hila bilaterally.
• Asymptomatic
• Cough, shortness of breath, fever, weight loss
• Spontaneous resolution
• Imaging, PFT, TBLB (yields diagnosis in 40-90%)
Ocular presentation - 25%  
- Eye: Anterior or posterior uveitis, mass  
- Blurred vision, pain, photophobia and dry eyes  
- Keratoconjunctivitis sicca, Papilledema  
- Testing: Slit-lamp eye exam, MRI, biopsy  
- Chronic uveitis leads to glaucoma, cataracts and blindness
Skin involvement - 20%

- Erythema Nodosum (biopsy non-specific)
- Lupus pernio (biopsy)
- Nodules, flat patches (biopsy)
- Cutaneous anergy is common.
- LOFGREN'S SYNDROME; acute triad of erythema nodosum, joint pains, and bilateral hilar adenopathy
- Diagnosis: Appearance can be classic, biopsy to support
ERYTHEMA NODOSUM
These reddish raised lesions.
Lupus pernio

- Indurated blue purple swollen shiny lesions on nose, cheeks, lips, ears, fingers, rarely buttocks.
- Papules, nodules, and plaques
- Psoriatic like lesions
- Lesions in scars and tattoos
RAISED PLAQUES

These raised plaques are the result of coalescence of nodules
Liver involvement

- 33% have hepatomegaly or biochemical evidence of disease
- Symptoms usually absent, jaundice may occur
- Cholestasis, fibrosis, cirrhosis, portal hypertension, and the Budd-Chiari syndrome have been seen
Musculoskeletal

- Acute polyarthritis
- Fever, Pain, joint swelling
- Usually self limited
- Chronic destructive bone disease with deformity is rare
- Polymyositis and chronic myopathy
PUNCHED OUT LYTIC LESIONS
Focal osteolytic lesions in the fingers are most common abnormality.
LACY TRABECULAR PATTERN
Osteolysis has left a lacy trabecular pattern in this phalanx (arrow)
Cardiac manifestations

• Dysrhythmia,
• Pericardial involvement
• Pulmonary hypertension
• breathlessness
• Testing: EKG, echo, MRI with Gadolinium
• Can biopsy heart, but not typical
• Presumed if sarcoidosis affecting other organs

5% symptomatic, 30% incidental
Nervous System

- Cranial nerves, and peripheral nerves can be involved
- 7th nerve facial palsy is most common
- Acute, transient, and can be unilateral or bilateral
- **HEREFORDT'S SYNDROME**; facial palsy accompanied by fever, uveitis, and enlargement of the parotid gland
Nervous system

- Optic nerve dysfunction
- Papilledema
- Palate dysfunction
- Hearing abnormalities
- Paresthesias
- Meningeal granulomas
- Encephalopathy
T2-W MR IMAGE
High signal intensity edema surrounding biopsy proven sarcoid lesion.
Kidney

- Granulomatous interstitial nephritis produces renal failure
- Develops over a period of weeks to months
- Rapid response to steroid therapy
- Kidney stones (nephrolithiasis) and nephrocalcinosis are very unusual secondary to hypercalcemia and hypercalciuria
Lymph nodes

- Lymphadenopathy
- Intrathoracic nodes enlarged in 75-90% patients including hilar nodes and paratracheal nodes.
- Peripheral lymphadenopathy, cervical, axillary
- Abdominal lymphadenopathy
<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Lymphangitic carcinomatosis</td>
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<tr>
<td>Lymphoma</td>
<td>Idiopathic hemosiderosis</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>Alveolar cell carcinoma</td>
</tr>
<tr>
<td>Metastases</td>
<td>Pulmonary eosinophilia</td>
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<tr>
<td>Pneumoconioses</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Enlarged pulmonary arteries</td>
<td>Fibrosing alveolitis</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>Collagen disorders</td>
</tr>
<tr>
<td></td>
<td>Parasitic infection</td>
</tr>
</tbody>
</table>
Bilateral hilar prominence

Widening of right paratracheal stripe

Plain films

Obliteration of AP window

Multiple small pulmonary nodules
### Table 2
Reversible and Irreversible Abnormalities of Pulmonary Sarcoidosis at High-Resolution CT

<table>
<thead>
<tr>
<th>Reversible parenchymal abnormalities*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronodules, macronodules</td>
</tr>
<tr>
<td>Airspace consolidation: confluent alveolar opacities</td>
</tr>
<tr>
<td>Ground-glass opacities</td>
</tr>
<tr>
<td>Interlobular septal thickening</td>
</tr>
<tr>
<td>Intralobular linear opacities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Irreversible parenchymal abnormalities†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honeycomb-like opacities, cysts, bullae, emphysema</td>
</tr>
<tr>
<td>Architectural distortion</td>
</tr>
<tr>
<td>Traction bronchiectasis, bronchiolectasis</td>
</tr>
<tr>
<td>Volume loss in upper lobes, retraction of hila</td>
</tr>
<tr>
<td>Myetoma (in 10% of patients with end-stage sarcoidosis and a preexisting cavity)</td>
</tr>
</tbody>
</table>

