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Physiological Manifestation in Pulmonary Sarcoidosis

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1. Introduction

Sarcoidosis is a granulomatous disease involving multiple organs with unknown cause. More than 90% of patients with sarcoidosis have lung disease [1–3]. However, respiratory function in patients with sarcoidosis often remains normal, even when pulmonary parenchymal involvement is extensive. Not only the lung parenchyma but also the lung airways are involved, which sometimes makes it difficult to evaluate the relationship between functional impairment and morphological/imaging patterns.

Respiratory function impairment in sarcoidosis has not been considered to be a major concern in either clinical or basic research. However, the marked restrictive ventilatory impairment in sarcoidosis with end-stage pulmonary fibrosis is a serious problem in clinical practice.

Obstructive disease is another manifestation of respiratory function impairment in sarcoidosis that is sometimes associated with the end-stage fibrosis of sarcoidosis, with marked reduction of vital capacity and total lung capacity. However, obstructive ventilatory impairment also appears without restrictive disease of sarcoidosis, especially in the early stage of sarcoidosis [4–6].

This chapter will review the functional impairment in patients with pulmonary sarcoidosis, especially restrictive and obstructive ventilatory impairments, taking the histological background into consideration.

2. Restrictive impairment

Restrictive impairment is mainly caused by extensive fibrosis secondary to sarcoid granulomas or by interstitial pneumonia coexistent with pulmonary sarcoidosis.

Histologically, sarcoidosis manifests itself as multiple nodules of nonnecrotizing granulomas consisting of epithelioid histiocytes and multinucleated giant cells with mononuclear inflammatory cells at the periphery of the nodules. Granulomas are usually situated in the interstitium (Figures 1, 2), and sometimes in the air spaces (Figure 3) [7–9], thus forming space-occupying lesions. Granulomas are typically scattered along the lymphatic routes. Peribronchial and perivascular tissues are richly supplied by lymphatics, where granulomas grow larger (Figures 1, 2). The imaging pattern is, therefore, quite characteristic; that is, opacities are situated along the bronchovascular bundles. High-resolution computed tomography (HRCT) describes well multiple nodules located along airways and pulmonary vasculatures and on the pleura, including the interlobar pleura (Figure 4). Sarcoid granulomas may spontaneously regress or become fibrotic (Figure 5).

It is reasonable to hypothesize that restrictive impairment in sarcoidosis depends on the extent of parenchymal involvement of the granulomas, even if they later become fibrotic [10]. Generally, respiratory function worsens with more advanced disease stages, but the radiographic stage does not correlate well with the severity of respiratory function impairment [11].

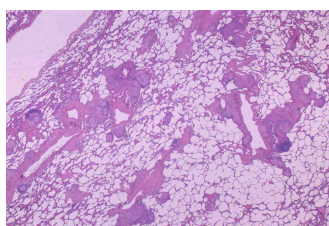


Figure 1. Low-magnification view of pulmonary sarcoidosis in a biopsy specimen. Nodular lesions are situated along the bronchovascular bundles. (Courtesy of Dr. Thomas V. Colby, Mayo Clinic, Arizona, USA.)

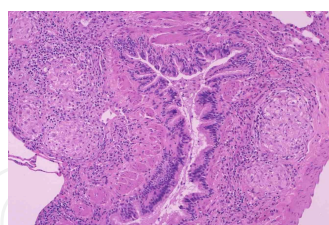


Figure 2. High-magnification view of the specimen shown in Figure 1. Nonnecrotizing epithelioid granulomas surround a bronchiole. (Courtesy of Dr. Thomas V. Colby, Mayo Clinic, Arizona, USA.)

A mild interstitial mononuclear cell infiltration is said to occur occasionally in pulmonary sarcoidosis, but in practice this is rarely seen [12]. However, some investigators have paid attention to coexistent interstitial pneumonia in patients with sarcoidosis. Interstitial pneumonia or secondary fibrosis in end-stage sarcoidosis may play a more important role in the restrictive impairment of sarcoidosis. Rosen et al. examined interstitial pneumonia in patients with sarcoidosis [13]. They found that the incidence of interstitial pneumonia decreases as the density of parenchymal granulomas increases, and that interstitial pneumonia is significantly more prevalent in patients with sarcoidosis of stage I than stages 2 or 3. They concluded that

sarcoid granulomas are preceded by lymphocytic infiltration or that interstitial pneumonia typically occurs in the early stage of sarcoidosis.

