

Sarcoidosis

Clinical Background

Sarcoidosis is a multisystemic disorder of unknown etiology, characterized by granuloma formation.

Epidemiology

- Incidence – 10-15/100,000 in U.S.; 40/100,000 in some North European countries and among African Americans
- Age – peak incidence in 20s-30s
- Sex – M<F
- Ethnicity – most prevalent in Swedish, Danish and African-Americans

Risk Factors

- Family member with sarcoidosis (5-fold increased risk)

Pathophysiology

- Result of chronic immunological response associated with a genetic susceptibility and specific infections or environmental factors
- Accumulation of activated T-cells and macrophages at site of disease activity
- Lymphocytes are CD4 type
- Macrophages release cytokines that drive inflammation, granuloma formation and eventual fibrosis

Disease Stages

- Stage I – isolated thoracic lymphadenopathy
- Stage II – lymphadenopathy plus lung infiltration
- Stage III – lung infiltration
- Stage IV – overt pulmonary fibrosis

Clinical Presentation

- Asymptomatic (30-50%) diagnosed by routine chest x-ray with abnormalities of hilar adenopathy
- Nonspecific (30%) – fever, weight loss, fatigue
- Pulmonary (30%)
 - Löfgren syndrome – bilateral hilar adenopathy, ankle arthritis, fever, myalgia, weight loss and erythema nodosum
 - Dyspnea, wheezing
- Dermatologic – maculopapular rashes, plaques and nodules (lupus pernio), erythema nodosum and lupus pernio
- Cardiac – rhythm disorders, infiltrative cardiomyopathy and pericarditis
- Ophthalmic – anterior uveitis
- Hepatic/splenic – granulomas, but dysfunction is rare
- Endocrine – hypercalcemia with nephrolithiasis
- Central nervous system (CNS) – neurosarcoidosis is an uncommon but serious manifestation of sarcoidosis, affecting about 5-10% of patients
 - Most common manifestations include myelopathy, cranial neuropathy and encephalopathy
 - Untreated patients may develop acute neurologic emergencies, including seizures, cord compression and increased intracranial pressure
 - Heerfordt syndrome – uveitis, parotid gland enlargement, fever and cranial neuropathy (usually 7th nerve)

Diagnosis

- Indications for testing – lymphadenopathy on chest x-ray or other appropriate clinical signs and symptoms consistent with diagnosis of sarcoidosis
- Laboratory testing
 - Rule out other granulomatous diseases – consider stains and cultures for fungi and tuberculosis (TB test)
 - Chemistry panel – may demonstrate hypercalcemia (~10%), hypercalcuria (~30%) or liver transaminase elevations (~20%)
 - Angiotensin converting enzyme (ACE) – may have elevated level (2x normal) but this is not diagnostic for disease
 - Reflects disease activity and may be useful to follow disease activity
 - Cerebrospinal fluid (CSF) ACE – elevated level supports diagnosis of neurologic sarcoidosis but is not diagnostic
- Histology – presence of noncaseating granulomas
 - Usually obtained by bronchoscopy; may be obtained from other organ sites
- Fiber optic bronchoscopy with bronchoalveolar lavage, transbronchial biopsy or endobronchial biopsy
 - CD4/CD8 ratio higher than 3.5 is suggestive of sarcoidosis and is further supported if ACE levels are abnormal (sensitivity 52-59%; specificity 94-96%)
 - Biopsy has better yield if 4-5 specimens are obtained
 - If criteria above are met and clinical presentation is consistent with sarcoidosis, absence of granulomas on biopsy does not negate the diagnosis of sarcoidosis
- Pulmonary function testing – full function testing with diffusing capacity of the lung for carbon monoxide (DLCO) demonstrates decreased volumes and diffusion capacity
- Imaging studies
 - Pulmonary disease – high resolution CT produces better diagnostic yield than a chest x-ray; classically shows widespread micronodules with perilymphangitic distribution in middle and upper lobes (unnecessary test for most patients)
 - Justified when there are atypical chest x-rays or normal chest x-rays but suspicion of disease
 - Useful for detection of lung disease complications
 - Central nervous system (CNS) disease
 - Gadolinium-enhanced MRI

