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Review Article

# Pulmonary Sarcoidosis

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## Introduction

Sarcoidosis is a granulomatous disease that affects a variety of populations.[1] It was first described in 1869 by Jonathan Hutchinson, a British dermatologist who defined a 58-year-old coal wharf worker with purple, symmetrical skin plaques on legs and hands that were not painful. In 1897, a Norwegian dermatologist, Caesar Boeck, presented a patient with "multiple benign sarcoid of the skin" which histologically showed well-defined foci of epithelioid cells with giant cells[2]. Although, nearly 150 years later, the etiology of sarcoidosis remains unknown and the course of the disease is unpredictable. The immune-pathogenesis involves a complex interaction between host, genetic factors and environmental or infectious triggers which produces granuloma formation. The disease can affect any organs but mostly involves the lungs and lymph nodes. The disease has a wide range of clinical manifestations, varies from asymptomatic patients with radiographic abnormalities to progressive disease causing morbidity and mortality.[1] Treatment depends on the severity of the disease and organ involvement. This review summarizes the pathogenesis, clinical manifestation, pathological and radiological features, and management focusing on pulmonary sarcoidosis.

## Epidemiology

Sarcoidosis is reported to occur worldwide. African Americans had a higher incidence and severity of the disease compared to Caucasians, Hispanics, and Asians. The disease can affect both men and women with a peak incidence at 30 to 50 years of age[1]. A slightly higher incidence has been reported in women[3]. It is uncommonly found in children, teenagers, and those aged over 70[4].

## Pathogenesis

The immunopathogenesis of sarcoidosis is not well understood. Most evidences suggest that the development of the disease is similar to other granulomatous diseases such as chronic beryllium disease. It involves the interaction between antigen exposure, HLA class II molecules, and T-cell receptors[5].

***Immune reaction***

After antigens entering the host and activating the innate immune response, they are phagocyted by antigen-presenting cells, mostly macrophages or dendritic cells, subsequently are presented to CD4 T cell receptor via class II major histocompatibility complex molecule (MHC II). The dendritic cells release cytokine, IL-12 to activate CD4 T cells resulting in differentiation into type 1 T helper cells (TH1 cells). TH1 cells secrete predominantly IL-2 and Interferon $\gamma$ leading to the production of cytokines (TNF $\alpha$, IL-12, matrix metalloproteinase) and chemokines causing cellular recruitment, proliferation, and differentiation which lead to the formation of sarcoid granuloma. Sarcoid granulomas are composed of a core of monocyte-derived epithelioid

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histiocytes and multinucleate giant cells with interspersed CD4 T lymphocytes. They may persist, resolve, or turn to fibrosis. Persistent granulomatous inflammation may arise from the failure of immune regulatory mechanisms with the following proposed mechanism[6]:

- Serum Amyloid A (SAA) protein is deposited in sarcoid granulomas and triggers cytokine release by interacting with Toll-like receptor 2 which results in the raising of TH1 responses to antigens.
- Regulatory T cells in sarcoid lesion are incapable of suppressing cell-mediated immune response causing prolonged inflammatory reactions associated with progression in fibrosis. Furthermore, the lesional regulatory T cells secrete pro-inflammatory cytokines including IL-4, which sustain granuloma formation via fibroblast amplification and mast cell activation.
- CD1d-restricted natural killer T cells (NKT cells) which normally moderate CD4-mediated immune response, markedly decrease in blood and bronchoalveolar lavage fluid of sarcoid patients, except in those with Löfgren syndrome. Because Löfgren syndrome is usually associated with resolving disease, the loss of NKT cells may lead to the persistence of sarcoidosis.