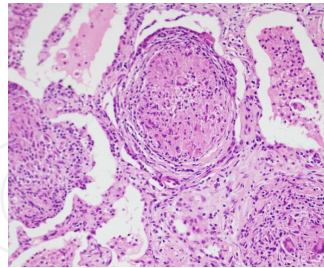


Figure 3. An epithelioid cell granuloma located in the peripheral airway. Another granuloma is embedded in the interstitium in the right lower quadrant (69-year-old woman).



Figure 4. Chest CT scan of a 28-year-old man with pulmonary sarcoidosis. Small nodules are found along the bronchial wall (short arrows) and pulmonary artery (arrowheads). Nodules are also found on the pleural surface, including the interlobar pleura (long arrows).

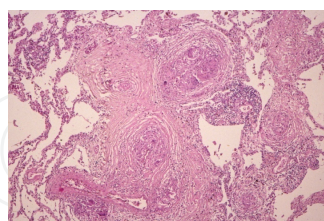


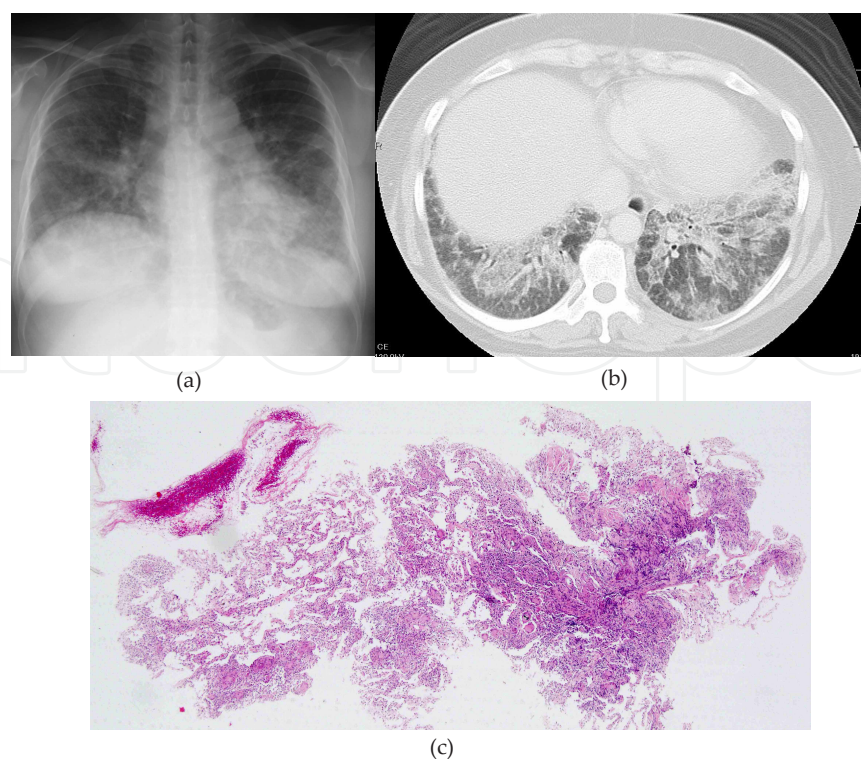
Figure 5. Nonnecrotizing epithelioid granulomas with giant cells are surrounded by concentric layers of fibrotic bundles.

Here, we present a 49-year-old woman with a nine-year history of progressive pulmonary sarcoidosis with stages from early cellular interstitial pneumonia to late fibrotic interstitial pneumonia. She underwent transbronchial lung biopsy at 40 years of age, when she noticed dyspnea and cough. Chest radiograph revealed bilateral diffuse ground-glass shadows and CT revealed ground-glass opacities along the bronchovascular bundles. The imaging features appeared like nonspecific interstitial pneumonia (Figures 6a and b). A transbronchial lung biopsy specimen collected at that time showed cellular interstitial pneumonia and focal

aggregates of epithelioid cells with giant cells, which is compatible with sarcoidosis (Figures 6c and d). But for the sarcoid granulomas, the histological features would be similar to those of cellular pattern of nonspecific interstitial pneumonia, a subset of idiopathic interstitial pneumonias [14]. The ground-glass opacities on chest CT were attributable to the infiltration of mononuclear cells in the alveolar septa. At that stage, restrictive impairment and gas exchange impairment were prominent (Table 1). The pathophysiological mechanisms underlying the functional impairment described in Figures 6c and 6d are probably similar to those of the cellular interstitial pneumonias described above. In contrast to the decrease in DLco, DLco/VA was normal. The decrease in DLco observed in the patient can be mainly attributed to diffusion impairment caused by thickened alveolar septa.

