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Pulmonary manifestations of sarcoidosis

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Summary

Sarcoidosis affects the lungs in more than 90% of cases. Symptoms include cough, dyspnea, and chest pain. The entire respiratory tract can be involved. The most common areas of involvement are the airways and interstitium. Airway disease can lead to airway obstruction while interstitial lung disease can lead to restrictive disease. Patients may have a mix of these areas of involvement. For the symptomatic patient, the identification of disease involvement can usually be determined by pulmonary function testing and chest imaging. The chest X-ray staging system has been widely used in sarcoidosis, high-resolution computer tomography (HRCT) can provide detailed information regarding lung involvement. Unfortunately the various patterns seen on HRCT have limited the ability to develop a simple scoring system. Special studies such as bronchoscopy can be useful for detecting large airway disease. Other chest manifestations include adenopathy, pulmonary hypertension, and pulmonary muscle weakness. Fibrotic lung disease can lead to bronchiectasis, which can become infected.

Sarcoidosis is a multi-organ disease. However, it affects the lungs in more than 90% of cases [1,2]. Patients can be asymptomatic, but the most common pulmonary symptoms are cough and dyspnea [2]. While sarcoidosis is often an interstitial lung disease, these symptoms can be a manifestation of other areas, which can be affected by sarcoidosis. These include the upper respiratory tract, respiratory muscle, and pulmonary hypertension. These are summarized in table I. In this chapter, we will discuss various components of respiratory involvement except sarcoidosis associated pulmonary hypertension.

Lung involvement in sarcoidosis is usually assessed by pulmonary function studies and chest radiograph imaging. Scadding had proposed a scoring system (table II) [3] which has been widely used. This staging has provided useful in separating groups of patients with different levels of lung disease [4]. However, the stage is less useful in the management of the specific patient. This is in part due to the poor reproducibility of the scoring system [5]. Also, the scoring system tends
to treat all interstitial patterns the same. A more detailed analysis of the chest roentgenogram has been developed by Muers et al. [6]. The widespread use of computer tomography (CT) and high-resolution CT (HRCT) has identified a wide array of patterns seen in patients with sarcoidosis [7–10]. While a scoring system for these findings has been proposed [11], to date the multiple findings on CT scan have limited application in management of sarcoidosis patients.

**Upper and large airway involvement**

Sarcoidosis of the upper respiratory tract (SURT) includes sinus, pharyngeal, vocal cord, tracheal, and bronchial involvement [12,13]. Its overall incidence is about 5% of sarcoidosis patients [14]. In this chapter, we will focus on tracheal and bronchial involvement. The symptoms of tracheal and endobronchial sarcoidosis include cough, dyspnea, wheezing, and hemoptysis

[15]. Bronchoscopy may reveal an endobronchial lesion (figure 1). The more common features are erythema, mucosal thickening, and a “cobblestone” pattern. In a prospective study of patients undergoing diagnostic bronchoscopy, bronchial abnormalities were identified in 24/34 (71%) of patients [16]. Endobronchial disease can lead to stenosis, which is often present in multiple areas [15]. Biopsy of the airway often will demonstrate granulomas [15,16]. Endobronchial biopsy in patients with a normal appearing airways will identify granulomas in up to 30% of sarcoidosis patients [16]. Radiographic imaging has proved quite useful in identifying endoluminal stenosis from sarcoidosis [15]. Figure 2 demonstrates a subglottic stenosis from sarcoidosis. Infrathoracic airway involvement may be more apparent with sagittal sections of the airway (figure 3) [8]. Occasionally a solitary endobronchial lesion can be seen on CT scan (figure 4).

Pulmonary function testing usually demonstrates airway obstruction in patients with symptomatic endobronchial sarcoidosis [15]. This is often a fixed obstruction and a flow volume loop may help in making the diagnosis [17]. Patients with endobronchial sarcoidosis often cough and wheeze. Methacholine challenge may be detect airway hyper reactivity

| Table I | Pulmonary manifestations of sarcoidosis |
| --- | --- | --- |
| Area involved | Symptoms | Method of detection |
| Upper and large airway | Cough, wheezing, stridor, hemoptysis | Direct visualization CT scan Flow volume loop |
| Bronchioles | Dyspnea | Expiratory HRCT |
| Adenopathy | None | Chest Roentenogram CT scan |
| Interstitial | Dyspnea | HRCT DLCO Lung volumes Bronchoalveolar lavage |
| Respiratory muscles | Dyspnea Fatigue | Peak inspiratory and expiratory muscle |
| Pulmonary hypertension | Dyspnea Edema | Right heart catheterization Echocardiography CT scan |

