SARCOIDOSIS
Definition

- Derives from Greek:
  - *sarco* - flesh
  - *eidos* - like
  - *osis* - condition
- “Formation of abnormal flesh”
- A systemic disorder of unknown etiology characterized by non-caseating, granulomatous inflammation that can affect virtually any organ
EPIDEMIOLOGY

- Prevalence - 10 to 20 per 100,000 population
  - less than 1 per 100 000 (Spain, Portugal, Italy, Saudi Arabia, and India)
  - 20-40 per 100 000 (US Puerto Ricans/Hispanics)
  - over 50 per 100 000 (Sweden, Denmark, and US African-Americans)

- Lifetime risk in US:
  - blacks - 2.4 %,
  - whites - 0.85%

- Young adults 20-40 years old
  - 70 % of cases

- Slightly higher rate for women
Heterogeneity in Disease Presentation and Severity

- Blacks - more severe disease
- Whites - more likely asymptomatic
- Chronic uveitis in US blacks
- Lupus pernio in Puerto Ricans
- Erythema nodosum in Europeans
- Cardiac and ocular sarcoidosis in Japan
- Mortality from sarcoidosis is 1 to 5 %
Sarcoidosis: clinical features

- Non-caseating granuloma in involved organs
- Arthritis, dactylitis
- Pulmonary parenchymal disease
- Hilar adenopathy
- Erythema nodosum
- Skin lesions
- Uveitis
- Keratoconjunctivitis
- Myopathy

- Parotitis
- Central and peripheral nervous system involvement
- Anergy
- Hepatosplenomegaly
- Lymphadenopathy
- Hypergammaglobulinemia
- Hypercalcemia, hypercalciuria
- Elevated angiotensin converting enzyme (ACE)
<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Presenting (%)</th>
<th>Cumulative (%)</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>25</td>
<td>95</td>
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<tr>
<td>Constitutional</td>
<td>24</td>
<td>33-70</td>
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<tr>
<td>Adenopathy</td>
<td>20</td>
<td>90</td>
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<tr>
<td>Joint disease</td>
<td>14</td>
<td>≤ 38</td>
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<tr>
<td>Uveitis</td>
<td>7</td>
<td>25-50</td>
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<tr>
<td>Hepatosplenomegaly</td>
<td>4</td>
<td>5-10</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>3</td>
<td>25-30</td>
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<tr>
<td>Other</td>
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<td>-</td>
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<tr>
<td>Heart</td>
<td>&lt;1</td>
<td>5-10</td>
</tr>
<tr>
<td>Neurologic</td>
<td>&lt;1</td>
<td>5-10</td>
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<tr>
<td>Muscle</td>
<td>&lt;1</td>
<td>5</td>
</tr>
<tr>
<td>Bone</td>
<td>&lt;1</td>
<td>3-13</td>
</tr>
</tbody>
</table>

*At autopsy, 20-67% have heart involvement; on biopsy, 50-80% have muscle and liver involvement*
Clinical manifestations of sarcoidosis in different groups

- Bone marrow
- Skin
- Hypercalcemia
- Liver
- Eye
- Lymph node
- Neurologic
- Hypercalcemia
- E. nodosum
- Eye
- Hypercalcemia
- Lymph node

- Caucasian
- African American
- Male
- Female
- Age <40 yrs
- Age ≥40 yrs

* Other than erythema nodosum
Respiratory tract

- The clinical spectrum ranges from asymptomatic hilar adenopathy to an interstitial lung disease with alveolitis
- Symptoms:
  - dry cough (30%)
  - dyspnea (28%)
  - chest pain (15%)
  - hemoptysis (rare)
- HRCT of the lungs may show abnormalities when chest radiographs are normal
- PFT’s: restricted lung volumes and loss of diffusing capacity
Classification of pulmonary involvement in sarcoidosis

The Scadding scale

- **Stage I** - bilateral hilar adenopathy
- **Stage II** - bilateral hilar adenopathy and interstitial infiltrates
  - upper more than the lower lung zones
- **Stage III** - interstitial disease with shrinking hilar nodes
- **Stage IV** - advanced fibrosis
Bilateral Hilar Adenopathy
Sarcoidosis, Stage 2