*These features are suggestive of granulomatous inflammation.
†These features are indicative of chronicity and fibrosis.
## Staging of Sarcoidosis on the Basis of Chest Radiographs

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No abnormalities</td>
<td>5%–10%</td>
</tr>
<tr>
<td>1</td>
<td>Lymphadenopathy (fig. A)</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>Lymphadenopathy + pulmonary infiltration (fig. B)</td>
<td>25%–30%</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary infiltration (fig. C)</td>
<td>10%–12%</td>
</tr>
<tr>
<td>4</td>
<td>Fibrosis</td>
<td>5% (up to 25% during the course of the disease)</td>
</tr>
</tbody>
</table>

![Chest Radiographs](image)
Stage 0

• Stage 0 - Normal findings on chest radiograph
Stage I

- Stage I - Bilateral hilar lymphadenopathy, which may be accompanied by paratracheal adenopathy
Stage II

Bilateral hilar adenopathy with pulmonary infiltrates
Stage III

Parenchymal infiltrates without hilar adenopathy
Stage IV

- Advanced fibrosis with evidence of honey-combing, hilar retraction, bullae, cysts, and emphysema
Diagnosis

Three criteria:

1. Compatible clinical picture

2. Demonstration of noncaseating granulomas in one or more tissues (requires biopsy)

3. Exclusion of other granulomatous diseases, particularly AFB (very important)
Patient referred for possible sarcoidosis

- Biopsy with granuloma from nonpulmonary source
  - Yes
    - Clinical features suggesting sarcoidosis
    - No
  - No
    - Clinical features suggesting sarcoidosis
      - Yes
        - Biopsy with granuloma from lung (bronchoscopy)
      - No
        - No evidence of alternative diagnosis
          - Features highly consistent with sarcoidosis:
            - Serum ACE level >2 times upper limit normal
            - BAL lymphocytosis (CD4/CD8 >3.5)
            - Panda/lambda sign on gallium scan

- Sarcoidosis

  - Yes
    - Possible sarcoidosis; seek other diagnosis
  - No
    - Possible sarcoidosis; seek other diagnosis
- Imaging
- Histopathology (TBLB, Lymph node biopsy, TBNA)
- Serum angiotensin converting enzyme levels
- Mantoux test
- Serum electrolytes, RFT,
- ECG, holter monitoring
- PFT
Laboratory Abnormalities

• Vary with site of organ involvement

• Calcium- Increased GI absorption common; hypercalciuria 10-30%, sustained hypercalcemia in only 2% due to Vit. D production by granulomas

• Anemia- 5%

• Lymphopenia common

• Polyclonal gammopathy common

• Cutaneous anergy common
Angiotensin Converting Enzyme

- ACE produced by epithelioid cells in granulomas
- Serum ACE increased in 60% of patients
- Diagnostic use limited
  - False negative rate of 40%
  - False positive rate of 10%
- May be valuable in following disease activity
Pulmonary Function Tests

• Normal

• Decreased diffusing capacity: Often earliest PFT abnormality. Tends to remain low in spite of clinical remission

• Restrictive changes: Decreased VC, TLC. May improve with clinical remission

• Obstructive changes: Rarely in Stage 1 disease due to endobronchial granulomas. More common in Stage 3 disease due to traction, distortion of airways by fibrotic tissue
Biopsy Procedures in Sarcoidosis

<table>
<thead>
<tr>
<th>Biopsy Procedure</th>
<th>Diagnostic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Transbronchial biopsy</td>
<td>40-90</td>
</tr>
<tr>
<td>2. Scalene node biopsy</td>
<td>60-79%</td>
</tr>
<tr>
<td>3. Conjunctival biopsy</td>
<td>17-55%</td>
</tr>
<tr>
<td>4. Liver biopsy</td>
<td>24-94%</td>
</tr>
<tr>
<td>5. Skin lesion biopsy (not E. nodosum)</td>
<td>100%</td>
</tr>
<tr>
<td>6. Lymph node biopsy</td>
<td>85% (if palpable)</td>
</tr>
</tbody>
</table>
Do you always need a biopsy?

- Bilateral hilar adenopathy alone (Stage 1)
  
  If the patient is asymptomatic (except for fever) and has no evidence of extrapulmonary disease (except for erythema nodosum), s/he can be watched without a biopsy.

  (Not true, if patient HIV+ !)