| Table II | Comparison of radiographic imaging in sarcoidosis |
| --- | --- | --- |
| Chest roentgenogram stage [3] | Chest roentgenogram finding | CT scan findings |
| 1 | Adenopathy | Adenopathy |
| 2 | Adenopathy plus infiltrate | Bronchovascular bundles Reticular patterns Mass densities Infiltrates Mosaic pattern Subpleural nodules |
| 3 | Infiltrates alone | Bronchovascular bundles Reticular patterns Mass densities Infiltrates Mosaic pattern Subpleural nodules Ground-glass |
| 4 | Fibrosis | Traction bronchiectasis Honeycombing Cysts |
| Other findings | Pleural effusions Mycetoma | Pleural effusions Mycetoma Emphysema |

**Glossary**

CPET cardiopulmonary exercise testing  
CT computer tomography  
FEV-1 forced expiratory volume in one second  
FVC forced vital capacity  
HRCT high-resolution CT  
MRRC Medical Research Council  
SURT sarcoidosis of the upper respiratory tract
in sarcoidosis patients. In one study, all patients with a positive methacholine challenge had a positive endobronchial biopsy for granulomas [18]. In one study, airway hyper reactivity after histamine challenge was detected in 19 of 43 (44%) of sarcoidosis patients. Airway hyper reactivity correlated with conglomerate fibrosis and reticular pattern on HRCT and inversely corrected with the baseline FEV-1 percent predicted [19].

Treatment of airway disease from sarcoidosis may be difficult [12]. Cough may improve with inhaled corticosteroids [20]. Endoluminal stenosis with fixed obstruction is usually not responsive to inhaled steroids. Intralobulon injection of corticosteroids has been reported as effective for laryngeal disease [21]. Airway lesions may respond to local dilation [22]. Since there is a correlation between more severe obstruction and increasing number of stenotic areas [15], mechanical dilation of individual airways was usually insufficient. Systemic therapy with corticosteroids with or without methotrexate has been reported to be helpful, especially if treatment is given with the first three months of onset of symptoms [15]. Unfortunately, chronic symptoms are often associated with fibrotic changes in the airways that do not respond well to anti-inflammatory therapy, including infliximab.
Bronchiole

Airflow obstruction occurs in a significant number of patients with sarcoidosis [2,23]. In one study, 14% of patients had a forced expiratory volume in one second (FEV-1) to forced vital capacity (FVC) ratio of less than 70% at time of diagnosis [2]. Airflow obstruction is often not responsive to bronchodilators [20,24]. In some series, there was an association between airflow obstruction and cigarette smoking [24], but airflow obstruction has clearly been observed in sarcoidosis patients who are non-smokers [23,25]. Airflow obstruction may be more common in African Americans than other sarcoidosis populations [23]. Bronchiole involvement appears to be an important source of airflow obstruction. One mechanism is the granulomatous involvement of the bronchovascular bundle [26], a common radiographic feature of sarcoidosis [9] (figure 5). Pulmonary function studies often detect small airway changes in sarcoidosis patients [27,28]. The use of high-resolution CT scan has improved our ability to detect bronchiole obstruction. In particular, expiratory HRCT has proved particularly useful with good intra-observer agreement in identifying localized air trapping [29,30]. In sarcoidosis, the presence of air trapping (figure 6) correlates well with evidence of small airway disease [31]. The localized air trapping represents bronchiole disease and could be due to other conditions, including infection and drug toxicity such as methotrexate pulmonary toxicity.

Figure 4
Endoluminal lesions of patient whose bronchoscopic findings are shown in figure 1

Figure 5
Peribronchial thickening in patient with sarcoidosis in patient with diffuse disease. Thickening can be of central airways (A) or peripheral airways (B)
airway disease was common but contributed little to airflow obstruction. They found that the extent of the reticulonodular pattern correlated best with airflow obstruction [7]. Because of the unclear correlation between small airway disease seen on HRCT and pulmonary function studies, the response to therapy has been difficult to quantitate. In a study of intense corticosteroid therapy for acute sarcoidosis, Plysongang and Roberts were able to demonstrate improvement in airway obstruction [27]. Patients with peribronchovascular bundle thickening appear more likely to respond to treatment than those with predominantly bronchial distortion [30].

