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Sarcoidosis: Overview of Pulmonary Manifestations and Imaging

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Introduction

Sarcoidosis is a multisystem disease of unknown etiology characterized by clusters of nonnecrotizing granulomas and distortion of surrounding tissue.[1] Although some patients are asymptomatic, sarcoidosis can cause a range of pulmonary complaints, from chronic cough to marked dyspnea and functional disability. Sarcoidosis has a mortality rate of up to 5%, with death most commonly due to respiratory failure.[2] On imaging, pulmonary findings are frequent and have a variety of characteristic appearances, ranging from isolated hilar and mediastinal adenopathy to severe pulmonary fibrosis. Knowledge of the wide range of clinical presentations and imaging appearances of sarcoidosis is essential for appropriate diagnosis and management.

Epidemiology and Clinical Characteristics

Sarcoidosis is most commonly seen in adults younger than 40 years, with peak incidence in patients 20-29 years of age; a second peak occurs in females older than 50 years in countries such as Japan.[2] Prevalence ranges widely across the world, from 64/100,000 individuals in Sweden to 0.2/100,000 in Portugal. In the United States, the disease has a prevalence of approximately 3/100,000 for white and a much higher prevalence of 47/100,000 for African Americans.[3]

Although many hypotheses have been proposed, the etiology of sarcoidosis remains unclear. Higher incidence in certain occupations, clustering of cases in time and space, and cases of recurrence of sarcoidosis in transplantation favor the role of 1 or more environmental agents.[3,4] A common pathway may be the activation of macrophages through T helper cells. Genetic factors likely play a role, with higher incidence of sarcoidosis in siblings than in unrelated individuals.[5] Infectious agents such as mycobacteria, propionibacteria, and viruses have been proposed as candidates, as have environmental exposures to inorganic substances such as molds, pesticides, and other materials.[6]

Up to 50% of patients with sarcoidosis are asymptomatic at diagnosis.[7] However, pulmonary involvement occurs in more than 90% of cases at some point in the course of the disease; common symptoms are dyspnea, chest pain, or cough.[2] A characteristic rash (*erythema nodosum*) and fatigue may also occur.[8] Hilar and mediastinal lymphadenopathy is common, but peripheral nodal groups can also become involved, most often axillary, inguinal, cervical, and epitrochlear nodes.[2] Many patients with sarcoidosis experience decreased quality of life owing to decreased functional capacity, impaired cognition, and disrupted sleep; up to 80% of patients with sarcoidosis experience fatigue as a chronic symptom.[9] Some constellations of clinical signs or symptoms are almost pathognomonic for sarcoidosis, including bilateral hilar nodal enlargement as an isolated clinical finding, erythema nodosum with bilateral hilar adenopathy ("Lofgren syndrome"), and uveitis, fever, and parotiditis (Heerfordt syndrome).[4]

Spontaneous remission of sarcoidosis occurs in approximately half of cases within 2 years, and in an additional fraction of cases within 5 years. A higher probability of spontaneous remission is associated with earlier radiographic stages at the time of presentation.[8] An acute onset of symptoms is associated with a more favorable, limited course, with a higher chance of remission than cases with a more insidious onset.[2] Sarcoidosis is chronic and progressive in 10%-30% of patients, and pulmonary involvement can lead to severe fibrosis and significant functional debilitation.[10]

Pathology and Diagnostic Options

In sarcoidosis, focal collections of macrophages, known as "nonnecrotizing" or "noncaseating" granulomas, are present at histology, often accompanied by adjacent fibrosis.[2] Activated helper T cells are often also present, suggesting an exaggerated immune response.[1,3] Because a granulomatous reaction is a normal response to many exogenous materials, the presence of

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Table Radiographic Staging of Sarcoidosis[20]

Stage	Hilar Adenopathy	Parenchymal Opacities	Fibrosis	Percent Radiographic Resolution at 5 Years[2]
Stage 0	−	−	−	Category later recognized
Stage 1	+	−	−	55%-90%
Stage 2	+	+	−	40%-70%
Stage 3	−	+	−	10%-20%
Stage 4	−	±	+	0%

granulomas at biopsy is not sufficient for a diagnosis of sarcoidosis,[4] but relies on accompanying clinical and imaging findings and the lack of evidence of other etiologies, such as fungal infection or tuberculosis.[8]