Chest radiograph. Bilateral enlarged hilar lymph nodes as well as right paratracheal and aortopulmonary lymph nodes are visible. Fine linear and reticular opacities are present in the perihilar lung parenchyma. Courtesy of Paul Stark, MD.
Sarcoidosis  Left: The chest radiograph shows interstitial disease (multiple small nodules in the mid-to-upper zones) with shrinking hilar nodes (Stage III). Right: HRCT shows the beaded or irregular thickening of the bronchovascular bundles, with nodules along bronchi, vessels, and subpleural regions. Courtesy of Talmadge E King Jr, MD.
Long standing sarcoidosis  The chest radiograph shows interstitial opacities with upper zone predominance, volume loss, and advanced fibrosis (Stage IV). Courtesy of Talmadge E King, Jr, MD.
Pulmonary sarcoidosis

(a) Radiograph of patient with pulmonary sarcoidosis showing minimal changes. 
(b) CT scan of the chest done at the same time shows extensive changes.
**Sarcoidosis**  Transbronchial biopsy findings are consistent with the clinical diagnosis of sarcoidosis. The histopathologic specimen shows granulomatous inflammation. Courtesy of Talmadge E King Jr, MD.
A 32-year-old woman is evaluated for possible systemic disease associated with right eye pain and redness. She was recently diagnosed with anterior uveitis by her ophthalmologist. She is otherwise healthy. Her only medication is a topical corticosteroid prescribed by the ophthalmologist.

On PE, vital signs are normal. The right eye is red, and there is ocular injection concentrated around the iris. The remainder of the examination is normal.
Which of the following is an appropriate initial test for this patient?

A. Anti–double-stranded DNA antibody assay
B. Anti-Ro/SSA antibody assay
C. Chest radiograph
D. Rheumatoid factor
Ophthalmologic

- All patients with sarcoidosis should have a baseline eye examination
- Acute anterior uveitis - the most common presentation (blurred vision, photophobia, excessive lacrimation)
- Frequently bilateral
- Approximately 20% of patients with uveitis will suffer some visual loss.
- Other:

  - interstitial keratitis
  - posterior uveitis
  - scleral plaques
  - lacrimal gland enlargement
  - corneal nodules
Dermatologic

- **Maculopapular eruption** on nares, lips, eyelids, forehead, rear of neck at the hairline, and previous trauma sites
- Waxy, pink **nodular lesions** on the face, trunk, and exterior surface of the arms and legs
- **Lupus pernio** - violaceous discoloration of the nose, cheeks, chin, and ears
- **Erythema nodosum** (panniculitis) - painful, erythematous nodules on the anterior surfaces of legs evolving into bruise-like lesions that resolve without scarring over a 2-8 weeks
Sarcoidosis Rash
Lupus pernio
Cardiovascular disease

- Arrhythmias: complete heart block, sudden death
- Symptoms: palpitations, syncope, dizziness, chest pain
- Chronic pulmonary hypertension and cor pulmonale
- Death from sarcoidosis commonly results from right ventricular failure
Neurologic disease

- Early phase - CNS
- Chronic stages - peripheral nerve and skeletal muscle
- Manifestations:
  - Hypothalamic hypopituitarism
  - Central diabetes insipidus
  - Hydrocephalus
  - Lymphocytic meningitis
  - Cranial nerve palsies, particularly facial palsy
Exocrine glands

- Painless swelling of the salivary glands
- Lacrimal gland enlargement, xerostomia, and xerophthalmia – sicca syndrome
- Pancreatitis
Renal and electrolyte abnormalities

- Increased intestinal calcium absorption
- Hypercalciuria
- Hypercalcemia
- Nephrocalcinosis
- Chronic renal failure and end-stage renal disease
Rheumatic manifestations of sarcoidosis