- 65% will remit spontaneously
All bilateral hilar lymphadenopathy is not sarcoidosis

Important to exclude lymphoma and tuberculosis
Not all patients with sarcoidosis require treatment

1. Sarcoidosis has a high likelihood of spontaneous remission

2. Treatment of end-stage pulmonary fibrosis (honeycombing, bullae) is of no value

3. It is not clear that steroids alter the natural history of the disease
<table>
<thead>
<tr>
<th>Stage</th>
<th>Remission Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (BHL)</td>
<td>55-90%</td>
</tr>
<tr>
<td>Stage 2 (BHL + infiltrates)</td>
<td>40-70%</td>
</tr>
<tr>
<td>Stage 3 (Pulm. infiltrates)</td>
<td>10-20</td>
</tr>
<tr>
<td>Overall</td>
<td>20-25% permanent loss of lung function</td>
</tr>
<tr>
<td></td>
<td>5-10% die</td>
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</tbody>
</table>
Indications for Steroids

1. Symptomatic pulmonary disease
2. Progressive parenchymal lung disease over 2 years
3. Posterior ocular disease (uveitis, iridocyclitis) or anterior disease not responding to topical steroids
4. Persistent fever, weight loss, anorexia, etc.
5. Significant liver disease
6. CNS disease
7. Hypercalcemia
8. Myocardial disease
9. Thrombocytopenia
10. Lupus pernio
11. Symptomatic bone cysts
Treatment options- first line

CONSIDER NOT TREATING!

– Can wait up to 6 months to see if spontaneous remission occurs (especially pulmonary)
Treatment options

**Steroids are the mainstay of treatment**

– Start at 20-40 mg/day of prednisone

– May need more or intravenous if severe, difficulty expected, or acute disease

– Slowly taper over 2-3 months with monitoring for clinical/radiological worsening, to lowest dose (5-10 mg every alternate day) and continue

– Total duration usually 9-12 months, may be prolonged
WATCH FOR STEROID SIDE EFFECTS

• Weight gain
• Blood sugar
• Blood pressure
• Thinning of skin
• Osteoporosis
Treatment options - second line

If prednisone intolerance, contraindicated or to spare its effects

**Methotrexate (5-20mg/week)**
- Liver toxicity, lung toxicity, mouth sores, abortion
- Blood counts, Cr, and liver function monthly, biopsy?

**Azathioprine (1-3mg/kg/day)**
- Low blood counts, diarrhea, small increase in malignancy
- Blood counts and liver function monthly

**Hydroxychloroquine**
mainly used in hypercalcemia and skin involvement
<table>
<thead>
<tr>
<th>Organ</th>
<th>Clinical Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>Dyspnea plus FEV&lt;sub&gt;1&lt;/sub&gt;, FVC &lt;70%</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Cough, wheezing</td>
<td>Inhaled corticosteroid</td>
</tr>
<tr>
<td>Eyes</td>
<td>Anterior uveitis</td>
<td>Topical corticosteroid</td>
</tr>
<tr>
<td></td>
<td>Posterior uveitis</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td>Skin</td>
<td>Lupus pernio</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Plaques, nodules</td>
<td>Hydroxychloroquine, 400 mg/day</td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
<td>Methotrexate, 10–15 mg/wk</td>
</tr>
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<td></td>
<td>Central nervous system</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Cranial-nerve palsies</td>
<td>Prednisone, 40 mg per day</td>
</tr>
<tr>
<td></td>
<td>Intracerebral involvement</td>
<td>Azathioprine, 150 mg/day</td>
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<tr>
<td></td>
<td></td>
<td>Hydroxychloroquine, 400 mg/day</td>
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<tr>
<td></td>
<td>Heart</td>
<td>Pacemaker†</td>
</tr>
<tr>
<td></td>
<td>Complete heart block</td>
<td>AICD</td>
</tr>
<tr>
<td></td>
<td>Ventricular fibrillation, tachycardia</td>
<td>AICD; prednisone, 30–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Decreased LVEF (&lt;35%)</td>
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<tr>
<td></td>
<td>Liver</td>
<td>Prednisone, 20–40 mg/day</td>
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<tr>
<td></td>
<td>Cholestatic hepatitis with constitutional symptoms</td>
<td>Ursodiol, 15 mg/kg of body weight per day</td>
</tr>
<tr>
<td></td>
<td>Joints and muscles</td>
<td>Prednisone, 20–40 mg/day</td>
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<tr>
<td></td>
<td>Arthralgias</td>
<td>NSAID</td>
</tr>
<tr>
<td></td>
<td>Granulomatous arthritis</td>
<td></td>
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<tr>
<td></td>
<td>Myositis, myopathy</td>
<td>Prednisone, 20–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Hypercalciuria and hypercalcemia</td>
<td>Prednisone, 20–40 mg/day</td>
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<tr>
<td></td>
<td>Kidney stones, fatigue</td>
<td>Hydroxychloroquine, 400 mg/day</td>
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THANK YOU