

## Review Article

# Sarcoidosis

### Durga Balagopalan

Asst. Professor, Dept. of Pulmonary Medicine,  
Malabar Medical College, Modakkallur, Kozhikode.

Sarcoidosis is a multisystem disorder of unknown origin characterized by non caseating granulomatous inflammation at sites of disease. The modern history of sarcoidosis goes back to 1899, when the Norwegian dermatologist Caesar Boeck coined the term to describe skin nodules characterized by compact, sharply defined foci of "epithelioid cells with large pale nuclei and also a few giant cells."<sup>1</sup> Thinking this resembled sarcoma, he called the condition "multiple benign sarcoid of the skin."<sup>1</sup> Ninety percent of sarcoidosis patients will present with some form of lung disease, which may be asymptomatic.

### Epidemiology

Sarcoidosis affects people of all racial and ethnic groups and occurs at all ages, although it usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years.<sup>3</sup> The incidence of sarcoidosis varies widely throughout the world, probably because of differences in environmental exposures, surveillance methods, and predisposing HLA alleles and other genetic factors. The highest annual incidence of sarcoidosis has been observed in northern European countries (5 to 40 cases per 100,000 people).<sup>1, 2</sup>

Sarcoidosis is an under diagnosed disease in India. However, owing to the increasing awareness, now-a-days it is being diagnosed more frequently than a few decades ago. Most Indian patients with sarcoidosis are males and present in the fourth or fifth decade of life.<sup>13</sup> Amongst few estimates that are available, sarcoidosis constituted 10-12 cases per 1000 new registrations annually at a respiratory unit in Kolkata, Marwari community being at a higher risk. Another estimate at an institute in Delhi found 61.2 / 100,000 new cases.

### Environmental Causes

Sarcoidosis most commonly involves the lungs, eyes, and skin. So the search for environmental causes has focused on exposures to airborne antigens. Various associations reported in different studies include

1. Emission from wood-burning stoves
2. Tree pollen<sup>3</sup>
3. Exposure to inorganic particles<sup>4</sup>
4. Insecticides<sup>5</sup>
5. Moldy environments<sup>5,6</sup>
6. Metal working<sup>6</sup>
7. Fire fighting<sup>7</sup>
8. Handling of building supplies<sup>8</sup>

Mycobacterial and Propionibacterium acne DNA and RNA have been recovered from sarcoid tissue by polymerase-chain-reaction technique.

### Genetic Features

Familial sarcoidosis was first reported in 1923 in two affected sisters.<sup>16</sup> The concordance appears to be higher in monozygotic twins than in dizygotic twins.<sup>17</sup>

### Genetic Associations

HLA genes

1. HLA-B8
2. HLA-DRB1 and DQB1
3. HLA-DQB1\*0201 and HLA-DRB1\*0301

Non-HLA candidate genes

1. Butyrophilin-like 2 (BTNL2) gene on chromosome 6p
2. Chromosome 3p
3. Chromosome 5q11.2
4. Chromosome 5p15.2.

## Immunopathogenesis

The development and accumulation of granulomas constitute the fundamental abnormality in sarcoidosis<sup>9</sup>. Granulomas are compact, centrally organized collections of macrophages and epithelioid cells encircled by lymphocytes. Main feature of sarcoidosis is the presence of CD4+ T cells that interact with antigen-presenting cells to initiate the formation and maintenance of granulomas. These activated CD4+ cells differentiate into type 1 helper T (Th1)-like cells and secrete predominantly interleukin-2 and interferon- $\gamma$ , augment macrophage Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) production, and amplify the local cellular immune response.<sup>10</sup> Although granulomas may resolve with little consequence, pulmonary fibrosis occurs in 20 to 25% of patients with sarcoidosis. Overproduction and unopposed activity of Matrix metalloproteinase(MMP), particularly matrix metalloproteinase 8 and 9 initiates extracellular-matrix breakdown and remodeling. A shift from cytokines produced by Th1 cells (mainly interleukin-2 and interferon- $\gamma$ ) to cytokines produced by type 2 helper T (Th2) cells (mainly interleukins 4, 10, and 13) also appears to be central to the development of fibrosis.<sup>11</sup> Alveolar macrophages activated in the context of Th2 cytokines produce high levels of fibronectin and the CC motif ligand 18 (CCL18) chemokine<sup>12</sup>, which up-regulates collagen production by lung fibroblast.