At the later stage, the ground-glass opacities disappeared and traction bronchiectasis became the main imaging finding (Figures 6e and 6f), although outer-zone-dominant honeycombing at both lung bases, which is the hallmark of usual interstitial pneumonia (UIP), was absent. Restrictive impairment progressed during the 8.6 years of follow-up, but the annual decrease in FVC was gradual (Table 2 and Figure 6g).

To summarize the disease of this woman, ground-glass opacities at the initial stage were replaced by traction bronchiectasis in the course of 8.6 years of follow-up. It is probable that cellular interstitial pneumonia associated with pulmonary sarcoidosis progressed to fibrosing interstitial pneumonia with gradual decrease in FVC. However, the pulmonary fibrosis in this case did not look like idiopathic pulmonary fibrosis (IPF).



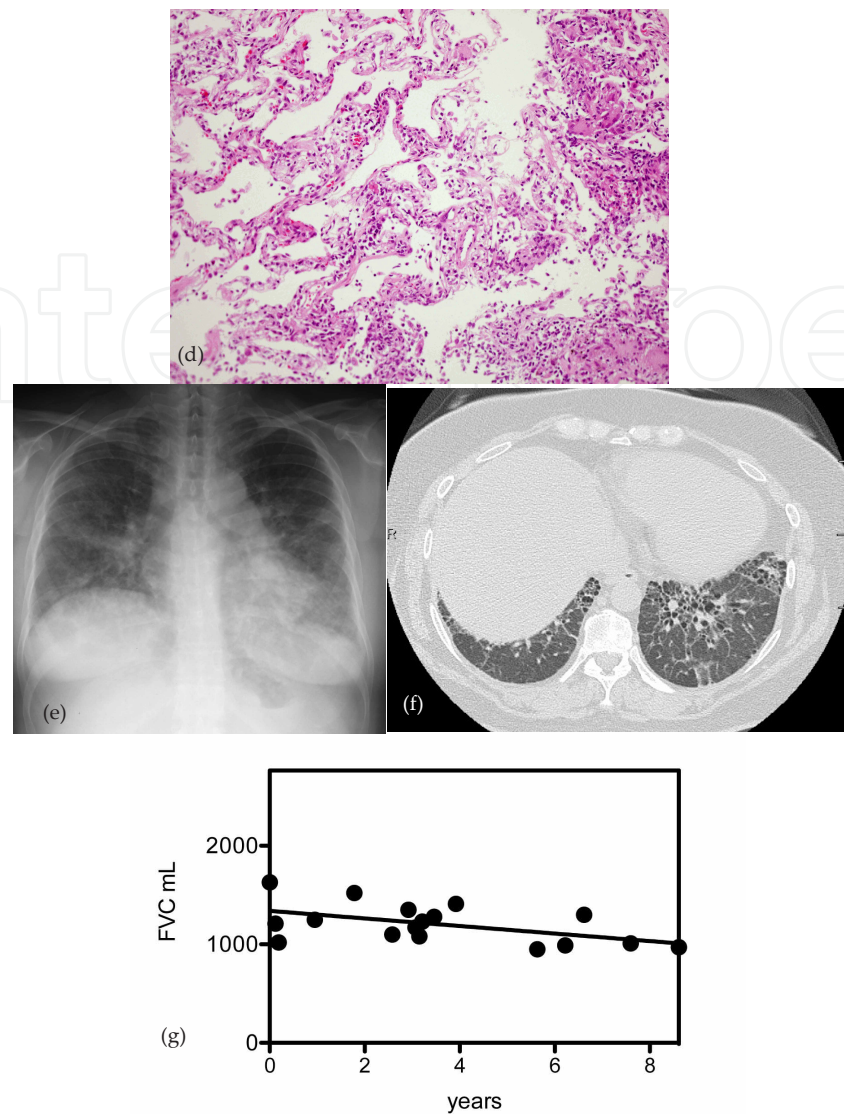


Figure 6. Chest radiograph (a) of a woman with sarcoidosis showing diffuse ground-glass opacities in the bilateral lung fields. Chest CT (b) of the same woman showing ground-glass opacities mainly along the bronchovascular bundles. (c) A transbronchial lung biopsy specimen obtained from the same woman. Alveolar septa are thickened. Granulomas are sparsely found. (d) A high-magnification view of Figure 6c. Alveolar septa are thickened with mononuclear cell infiltration. Small foci of epithelioid granulomas are found on the right side of the specimen. Thickened alveolar septa may be the barrier to gas exchange. Chest radiograph (e) and CT (f) of the woman with sarcoidosis, which were taken 7.1 years after the first CT (Figure b). Ground-glass opacities disappeared, but many bronchi were densely concentrated in the left lung base, forming traction bronchiectasis. (g) Yearly decline of FVC in the course of the 8.6 years of follow-up of advanced pulmonary sarcoidosis. The annual decline of FVC calculated using linear regression was 38 mL (2.9% of the initial FVC at year 0), which is far milder than that observed in IPF. The top of the vertical axis shows the 100% level for FVC as predicted for the patient at year 0.

Restrictive impairment and gas exchange impairment are serious presentations in advanced sarcoidosis, as is the case in IPF. However, honeycomb-like cysts, which are the imaging hallmark of IPF/UIP, are atypical radiographic manifestations in sarcoidosis [11]. Moreover, the most important diagnostic feature in sarcoidosis is the prognosis or the slope of the deterioration of respiratory functions, as seen in Figure 6g. Nardi et al. reported that

the 10-year survival of patients with stage IV sarcoidosis was 84.1%, which is far better than that of IPF [15].

FVC mL (% pred)	1210 mL (44%)
FEV ₁ mL (% pred)	870 mL (36%)
FEV/FVC %	71%
TLC mL (% pred)	2510 mL (68%)