1. Arthropathy
2. Bone disease
3. Myopathy
4. Vasculitis
Acute arthritis

- In isolation or as part of Lofgren's syndrome
- Usually involves the knees and ankles
- Occasionally small joints arthritis of the hands may mimic the acute onset of RA
- Among a group of patients with arthritis of less than 2-years duration, the prevalence of sarcoidosis was 4%

In a prospective follow-up study of 189 patients presenting with symptoms suggestive of reactive arthritis, 17 (9%) were eventually diagnosed with acute sarcoid arthritis

- 10 had Lofgren's syndrome
- All 17 had bilateral ankle involvement

Migratory polyarthritis can resemble rheumatic fever

Young children with uveitis juvenile rheumatoid arthritis

Hyperuricemia is also common and arthritis of the foot and ankle can mimic gout

Lofgren’s syndrome

- Ankle or knee periarthritis, bilateral hilar adenopathy, erythema nodosum, fever, frequently uveitis
- Primarily in young Caucasian women
- Joints x-rays - soft tissue swelling without bony changes
- Arthrocentesis - no or only minimal, mildly inflammatory with a lymphocyte predominance synovial fluid
- Synovial biopsies - mild, non-specific synovitis without granuloma formation
- Dramatic response to corticosteroids
- Usually resolves without sequelae
Lofgren's syndrome.
Chronic arthritis

- Nondeforming arthritis with granulomatous synovitis
- Jaccoud's type deformity
- Joint swelling adjacent to a sarcoid bone lesion
- Dactylitis of one or more digits due to granulomatous involvement of the bone and soft tissue of the fingers
Chronic polyarthritis
DACTYLITIS
DACTYLITIS AND SKIN LESIONS

© ACR
BONE INVOLVEMENT

- Proximal and middle phalanges most frequently involved
- Skull, vertebrae, ribs, maxilla, and nasal bones also may be affected
- Bony lesions - usually cystic
- Lytic or sclerotic lesions of the spine
- Bone scan – nonspecific
- Biopsy often required
**Sarcoid arthropathy**  Hand radiograph shows multiple phalangeal cysts with erosion of the cortex in a patient with sarcoid arthropathy.
Bone cysts and sarcoid dactylitis
SARCOIDOSIS: HAND
(PEARCE 8TH)
MYOPATHY

- 50 to 80% of individuals with sarcoidosis, with less than 0.5% being symptomatic
- Insidious onset of proximal muscle weakness with normal or elevated serum levels of muscle enzymes
- Can present as a nodular myopathy with single or multiple painful nodules
- Myopathic pattern on EMG
- MRI and biopsy with granulomatous infiltration further support the diagnosis
VASCULITIS

- Small, medium, or large arteries
- Infiltration of the vessels by granulomas or granulomatous inflammation of the vessel wall
- More benign than in Wegener's granulomatosis
- Usually does not require the use of cytotoxic agents
- Prednisone 40 to 60 mg/day adequate in most cases
Diagnosis

- Clinical and radiographic findings involving at least 2 organs
- Histologic evidence of noncaseating granulomas
- Exclusion of other granulomatous diseases
Pulmonary Mimics of Sarcoidosis