## Clinical Features

Sarcoidosis often comes to attention when abnormalities are detected on a chest radiograph during a routine screening examination. Systemic symptoms such as fatigue, night sweats, and weight loss are common. The organ system that is most affected varies with the given patient (Table 1). Löfgren's syndrome, an acute presentation consisting of arthritis, erythema nodosum, and bilateral hilar adenopathy, occurs in 9 to 34% of patients.<sup>1</sup> Erythema nodosum is observed predominantly in women, but marked ankle periarticular inflammation or arthritis without erythema nodosum is more common in men.

## Diagnosis

The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic findings, supported by histologic evidence in one or more organs

of non caseating epithelioid-cell granulomas in the absence of organisms or particles.<sup>1</sup>

The chest radiograph is abnormal in more than 90 percent of known cases and carries prognostic information

## Radiologic Classification

1. Stage 0 (5 to 10%) - A normal chest radiograph, with extrapulmonary manifestations.

2. Stage I (40 %) - hilar adenopathy without evidence of interstitial infiltrates. Often, hilar adenopathy has a discrete, symmetric "potato node" appearance, and is accompanied by right paratracheal lymphnodes. Calcification of hilar lymph nodes is uncommon.

3. Stage II (30 to 50 %) bilateral hilar adenopathy and pulmonary infiltrates (Infiltrates can be fine linear markings and small reticulonodules, particularly in mid- and upper lung zones. Occasionally, the infiltrates consist of discrete nodules or areas of fluffy "alveolar" consolidation. A miliary pattern may also be seen).<sup>20</sup>

4. Stage III Pulmonary infiltrates without bilateral hilar adenopathy

5. Stage IV Extensive pulmonary fibrosis and scarring

## Investigations

The Kveim-Siltzbach test has been used for many years in the diagnosis of sarcoidosis. The test is performed by injecting homogenate of human sarcoid tissue extract intradermally. The papule that develops at the site of injection after 4 weeks is biopsied. This test is now used less often for several reasons. First, no commercially available preparation of the antigen exists. Second, the use of human tissue extracts for clinical purposes presents many constraints. Third, each new Kveim-Siltzbach preparation requires validation in vivo.

Sarcoidal granulomas produce angiotensin-converting enzyme (ACE), and ACE levels are elevated in 60% of patients with sarcoidosis. However, the value of serum ACE levels in diagnosing or managing sarcoidosis remains controversial. Measurement of serum ACE levels lacks sensitivity and specificity.

A diagnosis of sarcoidosis is certain without biopsy when patients present with Löfgren's syndrome. In all other cases, a biopsy specimen should be obtained from

**Table 1 - Organ Involvement**

Organ System (Percent Clinical Disease)	Major Clinical Features
Pulmonary (>90%)	Restrictive and/or obstructive disease, fibrocystic disease, bronchiectasis
Upper respiratory tract and oral cavity (5-10%)	Hoarseness, laryngeal or tracheal obstruction, nasal congestion, sinusitis
Ocular (20-30%)	Anterior and posterior uveitis, chorioretinitis, conjunctivitis, optic neuritis
Skin (20-30%)	Erythema nodosum, chronic nodules and plaques, lupus pernio, alopecia
Hepatic/Abdominal (10-20%)	Hepatosplenomegaly, jaundice, cirrhosis, retroperitoneal lymphadenopathy
Cardiac (5-10%)	Arrhythmias, heart block, cardiomyopathy, sudden death
Neurologic (5-10%)	Facial and other cranial neuropathies (e.g., Bell's palsy) aseptic meningitis, brain mass, obstructing hydrocephalus, hypothalamic hypopituitarism, myelopathy, polyneuropathy
Exocrine gland (10-20%)	Salivary, lacrimal, and parotid gland enlargement, sicca syndrome
Hematologic (20-30%)	Peripheral or retroperitoneal lymphadenopathy, splenomegaly, hypersplenism, anemia, lymphopenia
Joints and musculoskeletal (10-20%)	Polyarthritides, Achilles tendinitis, heel pain, polydactylitis, bone cysts, myopathy
Endocrine (10-30%)	Hypercalciuria, hypercalcemia, hypopituitarism, diabetes insipidus
Renal (<5%)	Renal calculi, nephrocalcinosis, renal failure
Genitourinary (<5%)	Ovarian or uterine mass, dysmenorrhea, testicular mass, epididymitis
Psychosocial manifestations (30-60%)	Depression

the involved organ that is most easily accessed, such as the skin, peripheral lymph nodes, lacrimal glands, or conjunctiva. If diagnosis requires pulmonary tissue, transbronchial biopsy by means of bronchoscopy has a diagnostic yield of at least 85% when multiple lung segments are sampled.<sup>1</sup>