FRC mL (% pred)	1160mL (53%)
RV mL (% pred)	810mL (70%)
DLco mL/min/mmHg (% pred)	11.3 (54%)
DLco/VA mL/min/mmHg/L (%pred)	5.49 (103%)

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; TLC: total lung capacity; FRC: functional reserve capacity; RV: reserve volumeDLco: diffusing capacity of carbon monoxide; DLco/V_A: diffusing capacity of carbon monoxide/alveolar volume

Table 1. Respiratory function data for a 40-year-old woman with sarcoidosis

FVC mL (% pred)	970 mL (38%)
FEV ₁ mL (% pred)	800 mL (37%)
FEV/FVC %	82%

Table 2. Spirometry 8.6 years after the first measurement (Table 1)

In contrast to patients with sarcoidosis associated with interstitial pneumonia, functional impairment in patients with sarcoidosis without interstitial pneumonia may be less extensive, if present. We frequently encounter patients with sarcoidosis who have extensive imaging findings, but almost normal respiratory function. Such differences in functional impairment raise the possibility that interstitial pneumonia could be independently coexistent with pulmonary sarcoidosis [16], although the histological findings in which sarcoid granulomas are embedded in cellular interstitial pneumonia, as shown in Figures 6c and d, suggest that interstitial pneumonia is one of the fundamental histological manifestations of sarcoidosis.

Shigemitsu et al. reviewed the microscopic slides of explanted lungs to examine chronic interstitial pneumonia (interstitial infiltration by lymphocytes and/or plasma cells) in seven patients with end-stage sarcoidosis who ultimately underwent lung transplantation [17]. In their report, four of the seven patients had diffuse interstitial pneumonia, which was atypical

of end-stage sarcoidosis, and two of these four patients had a pattern that was indistinguishable from the UIP pattern, with fibroblastic foci. Furthermore, these four patients had undergone lung transplantation with a shorter time to transplant than the remaining three patients without interstitial pneumonia. These results raise the possibility that there is a subset of patients with sarcoidosis that progresses to pulmonary fibrosis resembling IPF/UIP with poorer prognosis [18].

Stage IV sarcoidosis might encompass two subsets of end-stage sarcoidosis, as described above: sarcoid granuloma-derived secondary fibrosis and fibrosing interstitial pneumonia, which is not secondary but coexistent, although it may be rare.

3. Obstructive impairment

1. Obstructive impairment as a minor component of functional impairment?

Although sarcoidosis involving thoracic lymph nodes and pulmonary parenchyma is familiar to most pulmonologists, airway involvement is often overlooked [19]. Airway dysfunction is an important component of the disease, but is often ignored when the interstitial disease is dominant.