Remission of the disease occurs when macrophage and T-helper cell activity are suppressed by IL-10 or when the possible antigen has been completely cleared. Persistent granulomatous inflammation can lead to fibrosis via cytokines, possibly transforming growth factor- $\beta$ (TGF-$\beta$), MMP, and insulin growth factor-1 which have been found at disease sites. Switching from TH1 to TH2 cytokine may occur in chronic cases and facilitate lung fibrosis. TH2 cytokines such as IL-13 increase TGF-$\beta$ which activates and transforms fibroblasts to myofibroblasts leading to fibrosis. The TH2 chemokine, C-C Motif Chemokine Ligand 2 (CCL2), also enhances fibroblast survival. Additionally, the macrophages in patients with pulmonary fibrosis can express CCL18 chemokines which aids fibrosis[6].

***Genetic causes***

A Case-Control Etiologic Sarcoidosis Study (ACCESS) presented that patients with sarcoidosis were five times more common than control subjects to have siblings or parents with sarcoidosis[4]. The phenotypic features of affected siblings show minimal concordance except for those with ocular or hepatic involvement[7]. Because HLA class II molecules and T cell receptors appear to the immunopathogenesis of sarcoidosis, various polymorphisms of these molecules have been examined.

- Human leukocyte antigen (HLA) genes: Sarcoidosis is associated with the DR subtypes of class II antigens (HLA-DRB1 and DQB1 alleles), for example, HLA-DRB1*03, HLA-DRB1*11, HLA-DRB1*12, HLA-DRB1*14 and HLA-DRB1*15 have been shown to increase the risk of sarcoidosis. HLA-DRB1*1501/DQB1*0602 was associated with severe and chronic pulmonary sarcoidosis.
- Non-HLA genes have also been shown to be associated with sarcoidosis. There is evidence that variants of the TNF gene show a 1.5-fold increased risk of having sarcoidosis[6.]

The genome-wide association study revealed an association of the annexin A11 gene on chromosome 10q22.3 which regulates calcium signaling, vesicle trafficking, cell division, and apoptosis. So its depletion or dysfunction may disturb the apoptosis pathway in individuals with sarcoidosis[8.]

***Environmental causes***

Sarcoidosis may require exposure to one or more exogenous antigens. Infectious agents have been suspected as possible causes of sarcoidosis. With the use of PCR techniques, mycobacterial and propionibacterial DNA and RNA have been found from sarcoid tissue[9]. Occupational studies have shown positive associations with service in the U.S. Navy, metalworking, firefighting, and the handling of building supplies. Moreover, associations between sarcoidosis and exposure to inorganic particles, insecticides, and moldy environments have been reported[10].

## Diagnosis

Sarcoidosis is diagnosed by exclusion and is most likely to be correct if clinical and radiological data are supported by the presence of non-caseating granulomas in a biopsy specimen, and if alternative causes of granulomatous inflammation are ruled out[1].

***1. Clinical manifestation***

The clinical manifestation may vary from radiologic abnormality in an asymptomatic case to a progressive disorder causing fibrosis and respiratory failure. The symptoms are nonspecific. Dyspnea and cough are reported in almost 90% of patients with acute exacerbation of sarcoidosis. Other symptoms are chest pain, wheezing, fatigue, weight loss. Additionally, the disease may affect other organs as well. The lung is the most commonly involved organ, at least 90 % of sarcoidosis patients demonstrated lung lesions. The skin, eye, liver, and lymph nodes are the next common affected organs. Symptomatic cardiac sarcoidosis is presented in approximately 5% of patients. The renal and gastrointestinal tract are rarely involved[11].

***2. Radiographic features***

Chest radiographs are abnormal in more than 90 % of patients with sarcoidosis. The most common finding of sarcoidosis is bilateral hilar lymphadenopathy, noted in 50–80% of cases, which is typically symmetrical and non-compressive. Pulmonary infiltrates, observed in 25–50% of cases, are usually bilateral and symmetrical micronodular or reticulonodular infiltrates in mid to upper lobe areas. Atypical radiographic findings are approximately 20% of cases[12]. More than several years ago, Scadding developed a staging system based on the pattern of chest radiographic findings into five stages (Table 1)[13].