- Granulomatous diseases
- Infections (fungal, mycobacterial, others)
- Chronic beryllium disease
- Hypersensitivity pneumonitis
- Other exposures (methotrexate, metals)
- Rheumatologic syndromes (Wegener's granulomatosis, Churg-Strauss syndrome)
- Lymphoma
- Tumor-associated granulomas
- Other parenchymal lung diseases (e.g. pulm fibrosis)
- Asthma
<table>
<thead>
<tr>
<th>Organ</th>
<th>Definite</th>
<th>Probable</th>
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</thead>
<tbody>
<tr>
<td><strong>Lungs</strong></td>
<td>1. Chest roentgenogram with one or more of the following:</td>
<td>1. Lymphocytic alveolitis by bronchoalveolar lavage (BAL)</td>
</tr>
<tr>
<td></td>
<td>- Bilateral hilar adenopathy</td>
<td>2. Any pulmonary infiltrates</td>
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<tr>
<td></td>
<td>- Diffuse infiltrates</td>
<td>3. Isolated reduced diffusing capacity for carbon monoxide</td>
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<td></td>
<td>- Upper lobe fibrosis</td>
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<td></td>
<td>2. Restriction on pulmonary function tests</td>
<td></td>
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<tr>
<td><strong>Skin</strong></td>
<td>1. Lupus pernio</td>
<td>1. Macular/papular</td>
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<tr>
<td></td>
<td>2. Annular lesion</td>
<td>2. New nodules</td>
</tr>
<tr>
<td></td>
<td>3. Erythema nodosum</td>
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<tr>
<td><strong>Eyes</strong></td>
<td>1. Lacrimal gland swelling</td>
<td>1. Blindness</td>
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<tr>
<td></td>
<td>2. Uveitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Optic neuritis</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td>1. Positive magnetic resonance imaging (MRI) with uptake in meninges or</td>
<td>1. Other abnormalities on magnetic resonance imaging (MRI)</td>
</tr>
<tr>
<td></td>
<td>brainstem</td>
<td>2. Unexplained neuropathy</td>
</tr>
<tr>
<td></td>
<td>2. Cerebrospinal fluid with increased lymphocytes and/or protein</td>
<td>3. Positive electromyogram</td>
</tr>
<tr>
<td></td>
<td>3. Diabetes insipidus</td>
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<tr>
<td></td>
<td>4. Bell’s palsy</td>
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<tr>
<td></td>
<td>5. Cranial nerve dysfunction</td>
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<tr>
<td></td>
<td>6. Peripheral nerve biopsy</td>
<td></td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td>1. Increased serum calcium with no other cause</td>
<td>1. Increased urine calcium</td>
</tr>
<tr>
<td><strong>Hypercalciuria</strong></td>
<td></td>
<td>2. Nephrolithiasis analysis showing calcium</td>
</tr>
<tr>
<td><strong>Nephrolithiasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>1. Treatment responsive cardiomyopathy</td>
<td>1. No other cardiac problem and either:</td>
</tr>
<tr>
<td></td>
<td>2. Electrocardiogram showing intraventricular conduction defect or nodal</td>
<td>- Ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>block</td>
<td>- Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>3. Positive gallium scan of heart</td>
<td>2. Positive thallium scan</td>
</tr>
</tbody>
</table>
## ACCESS Study Criteria for Organ Involvement in Patients With Biopsy-Confirmed Sarcoidosis-II

<table>
<thead>
<tr>
<th>Organ</th>
<th>Definite</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonthoracic lymph node</td>
<td></td>
<td>1. New palpable node above waist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Lymph node &gt;2 cm by computed tomographic (CT) scan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in patient with diabetes and/or hypertension</td>
</tr>
<tr>
<td>Renal</td>
<td>1. Treatment responsive renal failure</td>
<td>1. Compatible computed tomographic (CT) scan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Elevated alkaline phosphatase</td>
</tr>
<tr>
<td>Liver</td>
<td>1. Liver function tests &gt; three times normal</td>
<td>1. Enlargement by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Computed tomographic (CT) scan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radioisotope scan</td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
<td>1. Asymmetric painful clubbing</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>1. Unexplained anemia</td>
<td>1.</td>
</tr>
<tr>
<td></td>
<td>2. Leukopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Bone/joints</td>
<td>1. Cystic changes on hand or feet phalanges</td>
<td></td>
</tr>
<tr>
<td>Ears/Nose/Throat</td>
<td>1. Unexplained hoarseness with exam consistent with granulomatous involvement</td>
<td>1. Increased creatine phosphokinase (CK) aldolase which decreases with treatment</td>
</tr>
<tr>
<td>Muscles</td>
<td>1. Increased creatine phosphokinase (CK) aldolase which decreases with treatment</td>
<td>1. Increased creatine, phosphokinase (CK)/aldolase</td>
</tr>
</tbody>
</table>
Laboratory