**Adenopathy**

Presence of adenopathy alone (stage 1, figure 7) or with parenchymal disease (stage 2, figure 8) has been found in more than half of sarcoidosis patients at the time of diagnosis [1,2]. While adenopathy can often be appreciated on chest roentgenogram, CT scan is far more sensitive for detecting adenopathy. Various interstitial lung disease can cause some adenopathy, but the enlargement is usually only to a mild extent. Adenopathy of greater than 15 mm in maximum diameter can help distinguishes sarcoidosis from other interstitial lung diseases [32].

Adenopathy from sarcoidosis rarely leads to symptoms. However, adenopathy can rarely lead to compression of the pulmonary artery and the bronchial airway (figure 9). This can rarely lead to pulmonary hypertension [33]. The adenopathy can also rarely lead to chylothorax [34,35].

Chest pain is a common complaint of sarcoidosis patients [2,36]. In a prospective study of pulmonary sarcoidosis patients, two third of patients complained of chest pain. However, there was no correlation between the pain and either adenopathy or pleural disease [37].

**Interstitium**

Parenchymal lung involvement occurs in a significant number of patients with sarcoidosis. The most common symptom of parenchymal disease is dyspnea. Dyspnea can be assessed in several ways, including the Medical Research Council (MRC) scale [38]. However, a significant number of patients with parenchymal lung disease have no symptoms or a normal chest roentgenogram [4]. One of the striking features about sarcoidosis is the lack of correlation between chest roentgenogram or pulmonary function findings in individual patients. Figure 10 shows the correlation between chest roentgenogram stage and the percentage of patients with mild or moderate
**Figure 8**

A: Posterior anterior chest roentgenogram of sarcoidosis patient with both adenopathy and interstitial lung disease, scadding Stage 2 [3]. B: CT scan image from mid thorax showing the numerous small parenchymal nodules, many of them closely associated with bronchovascular bundle.

**Figure 9**

Patient with chronic pulmonary and cutaneous sarcoidosis

A: Late phase of a pulmonary angiogram demonstrating almost no blood flow through the right upper lung.

B: CT scan section at the take-off of the right upper lobe showing adenopathy and fibrosis with collapse of right upper lobe and compression of pulmonary artery.
reduction of forced vital capacity (FVC) (figure 10A) and level of exertion required to lead to dyspnea (figure 10B). While patients with a higher stage of disease were more likely to have a reduced FVC and complain of more dyspnea, there was considerable overlap between chest X-ray stages [4]. Similar observations have been made relating FVC and chest X-ray versus the six-minute walk distance [39]. Despite the limitations of pulmonary function studies, they remain the most widely used measures to assess pulmonary disease in sarcoidosis patients. The FVC is a simple and reproducible test, which estimates lung volume, while the FEV-1/FVC is a measure of airflow obstruction. Table III summarizes the FVC of sarcoidosis patients at the time of diagnosis for two groups of patients (United States and Germany) at the time of diagnosis and a cross sectional study of acute and chronic sarcoidosis patients of United States patients seen at one clinic. Overall, the majority of patients have normal FVC. However, airflow obstruction was seen in a significant percentage of patients. In the two United States studies, mild to moderate obstruction was encountered in the majority of patients. Severe obstruction was rarely identified. Abnormalities in the DLCO have been observed in patients with sarcoidosis [40]. This can lead to reduced exercise capacity [41]. While these usually represent interstitial lung disease, reduced DLCO can be a manifestation of pulmonary hypertension [42,43]. In patients with sarcoidosis associated pulmonary
Table III

<table>
<thead>
<tr>
<th>Forced vital capacity and FEV1/FVC ratio in sarcoidosis patients</th>
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<tr>
<td>Time of diagnosis</td>
</tr>
<tr>
<td>Number having pulmonary function studies</td>
</tr>
</tbody>
</table>

FVC (%)

- Normal
  - ≥ 80: 68.8
  - Mild: 70–79: 17.6, 65–79: 19.4
  - Moderate: 50–69: 11.1, Severe: ≤ 50: 2.5, ≤ 65: 1.5

FEV1/FVC (%)

- Normal
  - > 80: 46.9, Mild: 70–79: 39.0, 65–79: 9.4
  - Moderate: 50–69: 13.2, Severe: ≤ 50: 0.8, ≤ 65: 0.6

![Figure 11](image)

Comparison of the response to therapy with either placebo or infliximab in patients with chronic pulmonary sarcoidosis

For those patients with no reticulonodular infiltrates (R-score = 0), there was no difference between active drug and placebo. For patients with a positive R-score, there was a significantly higher probability of ≥ 5% absolute improvement in FVC for those treated with infliximab versus those treated with placebo (P < 0.05). Source: Adapted from Baughman et al. [5].