**Table 1** Scadding staging system of sarcoidosis, frequency, and probability of spontaneous resolution of each stage[12-13].

| Radiographic stage | Frequency (%) | Resolution (%) |
|---|---|---|
| Stage 0: Normal appearance at chest radiography | 5-15 | |
| Stage 1: Bilateral hilar lymphadenopathy | 25-65 | 60-90 |
| Stage 2: Bilateral hilar lymphadenopathy followed by parenchymal infiltrates | 20-40 | 40-70 |
| Stage 3: Parenchymal infiltrates without bilateral hilar lymphadenopathy | 10-15 | 10-20 |
| Stage 4: Pulmonary fibrosis | 5 | 0 |

High resolution computed tomography (HRCT) of the chest, 1 to 1.5 mm section thickness, is superior to conventional CT to identify the parenchymal details such as nodular and reticular opacities, interlobular septal thickening, and ground-glass opacities, and is useful to identify air trapping in patients with small-airway involvement[14]. The typical characteristic features on HRCT include mediastinal and/or hilar adenopathy, nodular and micronodular opacities along bronchovascular bundles and subpleural areas, mass-like lesions from confluenced nodular opacities adjacent to airways, vessels, and subpleural locations. Some nodules gather densely until they become conglomerate, like the appearance of a cluster galaxy, called “galaxy sign,” it is highly suggestive of pulmonary sarcoidosis. Additional HRCT findings of sarcoidosis include ground-glass opacities, interlobular septal thickening, fibrotic changes which are predominantly in the upper and middle zones[11]. The typical and atypical characteristics of pulmonary sarcoidosis on HRCT are shown in Table 2[14]. It is essential to note that, the radiographic findings of lung fibrosis do not definitely suggest a “burnt-out” or inactive disease. Mostard and colleagues demonstrated that 85% of patients had positive PET findings on the lungs, suggesting active disease[15].

**Table 2** Typical and Atypical Features of Pulmonary Sarcoidosis at High-resolution CT[14]

| Typical features |
|---|
| • Lymphadenopathy: hilar, mediastinal, bilateral, symmetric, and well-defined |
| • Nodules: micronodules (2-4 mm in diameter; well defined, bilateral); macronodules (≥5 mm in diameter, coalescing) |
| • Lymphangitic spread: peribronchovascular, subpleural, interlobular septal |
| • Fibrotic changes: reticular opacities, architectural distortion, traction bronchiectasis, bronchiolectasis, volume loss |
| • Bilateral perihilar opacities |
| • Predominant upper- and middle-zone locations of parenchymal abnormalities |
| **Atypical features** |
| • Lymphadenopathy: unilateral, isolated, anterior and posterior mediastinal |
| • Airspace consolidation: mass-like opacities, conglomerate masses, solitary pulmonary nodules, confluent alveolar opacities (alveolar sarcoid pattern) |
| • Ground-glass opacities |
| • Linear opacities: interlobular septal thickening, intralobular linear opacities |
| • Fibrocystic changes: cysts, bullae, blebs, emphysema, honeycomb-like opacities with upper- and middle-zone predominance |
| • Miliary opacities |
| • Airway involvement: mosaic attenuation pattern, tracheobronchial abnormalities, atelectasis |
| • Pleural disease: effusion, chylothorax, hemothorax, pneumothorax, pleural thickening, calcification |
| • Pleural plaque-like opacities |
| • Mycetoma, aspergilloma |

***3. Pulmonary function***

The majority of sarcoidosis patients will have normal pulmonary function tests (PFTs) at the time of diagnosis. Over time, some of these patients will develop a restrictive pattern with a reduction of lung volumes[16]. However, airflow obstruction has been more prevalent than restriction in some sarcoidosis cohorts. The isolated reduction in diffusing capacity for carbon monoxide (DLco) is also frequent that is caused by parenchymal involvement or pulmonary hypertension[1,17]. The severity of impairment of lung function is not correlated well with the extent of the disease on HRCT.[1] Six-minute walk test (6MWT) distance is frequently reduced. Patients with more severe sarcoidosis tend to have a greater decline in oxygen saturation during the 6MWT[17].