As sarcoidosis commonly affects the pulmonary parenchyma, one could often misunderstand that airways are less commonly involved and restrictive impairment occurs more frequently than does obstructive impairment. However, airway involvement, as judged based on clinical features, physiological testing, imaging techniques, bronchoscopy, and airway mucosal biopsy, has been observed in two-thirds of patients with sarcoidosis [19]. According to a case-control etiologic study of sarcoidosis consisting of 736 patients [3], the majority of patients (477/736) had normal FVC defined as $> 80\%$ of FVC, in contrast to a smaller percentage of normal FEV1/FVC% defined as $> 80\%$ of FEV1/FVC% (340/736). As described above, clinicians should notice that airflow obstruction is more frequently encountered than is restrictive impairment and is the commonest physiological abnormality in patients with sarcoidosis in clinical practice.

Airway sarcoidosis occurring over the entire length of the respiratory tract – from the upper airway to the lower airway, including the respiratory bronchioles – causes a broad spectrum of airway dysfunction or obstructive ventilatory impairment [20]. In addition, airway sarcoidosis causing obstructive impairment and lung parenchymal sarcoidosis causing restrictive impairment could modify their physiological manifestations mutually.

As airway obstruction in sarcoidosis is reported to be associated with increased morbidity and increased mortality risk [21, 22], obstructive impairment, as well as restrictive impairment, should be checked carefully in the routine follow-up.

2. Upper-airway sarcoidosis

In this section, the trachea is conveniently included in the upper airway. The nose, sinuses, oropharynx, supraglottic structures, larynx, and trachea are less frequently affected with

sarcoidosis than is the lower airway [1, 2, 19, 20, 23]. The presenting symptoms of laryngeal sarcoidosis are dysphagia, hoarseness, dyspnea, stridor, and cough [20, 23]. Hoarseness can occur from the granulomatous lymphadenopathy in the mediastinum compressing recurrent nerve or from polyneuropathy by granulomatous inflammation of the vagus nerve [24–26]. Sometimes, these may cause respiratory distress, requiring tracheostomy.

Obstructive sleep apnea syndrome occurs with increased frequency in patients with laryngeal sarcoidosis. Turner et al. reported that 14 of 83 consecutive patients with sarcoidosis (17%) had sleep apnea, which was significantly more frequent than that observed in the general population [27]. It may be secondary to laryngeal sarcoidosis, or may result from obesity associated with the long-term administration of corticosteroids.

Tracheal stenosis and dystonia are the primary manifestations of tracheal sarcoidosis, although tracheal involvement is rare compared with sarcoidosis of lobar or segmental bronchi. Cough is the main symptom.

The flow-volume curve is quite characteristic. Sarcoid lesions located in the upper airway cause flattening of the inspiratory and/or expiratory loops of the flow-volume curve, although this is not specific to sarcoidosis. In general, fixed airway stenosis caused by upper-airway sarcoidosis, regardless of whether it is extrathoracic or intrathoracic, induces flattening of both the inspiratory and expiratory loops. Variable extrathoracic or intrathoracic stenosis induces flattening of the inspiratory and expiratory loops of the flow-volume curve, respectively [28, 29] (Figures 7a–d).

3. Lower-airway sarcoidosis

As described above, the lower airways are also affected, similarly to the lung parenchyma. As granulomatous lesions also occur in the bronchial mucosa and submucosa [30], endoscopic examination frequently identifies these submucosal lesions. Endoscopic examination also identifies indirect findings derived from peribronchial lesions, such as extrinsic bronchial compression by enlarged lymph nodes. The morphological characteristics of airway involvement include bronchial stenosis, mucosal nodularity, hypervascularity, and mucosal edema (Figures 8a–d) [19, 20, 23, 31–33]. Some investigators have emphasized the mucosal vessels that run perpendicular to cartilaginous rings as an early manifestation of sarcoidosis (Figure 8c) [31, 32, 34].

Bronchial mucosal biopsy confirms the histological diagnosis (Figure 9). These lesions can lead to respiratory symptoms and signs, such as cough and wheezes in auscultation, which are often misdiagnosed as asthma.

Lower-airway involvement in sarcoidosis may lead to airflow limitation (Figure 10, Table 3). However, bronchial mucosal findings in fiberoptic bronchoscopy are not always correlated with the severity of airflow limitation, because airflow limitation is due not only to proximal airway lesions but also to distal airway lesions that are not visible using conventional fiberoptic bronchoscopy. According to the report of Stjernberg et al., an obstructive spirometry pattern was found in only three patients among 21 patients with bronchial sarcoidosis that was confirmed by bronchoscopy [5].