Differential Diagnosis

- Lung
 - Infectious
 - *Mycobacterium tuberculosis*
 - Atypical mycobacterium
 - Fungi
 - *Pneumocystis jiroveci*
 - Occupational
 - Hypersensitivity pneumonitis
 - Pneumoconiosis – beryllium, aluminum, titanium
 - Drug reactions
 - Wegener granulomatosis
- Lymph node
 - Infectious

- *Mycobacterium tuberculosis*
- Atypical mycobacterium
- Toxoplasmosis
- Brucellosis
- *Bartonella*
- Malignancy
 - Hodgkin lymphoma
 - Non-Hodgkin lymphoma
- Skin
 - Infectious
 - *Mycobacterium tuberculosis*
 - Atypical mycobacterium
 - Fungi
 - Rheumatoid nodules
- Liver
 - Infectious
 - *Mycobacterium tuberculosis*
 - Atypical mycobacterium
 - Brucellosis
 - Schistosomiasis
 - Autoimmune
 - Primary biliary cirrhosis
 - Crohn disease
 - Malignancy
 - Hodgkin lymphoma
 - Non-Hodgkin lymphoma
- Bone marrow
 - Infectious
 - *Mycobacterium tuberculosis*
 - Atypical mycobacterium
 - Histoplasmosis
 - Cytomegalovirus
 - Epstein-Barr virus

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Angiotensin Converting Enzyme, Serum 0080001 Method: Enzymatic	Support diagnosis of sarcoidosis or neurosarcoidosis via ACE levels in serum Evaluate response to treatment via ACE	Antihypertensive medications such as ACE inhibitors, ACE receptor blockers and diuretics may interfere with test results This test is not specific for diagnosis of sarcoidosis Test is a nonspecific indicator of response to treatment In neurosarcoidosis, serum ACE concentrations are less likely to be elevated than CSF ACE concentrations. CSF ACE levels are increased in about 55% of patients with neurosarcoidosis, 5% of those with sarcoidosis (without neurologic abnormality) and 13% of those with other neurological diseases	Further tissue biopsy and evaluation for granulomas is necessary to confirm the diagnosis
Angiotensin Converting Enzyme, CSF 0098974 Method: Spectrophotometry	Support diagnosis of sarcoidosis or neurosarcoidosis via ACE levels in CSF Evaluate response to treatment via ACE	Antihypertensive medications such as ACE inhibitors, ACE receptor blockers and diuretics may interfere with test results This test is not specific for sarcoidosis Test is a nonspecific indicator of response to treatment	

<p>Lymphocyte Subsets Panel 4 - T-Cell Subsets Percents & Ratio, Bronchoalveolar Lavage 0093420</p> <p>Method: Flow Cytometry</p>	<p>Assist in the diagnosis of sarcoidosis when biopsy is negative</p>		
<p>Calcium, Serum or Plasma 0020027</p> <p>Method: Spectrophotometry</p>	<p>Evaluate for presence of hypercalcemia</p>		
<p>Calcium, Urine 0020472</p> <p>Method: Spectrophotometry</p>	<p>Evaluate for presence of hypercalcemia</p>		
<p>Aspartate Aminotransferase, Serum or Plasma 0020007</p> <p>Method: Enzymatic</p>	<p>Evaluate for liver disease involvement</p>		
<p>Alanine Aminotransferase, Serum or Plasma 0020008</p> <p>Method: Enzymatic</p>	<p>Evaluate for liver disease involvement</p>		
<p>Alkaline Phosphatase, Serum or Plasma 0020005</p> <p>Method: Enzymatic</p>	<p>Evaluate for liver disease involvement</p>		
<p>QuantiFERON®-TB Gold In Tube & <i>Mycobacterium tuberculosis</i> Antibody, IgG 2001627</p> <p>Method: Cell Culture/Enzyme-Linked Immunosorbent Assay</p>	<p>Rule out other granulomatous diseases</p>		

<p>Hepatic Function Panel 0020416</p> <p>Method: Refer to individual components.</p>	<p>Evaluate for liver disease involvement</p>		
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Guidelines

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General References

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