Developed scoring system, which separately scored the reticulonodular component (R-score) from the confluent areas (C-score) and mass like infiltrates (M-score) and fibrosis (F-score) [6]. This scoring allowed one to separate the different features seen on chest roentgenogram. Figure 11 summarizes the findings of a study of patients with chronic pulmonary sarcoidosis treated with either infliximab or placebo. For patients with an R-score equal zero, that is no reticulonodular markings, there was no difference in the proportion of patients with a > 5% absolute change in their FVC after 24 weeks of therapy with either infliximab or placebo. However, for those who had a positive R-score, there was a significantly higher probability of improvement if the patient was treated with infliximab rather than placebo [5].

While the chest roentgenogram is the standard method of describing the chest findings in sarcoidosis, high-resolution CT (HRCT) scanning provides much more detail regarding the findings in the lung. Figure 12 demonstrates a chest X-ray (A) and HRCT (B) of a patient with adenopathy and confluent areas of infiltrate. The nodularity in sarcoidosis can be small but numerous (Figure 13) and these nodules are often subpleural [48]. This nodularity may not be seen on routine chest X-ray. Pulmonary fibrosis in sarcoidosis has a variety of manifestations [49]. This includes traction bronchiectasis (Figure 14). This tends to be an upper lobe predominant process. Mycetomas can occur in these areas of bronchiectasis. In addition, one can see honeycomb as a consequence of the fibrosis, which can be subpleural (Figure 14). The fibrosis tends to be upper lobe...
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and can have relative sparing of the lower lobes. The honeycomb pattern can be associated with a usual interstitial pneumonia pattern on pathology [50].

As noted, there is only a mild correlation between chest X-ray stage and forced vital capacity [4]. This is especially true for comparing patients with stage 1 versus those with stage 2 or 3 [51,52], that is patients with parenchymal lung disease on chest X-ray. Patients with fibrosis (stage 4) will have lower lung function than other groups [52,53].

Serial chest roentgenograms have been studied, often with changes in therapy. Several methods have been used, including comparison chest X-ray stage [54], changes in the Murers’ score [5,55], and comparison of chest roentgenogram before and after intervention [5,54,56]. The changes in chest roentgenogram seem to provide the best scoring system [54]. Part of its appeal is that it is reproducible [5,54] and it is what is the most commonly reported outcome of paired chest roentgenograms. In several studies, changes in chest X-ray compared well with changes in lung function [5,54,56]. The use of HRCT scan provides more precise imaging of the lungs [57,58]. It is more sensitive than chest X-ray in detecting lung function abnormalities [57] and may help in making a diagnosis of sarcoidosis [59]. The HRCT may classify with a detailed scoring system [11], but this system does not provide a global score of the chest involvement. Other authors have correlated the FVC and DLCO with the presence or absence of features such as bronchial distortion, honeycombing, and linear densities [7,60,61]. HRCT may be especially useful in assessing advanced fibrotic sarcoidosis [8]. Table IV is a comparison between HRCT findings and the FVC and DLCO from two groups. Both groups found that bronchial distortion and honeycombing were associated with more severe disease. The presence of honeycombing was associated with the lowest functional capacity [61].

The lack of correlation of pulmonary function testing and chest X-ray staging [4,40,52] has led to studies of the value of functional testing such as the six-minute walk test and cardiopulmonary exercise testing (CPET). The six-minute walk test is a simple and reproducible test [62] applied to a wide variety of lung diseases, including pulmonary fibrosis [63]. It has been studied in sarcoidosis patients [39,64]. It has been shown to independently correlate with FVC [39]. However, it is influenced by a large number of factors encountered in sarcoidosis including fatigue, depression, cardiac disease, and pulmonary hypertension [65]. Muscle weakness is common in sarcoidosis and can impair the six-minute walk distance [64]. Pulmonary hypertension can independently reduce six-minute walk distance [39]. A reduced six-minute walk test, especially with desaturation, is an important indicator of pulmonary hypertension in sarcoidosis [66].