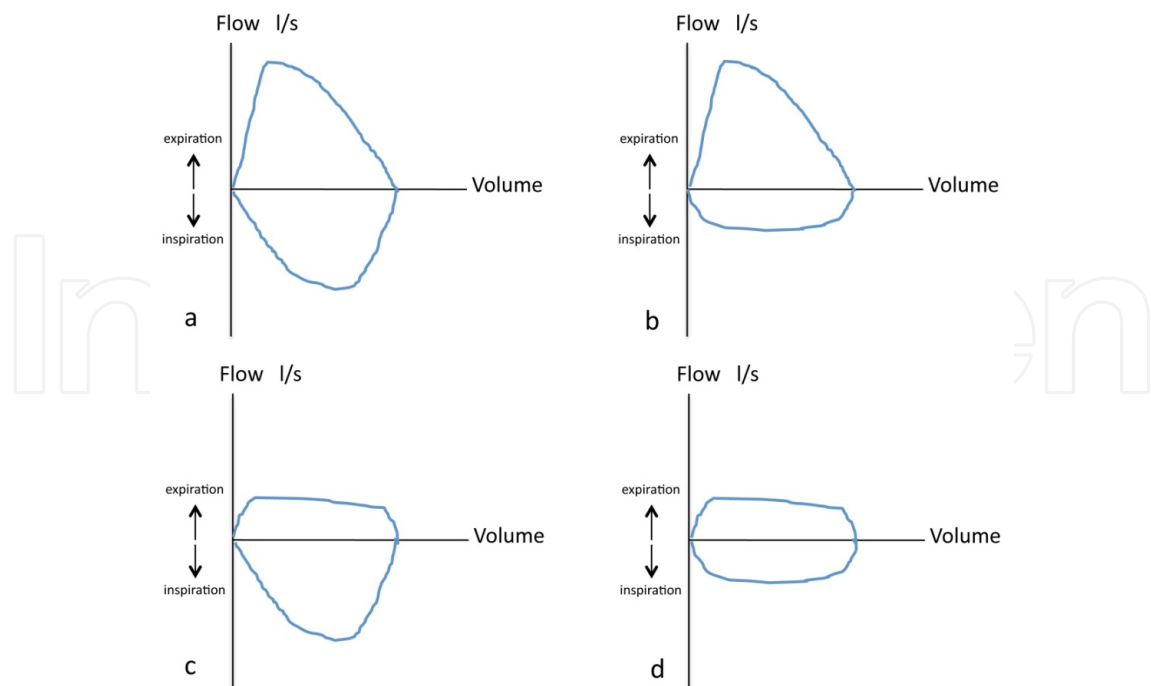


Figure 7. a) Normal flow-volume curve, b) Variable extrathoracic stenosis, c) Variable intrathoracic stenosis, d) Fixed extrathoracic or intrathoracic stenosis.

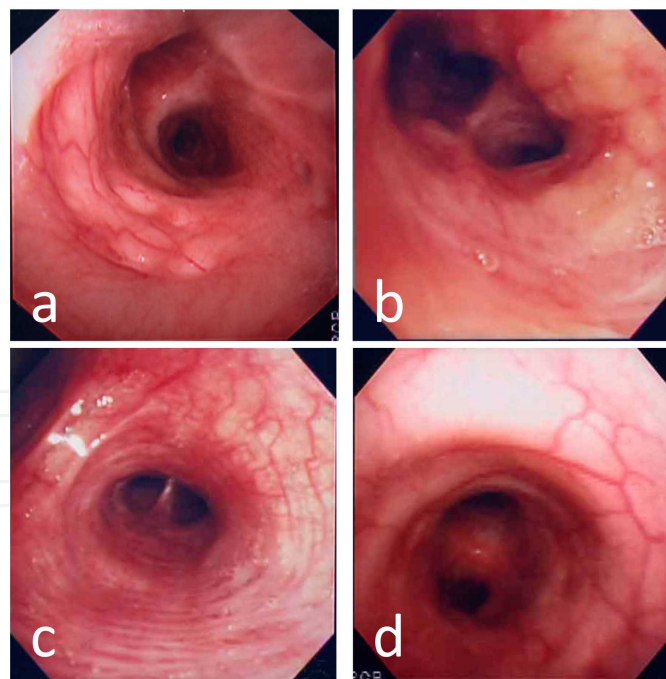


Figure 8. Endoscopic findings of bronchial sarcoidosis. a) Flattened and pale-colored plaques arising from the bronchial mucosa, forming a “cobblestone appearance” (right main bronchus, 38-year-old woman), b) Bronchial lumen is crowded by pale-colored multiple nodules (left upper lobe bronchus, 61-year-old woman), c) Mucosal hypervascularity with vessels running perpendicular to cartilaginous rings (left lingular bronchus, 38-year-old man), d) Network formation of mucosal vessels in the left main bronchus, and mucosal edema of the left second carina (29-year-old man).