- CBC, chemistry panel, LFT’s, 1,25-dihydroxyvitamin D level, ESR, CRP, SPEP
- RF (38%), ANA (speckled pattern 34%)
- Angiotensin-converting enzyme (ACE) level (40-90%) - produced by epithelioid cells and alveolar macrophages at the periphery of granuloma in response to an ACE-inducing factor released by T lymphocytes (not diagnostic)
Peripheral Blood

- T cell lymphopenia
- Decrease in the number of CD4+ T cells
- Decreased CD4+/CD8+ T cell ratio
- Hypergammaglobulinemia secondary to generalized B cell hyperactivity

Radiology

- CXR, HR CT lungs
- Gallium-67 citrate scanning
- MRI with gadolinium for brain involvement, myocardial disease, muscle disease and bone involvement
- Myocardial scintigraphy with thallium-201 and technetium-99
- Technetium-99 diphosphonate scanning can be used to detect bone lesions
Abnormal gallium scan in sarcoidosis

- The scan shows uptake in the lacrimal, parotid and salivary glands (panda sign) as well as mediastinal lymph nodes (lambda sign) and lungs.
Biopsy

- Tissue biopsy – the gold standard (transbronchial, LN, skin - the most common)
- The diagnostic yield:
  - transbronchial lung with normal CXR - 30-50%
  - transbronchial lung with abnormal CXR >90%
  - lymph node > 90%
  - minor salivary gland - 36%
  - parotid - 93%
  - muscle - 50-80%
  - liver - 50-80%
  - synovium in chronic arthropathy - 80%
  - conjunctival and lacrimal gland - 10-55%
  - skin > 90%
- Not diagnostic until other granulomatous diseases are excluded
BAL

- A total cell count of $60.7 \times 10^6$ compared to $24.8 \times 10^6$ cells in controls.
- Lymphocytic pleocytosis (>30-50%) with a predominance of CD4+ T cells as compared to peripheral blood or to lung lymphocytes in healthy controls.
- CD4/CD8 T-cell ratio > 3.5
  - 94% specific, 52% sensitive

Additional tests

- PFT’s (restrictive pattern, with a reduction in vital capacity, residual volume and total lung capacity)
- Tuberculin and anergy skin testing
- ECG
- 24-hour Holter monitor
- 2-D ECHO (pericardial effusions, concentric LVH with 'snowstorm' pattern, restrictive cardiomyopathy, ventricular dyskinesis, valvular incompetence)
- Ophthalmologic examination with slit-lamp
- Fluorescein angiography (posterior uveitis)
NATURAL HISTORY AND PROGNOSIS

Spontaneous Remission - 60%
Remission with steroids - 25%
Chronic Disease - 15%
Adverse Prognostic Factors in Patients with Sarcoidosis

<table>
<thead>
<tr>
<th>Adverse Prognostic Factor</th>
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<tbody>
<tr>
<td>Age on onset &gt; 40 years</td>
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<tr>
<td>Black race</td>
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<tr>
<td>Cardiac involvement</td>
</tr>
<tr>
<td>Chronic hypercalcemia</td>
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<tr>
<td>Chronic uveitis</td>
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<tr>
<td>Cystic bone lesions</td>
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<tr>
<td>Lupus pernio</td>
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<tr>
<td>Nasal mucosa involvement</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td>Neurosarcoidosis</td>
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<tr>
<td>Progressive pulmonary fibrosis</td>
</tr>
</tbody>
</table>
Management

- Patients with good prognostic signs - observe for the first 3-6 months
  - the potential for spontaneous resolution
- Corticosteroids - first-line treatment
- Immunomodulators:
  - Methotrexate
  - Azathioprine
  - Leflunomide
  - Antimalarial agents
Therapy

- **Pulmonary**- prednisone 40-60 mg for 8-12 weeks, chloroquine (750 mg/day, tapering by 250 mg every 2 months), MTX, AZA

- **Ophthalmic**- topical, injectable and systemic corticosteroids, AZA, MTX

- **Cutaneous**- topical or monthly intralesional injections of corticosteroids, systemic steroids, chloroquine (500 mg/day for 2 weeks, then 250 mg/day), HCQ, MTX
  - Anecdotal: Thalidomide, allopurinol, minocycline, PUVA and retinoids

- **Arthritis**- NSAIDs, Colchicine, Prednisone, Immunosuppressants
Other Treatments

- Anti-TNF-α
- Pentoxifylline (400 mg TID)
  - inhibits the synthesis of TNF-α
- Cyclophosphamide
- Endothelin receptor antagonists
  - antifibrotic effect
- Mycophenolate mofetil
- Thalidomide
Case report of refractory sarcoidosis, involving the lung, eyes, skin, and heart, which flared despite aggressive therapy.