Cardiopulmonary exercise testing (CPET) is a more complex method for assessing lung impairment in sarcoidosis. However, it does provide information regarding both cardiac and pulmonary dysfunction. The type of exercise and stress load with exercise can vary considerably, making comparisons between studies difficult and CPET has not been routinely used to assess sarcoidosis patients [40]. In one study, the CPET was poorly predicted by pulmonary function testing [52]. However, in another study, a reduced DLCO was often associated with reduced exercise tolerance [67]. Reduced exercise capacity
was significantly more common in patients with chest X-ray stage 4 [52] or traction bronchiectasis and/or honeycombing is seen on CT scan of chest [57,60]. In many cases, airway obstruction and distortion seems to be the major contributor to reduced exercise capacity [68]. In some cases, CPET may suggest a cardiac source for abnormal exercise tolerance.

**Pulmonary complications**

Hospitalization for sarcoidosis is usually related to comorbid respiratory conditions, such as pneumonia. In the United States, African American women have a higher rate of hospitalization [69]. Infection can be a result of pulmonary sarcoidosis itself or of the use of immunosuppressive therapy to treat the disease. In a prospective 18-month study of 753 patients seen at one sarcoidosis clinic, seven (0.9%) fungal infections were diagnosed (histoplasmosis, blastomycosis, and cryptococcosis) [70]. All patient were on corticosteroids at time of the infection and four had also been treated with methotrexate. Others have reported cryptococcal infections at an increased rate in sarcoidosis patients even when patients were on no immunosuppressive therapy [71–73]. Among the infections encountered is aspergillomas, which can lead to massive bleeding and invasive disease [74]. The mycetomas usually occur in preexisting cavities (figure 15) [8]. In one series, 2% of sarcoidosis patients had mycetomas

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**Table IV**

Comparison between high-resolution CT (HRCT) findings and pulmonary function studies

<table>
<thead>
<tr>
<th>Lopes [60]</th>
<th>Number</th>
<th>FVC (%)</th>
<th>DLCO (%)</th>
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<tbody>
<tr>
<td>Grade 1: Predominantly nodules</td>
<td>18</td>
<td>104²</td>
<td>101²</td>
</tr>
<tr>
<td>Grade 2: Predominantly ground-glass opacity</td>
<td>10</td>
<td>87.5²</td>
<td>83.5²</td>
</tr>
<tr>
<td>Grade 3: Predominantly traction bronchiectasis and honeycombing</td>
<td>14</td>
<td>85²,3</td>
<td>72.5²,3</td>
</tr>
</tbody>
</table>

| Abeshera [61] | Linear pattern | 19 | 84⁴ | 65⁴ |
|               | Bronchial distortion | 38 | 76⁴ | 58⁴ |
|               | Honeycombing | 23 | 58⁴,5 | 58⁵ |

¹FVC = forced vital capacity, DLCO = diffusing lung capacity for carbon monoxide.
²Median.
³Significantly lower than Grade 1.
⁴Mean.
⁵Significant difference between groups.

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**Figure 13**

High-resolution CT (HRCT) representation of a reticulonodular pattern in patient with chronic pulmonary sarcoidosis. The nodules are often subpleural (arrow)
The air crescent sign which changes location within the cavity with change in position of the patient helps confirm that this is a free moving mass rather than a tumor growing out of the wall of the cavity. The reverse halo sign has proved useful diagnosing locally invasive fungal infections such as aspergillosis.
However, the sign has also been reported in sarcoidosis patients with fungal infections [59,76]. Pulmonary hypertension is another complication of pulmonary sarcoidosis [77]. In patients with significant dyspnea, pulmonary hypertension has been found in more than half of the patients [43,78]. Pulmonary hypertension is discussed elsewhere in this monograph.

**Conclusion**

There are a wide variety of pulmonary manifestations from sarcoidosis. The most commonly used tools to detect these are pulmonary function testing and chest imaging. Treatment decisions in sarcoidosis are usually based on symptoms [79]. Dyspnea and cough are the most common symptoms leading to treatment for sarcoidosis. The most commonly used tools to detect lung involvement are pulmonary function testing and chest imaging. However, these tests only mildly correlate with dyspnea [4] and are not predictive of cough. These different measures of lung disease appear complimentary, with no single test summarizing all the pulmonary manifestations.

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**References**


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