Airflow obstruction is reported in 4–63% of patients with sarcoidosis, depending on the spirometry criteria used by different authors [3, 5, 6, 10, 22, 35–40]. Sharma et al. reported that airway obstruction defined as less than 75% of FEV₁/FVC was found in 63% of black American nonsmoking patients with sarcoidosis [37]. Airflow obstruction defined as less than 70% of FEV₁/FVC, the criterion for COPD, occurs in 9–14% of patients with sarcoidosis [3, 39]. We demonstrated that 21% of patients with sarcoidosis (12/56) had airflow obstruction, which was defined as less than 70% of FEV₁/FVC, obtained at least once in repeated spirometry during the entire follow-up period [41].

Airflow obstruction is often associated with an advanced stage of sarcoidosis or decreased VC and FVC [39], but occurs without any relationship to radiographic stage or restrictive impairment [6, 37]. Small airway dysfunction is common in early sarcoidosis without restrictive defects [4–6]. The previous investigations described above tell us that airflow obstruction occurs in all stages of sarcoidosis and should always be looked for in patients with sarcoidosis who have respiratory symptoms [38].

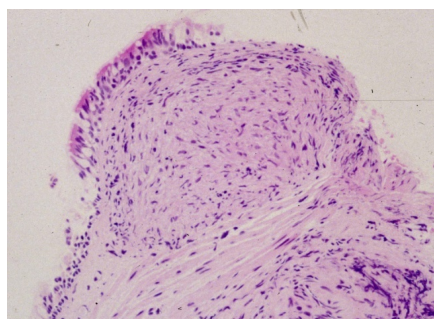


Figure 9. An epithelioid cell granuloma obtained using bronchial mucosal biopsy.

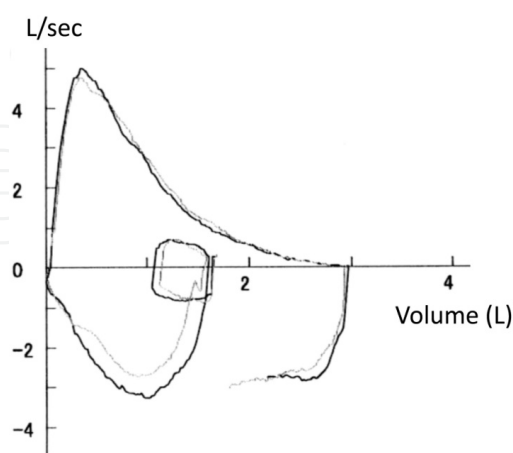


Figure 10. Flow-volume curve of a 61-year-old woman with bronchial sarcoidosis. Her mucosal finding under bronchoscopy is shown in Figure 10b. She never smoked and the expiratory flow is reduced, with a downward convex, as observed bronchial asthma. However, FEV₁ did not significantly improve after the inhalation of a β -2 agonist (thick line: basal flow-volume curve; thin line: flow-volume curve after inhalation of salbutamol).

FVC mL (% pred)	3150 mL (120%)
FEV ₁ mL (% pred)	1990 mL (94%)
FEV/FVC %	63%
TLC mL (% pred)	4540 mL (115%)
FRC mL (% pred)	2710 mL (105%)
RV mL (% pred)	1240 mL (81%)
DLco mL/min/mmHg (% pred)	21.3 (137%)
DLco/VA mL/min/mmHg/L (%pred)	5.63 (121%)

FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 second; TLC: total lung capacity; FRC: functional reserve capacity; RV: reserve volume; DLco: diffusing capacity of carbon monoxide; DLco/V_A: diffusing capacity of carbon monoxide/alveolar volume

Table 3. Respiratory function data for a 61-year-old woman with sarcoidosis

As described above, airflow obstruction is frequently encountered in sarcoidosis. Lavergne et al. demonstrated that airway obstruction by sarcoid granulomas in the bronchial mucosa that were histologically confirmed via endobronchial biopsy was partially or completely reversed by steroid treatment, with improved pulmonary symptoms [21]. However, airflow obstruction in sarcoidosis is often refractory to inhaled steroid or bronchodilator therapy in clinical practice [20, 23, 38, 39, 41]. This presentation is not likely to be caused by coexistent asthma or COPD, because of its poor response to inhaled steroids and/or β -agonists. At what level of the airways does airflow obstruction occur?