***4. Radionuclide imaging***

Fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$FDG-PET) is not recommended in the standard investigation, but it may help to solve some difficult issues that are unanswered by conventional imaging[18]. $^{18}$FDG-PET is a sensitive technique to assess inflammatory activity by identifying the area of increased glucose metabolism from inflammatory cells. Based on literature, the roles of FDG-PET in sarcoidosis could be beneficial for evaluation of inflammatory active disease in patients with persistent symptoms and negative inflammatory markers, assessment of inflammation in stage IV sarcoidosis with lung fibrosis, evaluation of active extrathoracic sarcoidosis or assessment of cardiac sarcoidosis, identification of active sites for diagnostic biopsy and evaluation of treatment response in refractory disease[19].

***5. Bronchoscopy***

Bronchoscopy has a high diagnostic yield includes sampling the airways (endobronchial biopsy), lung parenchyma (transbronchial lung biopsy [TBLB]), or intrathoracic lymph nodes (conventional transbronchial needle aspiration or endobronchial ultrasonography). The choice of procedure depends on the skill of the clinician, and the radiographical stage of the disease[1]. Bronchoalveolar lavage shows a 20–50% lymphocytosis in 80% of sarcoidosis cases and a BAL CD4/CD8 ratio increases more than 3.5 in 50% of cases. Because the profile of BAL fluid examination is not specific, therefore differential diagnosis should be considered, such as infection, especially tuberculosis, fungus; sarcoid-like reactions in cancers and lymphomas; environment-related diseases (berylliosis, hypersensitivity pneumonitis) or drug-induced lung diseases; common variable immune deficiency; and other idiopathic granulomatosis[20].

***6. Pathology***

The histologic hallmark of sarcoidosis is the granuloma. The classic sarcoid granulomas are well-formed, generally non-necrotizing, and typically surrounded by a rim of lamellar hyaline collagen, which leads to their compact character. They are favorably located along the lymphatic routes of the pleura, interlobular septa, and bronchovascular bundles[21]. In chronic disease, granulomas tend to have increased fibrosis and form hyalinized nodules rich with dense eosinophilic collagen. End-stage of the disease may not have granulomas and show a pattern of usual interstitial pneumonia, which can be difficult to distinguish from idiopathic pulmonary fibrosis[1].

Intracytoplasmic inclusions in giant cells are often present in sarcoid granulomas, including calcium oxalate crystals and asteroid and Schaumann bodies: the latter is more frequent in sarcoidosis than in other granulomatous diseases. However, none of them is specific. Thus, they may mislead the pathologist to diagnose foreign-body granulomas. Additionally, sarcoid granulomas also display necrosis in about 20% of transbronchial

biopsies[21]. It mainly consists of tiny foci of central fibrinoid necrosis[22], but rarely large areas of fibrinoid, infarct or suppurative necrosis. In general, the necrosis within granulomas should always be differentiated from infection. Inflammation of sarcoidosis is generally mild and limited to a thin rim of lymphocytes surrounding granulomas (naked granulomas) so a significant cellular interstitial infiltration with organizing pneumonia is unusual, as a result, its presence should suggest an alternative diagnosis particularly infection, hypersensitivity pneumonitis, collagen vascular disease, aspiration, or drug reaction[21].

In chronic sarcoidosis, hyaline collagen penetrates and destroys the granulomas which may become fragmented that they are hardly recognizable. Occasionally, giant cells embedded in dense fibrosis may remain as the only clue of an old, scarred sarcoidosis[21].

## Treatment

Sarcoidosis patients are treated when they become symptomatic. At least 50% of patients will have spontaneous resolution within 6 months, therefore, not every patient requires treatment[23]. Currently, there are no clear criteria for initiating treatment in pulmonary sarcoidosis[24]. The decision is based on symptoms, a decline of pulmonary function, radiologic staging, or evidence of active granulomatous inflammation related to sarcoidosis[25]. Treatment should be considered for patients with symptomatic or progressive stage 2 or 3 pulmonary disease or major extrapulmonary organ involvement.