Angiotensin-converting enzyme is produced in granulomas, and serum levels can be elevated in sarcoidosis, suggestive of the diagnosis. However, the sensitivity of an elevated serum angiotensin-converting enzyme level is only 57%, whereas the specificity of 90% has been deemed inadequate for the test to be used in isolation, as fungal infection, tuberculosis, and other diseases can be the sources of elevated levels.[4] Bronchoscopy with bronchoalveolar lavage can show abundant lymphocytes with a CD4:CD8 ratio higher than 3.5 in 50% of cases,[8] but this profile is neither specific for sarcoidosis nor typically used for diagnosis or assessment of disease activity.[10]

Lymph node sampling may not be necessary in patients for whom the diagnosis of sarcoidosis is strongly suspected on the basis of imaging, classic constellations of signs and symptoms, and lack of probable alternative diagnoses.[11] In patients with thoracic lymphadenopathy for whom a tissue diagnosis is elected, mediastinoscopy has generally been replaced by transbronchial needle aspiration (TBNA), transbronchial lung biopsy, and endobronchial ultrasonography-guided TBNA (EBUS-TBNA).[8] EBUS-TBNA was shown to have a sensitivity of 83.3% and specificity of 100% for diagnosis of sarcoidosis in patients with clinically suspected sarcoidosis and hilar or mediastinal adenopathy, whereas standard TBNA had a lower sensitivity of 60.9%.[12] A higher yield of EBUS (80%) over standard bronchoscopy (53%) in diagnosis of nonnecrotizing granulomas was confirmed by the GRANULOMA study, a large multicenter randomized trial.[13] EBUS-TBNA in combination with standard bronchoscopic sampling techniques was shown to have a 93% diagnostic yield in the setting of thoracic lymphadenopathy and suspected sarcoidosis.[14] Video-assisted thoracoscopic lung biopsy and open lung biopsy are usually reserved for patients in whom lymphadenopathy is not present or not amenable to biopsy.[2]

Diagnostic Imaging of Pulmonary Sarcoidosis

Up to 90% of patients with sarcoidosis have pulmonary involvement at some time in the disease course, and chest imaging is a mainstay of disease detection, diagnosis, and management.[11] Thoracic lymphadenopathy is exceedingly common at both chest radiography and computed tomography (CT), and occurs in greater than 85% of patients; bilateral hilar adenopathy occurs in up to 95% of patients with thoracic nodal involvement.[7] Parenchymal disease includes perilymphatic "micronodules" measuring less than 5 mm, larger nodules, ground-glass opacities, consolidation, reticulation, and fibrosis; airway abnormalities are also common.[15]

Radiography

Often the first imaging study to show evidence of the disease, radiography plays an important role in the diagnosis and surveillance of pulmonary sarcoidosis and can demonstrate a spectrum of typical lymph nodal and parenchymal findings. Chest radiographs show evidence of disease in 90% of patients with sarcoidosis.[8]

The first published accounts of the typical radiographic findings of sarcoidosis date from the early 20th century, with parenchymal opacities described as a possible sign of the disease in 1915, and recognition in the 1930s of hilar and mediastinal adenopathy as an associated finding.[16] In 1950, Scadding[17] proposed 5 morphologic categories based on his observations of 16 cases of saroidosis. Nitter[18] first associated morphologies with progressive stages of disease in a study of 90 patients, and Wurm et al[19] demonstrated progression among 3 radiographic stages in their large scale longitudinal study. In 1961, Scadding[20] proposed the 4 stages used for the remainder of the 20th century and still accepted today (Table). "Stage 1" represents hilar adenopathy or mediastinal adenopathy or both, "stage 2" corresponds to adenopathy and lung parenchymal abnormalities, "stage 3" refers to parenchymal abnormalities without visible thoracic adenopathy, and "stage 4" indicates pulmonary fibrosis (Fig. 1). Although not originally included by Scadding, a "stage 0" eventually was added to the staging system and designates a radiograph without evidence of sarcoidosis.[2]

Approximately 8%-10% of patients with sarcoidosis have a normal radiograph finding, corresponding to stage 0.[21,22] The remainder of patients have abnormal radiograph findings, with lymphadenopathy the most commonly detected abnormality (25%-65%).[8] Bilateral hilar and mediastinal adenopathy is the most common pattern at radiography, with right paratracheal adenopathy most commonly detected of the mediastinal stations. However, as detailed later, chest CT is more sensitive in detecting lymphadenopathy in other mediastinal stations. Pulmonary parenchymal abnormalities are seen in approximately 40% of patients, corresponding to stage 2 or 3; findings can include nodules, reticular opacities, masses, and consolidation.[8,23] Fibrosis occurs in up to 10%-30% of patients.[1]