BAL can be used as an adjunctive measure to support the diagnosis of sarcoidosis by demonstrating a reduced number of CD8 cells and an elevated CD4/CD8 ratio. EBUS-TBNA allows real-time ultrasound localization and aspiration of hilar and mediastinal lymph nodes.<sup>18</sup>

Recently, several reports suggested that 18F-fluorodeoxyglucose positron-emission tomography (<sup>18</sup>FDG

PET) may be useful in assessing the extent of organ involvement and indicating the organs that are candidates for diagnostic biopsy.<sup>14</sup>

### **Biomarkers of Disease Activity**

To date, practical and reliable biomarkers of disease activity have not been identified. Chitinase, an enzyme involved in the degradation of chitin, is expressed by activated macrophages. Certain studies showed significantly higher levels in patients with active sarcoidosis than in those with inactive sarcoidosis. Recent evidence suggests that IL-2 receptor is elevated in serum and BAL fluid of patients with sarcoidosis and that it may have prognostic value in sarcoidosis.<sup>18</sup>

## Treatment

In view of the high rate of spontaneous remission and significant side effects, treatment is not indicated for:<sup>15</sup>

1. Asymptomatic stage I disease;
2. Asymptomatic stage II disease with mildly abnormal lung function and stable disease (measured 3–6-monthly);
3. Asymptomatic stage III disease with mildly abnormal lung function and stable disease (measured 3–6-monthly).

Treatment should be considered for patients with Pulmonary Sarcoidosis if :

1. Deteriorating lung function over 3–6 month intervals
2. Deteriorating radiological changes
3. Significant pulmonary symptoms of cough, shortness of breath, chest pain or haemoptysis.<sup>15</sup>

**Table 2 - Indications for treatment of Sarcoidosis with systemic agents<sup>20</sup>**

- Threatened organ failure—severe ocular, cardiac, or neurological disease
- Progressive or persistent pulmonary disease
- Uveitis unresponsive to topical corticosteroids
- Persistent hypercalcemia, renal or hepatic dysfunction
- Palpable splenomegaly or hypersplenism
- Severe myopathy
- Disfiguring skin disease
- Painful lymphadenopathy
- Severe fatigue and weight loss

Lofgren syndrome is usually managed with bed rest and nonsteroidal anti-inflammatory drugs.

Oral corticosteroids are the first line of therapy in patients with progressive disease (determined by radiology or on lung function), significant symptoms or extrapulmonary disease requiring treatment. BTS guidelines suggest a dose of 0.5 mg/kg/day of oral prednisolone and as patient responds, the dose should then be reduced gradually to a maintenance dose which will control symptoms and disease progression and should be used for a period of 6-24 months. Current British ILD guidelines

recommend other immunosuppressive agents when corticosteroids alone are not effective, or when side-effects are unacceptable, then methotrexate is the usual choice. Lung transplantation should be considered in end-stage pulmonary sarcoidosis. Bisphosphonates should be used to minimise steroid induced osteoporosis. Inhaled corticosteroids may be considered for symptom control (cough) in a subgroup of patients.<sup>15</sup>

TNF inhibitors have been investigated for the treatment of sarcoidosis. In a preliminary clinical trial of patients assessing the efficacy of etanercept, treatment failure was observed in nearly 65% of patients. Judson and colleagues found infliximab was effective for the treatment of both extrapulmonary and chronic steroid-dependent pulmonary sarcoidosis.<sup>18</sup> Patients currently are being recruited for clinical trials evaluating the safety and efficacy of ustekinumab and golimumab, a TNF-  $\alpha$  antagonist, in the treatment of chronic sarcoidosis.<sup>19</sup>

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