### *1. Glucocorticoids*

Glucocorticoids are the first line of initial therapy. The recommended starting dose is 20-40 mg/day of prednisolone that should be continued for 1-3 months and tapered to a maintenance dose of 5-10 mg/day of prednisolone[25-26]. The duration of treatment varies between 6-12 months[24]. Previous systematic review included data from 8 randomized controlled trials (RCTs) concluded that oral corticosteroids improved chest radiograph following 6 to 24 months of treatment in patients with stage 2 and 3 diseases and showed a small improvement in vital capacity and diffusing capacity. There is no data suggesting the benefit of long-term corticosteroid used over 2 years[27]. If patients cannot be weaned to prednisone less than 10 mg per day, the use of steroid-sparing medications should be considered[28].

In acute pulmonary exacerbations of sarcoidosis (APES), 20-40 mg/day of prednisolone for 3 weeks with decreased dose thereafter is recommended. Patients should be evaluated within 3-4 weeks after the treatment for appropriate tapering of steroid dose or initiation of a steroid-sparing agent if indicated. If APES occurs frequently, consider initiation of a steroid-sparing agent to control disease flares[26].

### *2. Alternative immunosuppressive agents*

#### *2.1 Methotrexate*

Low dose methotrexate has anti-inflammatory properties by enhanced releasing of adenosine which inhibits TNFα release from monocytes, macrophages, and neutrophils[24]. In a randomized, double-blind, controlled trial of 24 patients with acute sarcoidosis received methotrexate (10 mg once weekly) or placebo plus oral prednisolone, showed that patients taking methotrexate required significantly less prednisolone than placebo group in the 12-month period[29]. However, major concerns of this drug have been related to hepatotoxicity, bone marrow suppression, and pulmonary toxicity[25], therefore, co-treatment with 5 to 10 mg once weekly of folic acid to limit toxicity and regular monitoring liver function and complete blood count is suggested[24]. The World Association of Sarcoidosis and Other

Granulomatous Disorders (WASOG) recommended methotrexate as a second-line treatment option in steroid-refractory cases, steroid-related adverse effects or as a steroid-sparing agent [30].

***2.2 Azathioprine***

Azathioprine has also been reported as an effective sarcoidosis treatment, with limited case series [31]. In a retrospective study, both methotrexate and azathioprine provided significant steroid-sparing potency, equally improved pulmonary function and had comparable side effects, except for a higher infection rate in the azathioprine group[32]**.** Regular blood counts and liver function monitoring, are essential in patients taking azathioprine to monitor side effects[24].

***2.3 Leflunomide***

Leflunomide is a cytotoxic agent that has been reported as an effective treatment for pulmonary and extrapulmonary sarcoidosis[31]. A cohort of 76 patients with sarcoidosis, reported significant improvement in FVC with the add-on leflunomide treatment to background therapy of glucocorticoids or methotrexate. There was a trend for a better result in patients on combination methotrexate/leflunomide therapy than leflunomide alone[33]. It is associated with less gastrointestinal and pulmonary toxicity but the incidence of leukopenia and hepatotoxic effects are similar to methotrexate[31]. Thus, it can be used for a steroid-sparing agent or treatment failures from other medications. However, there is a need for a prospective studies to evaluate the relative efficacy of monotherapy or combination therapy compared with other alternative drugs[33].

***2.4 Mycophenolate mofetil (MMF)***

MMF is an antiproliferative immunosuppressant like azathioprine but more selective action. It has been used safely in patients with renal failure. There are no controlled studies in pulmonary sarcoidosis , and the current data are inadequate to recommend its use[24,31].