Oculocutaneous sarcoid dramatically improved after treatment with the anti-TNF antibody infliximab.
Results: The study was terminated after the enrollment of 17 patients due to excessive treatment failures. Neither absolute levels of TNF-α nor TNF-α activity in the serum, BAL fluid, or alveolar macrophages were able to predict which patients would respond to etanercept.
Progressive cutaneous sarcoidosis responding to anti-TNF-α therapy


Lotus Mallbris MD
Anders Ljungberg MD
Mari-Anne Hedblad MD
Per Larsson MD, PhD
Mona Ståhle-Bäckdahl MD, PhD

Case report
Infliximab 5 mg/kg

**Conclusion:** inhibition of tumor necrosis factor-α may be useful as targeted treatment in cutaneous sarcoidosis
Chronic Recalcitrant Sarcoidosis Responding to Adalimumab

ACR abstract 2004

Jacob A. Aelion, Satish K. Odhav. The Arthritis Clinic, Jackson, TN

Three cases with chronic recalcitrant sarcoidosis of the bone and skin treated successfully with Adalimumab after failing other immunomodulating modalities.
TNF Inhibition as Novel Therapy for Refractory Sarcoidosis, Long Term Follow up

Nadera J. Sweiss¹, Madhu Gundavaram², James J. Curran¹, Michael H. Ellman¹.
¹University of Chicago, Chicago, IL; ²Weiss Memorial Hospital, Chicago, IL

ACR 2004 Abstract

Methods:

Results: A total of nine patients were identified. Infliximab was started at a dose of 3mg/kg, weeks, 0, 2 and every eight weeks. In one patient the treatment had to be discontinued because of recurrent infections, 8/8 patients receiving infliximab showed significant improvement as early as the second week of therapy. 8/8 patients had no recurrence of symptoms, the duration of follow up ranges between 4 weeks to 37 months. No adverse reactions were noted in eight patients.

Conclusion:
TNF inhibition is safe and effective in inducing remission in patients with refractory sarcoidosis; long-term side effects can’t be excluded.
Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement

- A phase 2, multicenter, randomized, double-blind, placebo-controlled study
- 138 patients with chronic pulmonary sarcoidosis randomized to IV infliximab (3 or 5 mg/kg) or placebo at Weeks 0, 2, 6, 12, 18, and 24
- Patients in the combined infliximab groups (3 and 5 mg/kg) had a mean increase of 2.5% from baseline to Week 24 in the percent of predicted FVC, compared with no change in placebo-treated patients (p = 0.038).

Am J Respir Crit Care Med. 2006 Oct 1;174(7):795-802
# Surveillance Intervals for Patients with Sarcoidosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surveillance Intervals</th>
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<tbody>
<tr>
<td>I</td>
<td>Initially every 6 months, then annually if stable</td>
</tr>
<tr>
<td>II, III, IV</td>
<td>Initially every 3 – 6 months</td>
</tr>
<tr>
<td>Serious extrapulmonary involvement</td>
<td>Monitor indefinitely</td>
</tr>
<tr>
<td>Monitor three years after cessation of therapy for potential relapse, subsequent follow-up not necessary if stable</td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

- Sarcoidosis is a systemic inflammatory disorder of unknown etiology characterized by non-caseating, granulomatous inflammation that can affect virtually any organ.
- In addition to non-caseating granulomas on histology, characteristic clinical, radiologic findings and exclusion of alternative granulomatous diseases are required for the diagnosis.