***2.5 Anti-TNF treatment***

Targeted TNFα inhibition is usually reserved as a third-line therapy, especially in refractory or organ-threatening cases. Best treatment outcomes have been reported for infliximab and adalimumab[31]. Infliximab had been shown in RCTs to significantly improve forced vital capacity (FVC) at the mean of 2.5% predicted in 24 weeks in chronic pulmonary sarcoidosis and 6.6% predicted in patients refractory to conventional treatment[34-35]. The treatment failed to show improvement of dyspnea score or symptoms[34]. Adalimumab was shown in a small open-label study to improve symptoms and FVC [36]. It can be used as an alternative drug for patients intolerant to infliximab[37]. Other anti-TNF agents, such as etanercept and golimumab, do not appear to be beneficial in sarcoidosis[38]. Adverse effects of TNFα inhibitors include infusion and anaphylactic reactions, increased risk of infection, reactivation of latent infections (eg. tuberculosis and fungal infections), autoimmune and neurological effects, and malignancy. Therefore, before treatment, patients should be screened for tuberculosis, fungal, and viral infections, and regular clinical and laboratory surveillance for infection during treatment should be performed [31].

***3. Other potential therapies***

Rituximab, an anti CD-20 monoclonal antibody, was recently tested in sarcoidosis. An open-label, prospective study of rituximab treatment in 10 refractory pulmonary sarcoidosis patients reported a response for half at 24 weeks but was maintained in only two cases in 1 year. So Further research is needed. There is an open-label trial in pulmonary sarcoidosis suggested that anti-mycobacterial antibiotics - levofloxacin, ethambutol, azithromycin, and rifampin (CLEAR regimen) over 8 weeks may lead to the improvement of FVC, dyspnea

score and 6-minute walk distance**.** Currently, a phase II trial of efficacy of CLEAR in patients with progressive pulmonary sarcoidosis is still ongoing. Other new drugs that will be developed to block new mechanisms of disease are now in clinical trials such as vasoactive intestinal peptide (VIP), human placenta-derived antigen (PDA-001), nintedanib, rilonocept, canakinumab, atorvastatin[38].

***4. Lung transplantation***

A small number of pulmonary sarcoidosis patients with severe disease and progression to lung fibrosis, despite maximized medical treatment, may be candidates for lung transplantation. Post-transplant survival is similar to other lung diseases[24]. The International Society for Heart and Lung Transplantation data reported 1-, 5- and 10-yr survivals of 72.2, 50.6 and 31.1%, respectively[39]. Sarcoidosis is the most common disease, with reported recurrence rates of 35% to 62.5% after lung transplantation, but it seems to have a good prognosis and often be asymptomatic and self-limiting[24].

## Disease monitoring and prediction of prognosis

The optimal timing and tools to evaluate the response of treatment in patients with pulmonary sarcoidosis are unclear [1]. According to expert opinion, clinical examination and chest radiograph should be done every 3-6 months. Pulmonary function tests and ECG should be monitored every 6 months. Because disease relapse mostly occurs 2 to 6 months after discontinuing treatment and is rare after 3 years, so expert recommended to follow up patients at least 3 years[20].

The clinical courses of the disease are variable. In half of the cases, the disease resolves spontaneously within 2-5 years. After 5 years, remission is less likely. Advanced disease occurs in approximately 5% of patients with sarcoidosis and causes morbidity and mortality. Frequent complications of end-stage disease include pulmonary hypertension and mycetomas[1].

## Conclusion

There is no standard guideline for the diagnosis and treatment of pulmonary sarcoidosis. Clinical manifestation may range from asymptomatic to chronic progressive lung fibrosis. The symptoms are non-specific. The diagnosis requires radiological findings and histological confirmation. There are no reliable factors that can predict disease outcome. Glucocorticoid remains the first drug of choice for initial therapy. Steroid sparing regimens should be initiate for steroid-dependent or relapse disease. Nowadays, the knowledge of immunopathogenesis has been increasingly understood, so numerous novel targeted therapies have recently been proposed for treatment benefit. In advanced disease, treatment planning should be done in expert centers and a multidisciplinary approach.

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