Airways with endobronchial lesions that are visible on fiberoptic bronchoscopy are not the only airways that are responsible for airflow obstruction. Small airways or the lung parenchyma may also be involved in airflow obstruction. In general, the extent of decreased attenuation with a mosaic pattern is related to small airway disease, whereas a reticular pattern is considered to be a typical pattern of pulmonary fibrosis on CT. Air trapping, which presents as decreased attenuation exaggerated at expiratory CT, is a common feature of sarcoidosis, and there have been reports examining the correlation between air trapping and airflow obstruction [42, 43]. However, Hansell et al. reported that airflow obstruction is more closely related to a reticular pattern than to the extent of decreased attenuation on expiratory CT [44]. It is possible that progression to fibrosis of granulomatous inflammation adjacent to the small airways is critically associated with airflow obstruction.

4. Treatment of obstructive impairment

As described above, obstructive impairment appears at an early stage of sarcoidosis and also with advancing radiographic stage. The efficacy of treatment may depend on the anatomical sites of sarcoid granulomas, associated fibrosis, and severity of the symptoms.

Upper-airway or tracheal sarcoidosis with airway stenosis needs systemic corticosteroids. In some cases, methotrexate or cytotoxic drugs, such as azathiopurine, may be added. Laryngeal sarcoidosis may cause life-threatening upper-airway obstruction. Surgical intervention is indicated for patients with well-localized, life-threatening lesions. When stridor is present, emergent tracheostomy may be needed [20, 45].

As the symptoms of bronchial sarcoidosis are, if present, cough and wheezing, and spirometry shows reduced rate of FEV1/FVC, which is misdiagnosed as asthma, inhaled β_2 -agonists and/or corticosteroids are often administered. However, we have often experienced unfavorable results in such cases, especially when parenchymal lesions are associated with the condition.

As described above, Lavergne et al. [21] examined the effect of systemic steroid therapy for patients who had histologically proven bronchial sarcoidosis with airflow obstruction ($< 70\%$ of FEV1/FVC), but their radiographic stages were 1 to 3. They obtained a favorable result after administration of 0.6 mg/kg of oral corticosteroids initially, and concluded that airflow obstruction by bronchial sarcoidosis without fibrosis-related airway obstruction is treatable.

5. Airway hyperreactivity

The prevalence of airway hyperreactivity, as demonstrated by a positive methacholine or histamine challenge test, is significantly higher in patients with sarcoidosis compared with normal controls [46–49]. It is unclear whether airway hyperreactivity is a physiological manifestation of endobronchial sarcoidosis or is due to concomitant asthma [20]. However, Wilsher et al. examined the prevalence of asthma in patients with sarcoidosis and demonstrated that it was the same as that observed in the normal population [50]. Airway hyperreactivity in sarcoidosis and asthma can be distinguished by the response to inhaled corticosteroids and β_2 -agonists. Airway hyperreactivity associated with asthma is improved by these agents, whereas airway hyperreactivity caused by sarcoidosis requires oral corticosteroids [20, 47, 48].

6. Pulmonary hypertension

Pulmonary hypertension (PH) occurs in 1–28% of patients with sarcoidosis [51–53]. PH is a serious complication in advanced stage VI sarcoidosis and has a poor prognosis. PH is largely attributed to the destruction of the capillary bed by pulmonary fibrosis. As the severity of PH does not always correlate with parenchymal changes, other factors may contribute to the development of PH, such as specific vasculopathy, local increased vasoreactivity, mechanical compression of pulmonary vessels, and portopulmonary hypertension.

According to the Dana Point Classification of 2008 [54], PH in sarcoidosis falls under category 3 (PH owing to lung disease and/or hypoxia) or 5 (PH with unclear multifactorial mechanisms) [53].

There is no specific therapy for PH associated with sarcoidosis. The management of sarcoidosis with PH mainly relies on supportive therapy (supplemental O₂ and diuretics, as needed) [52]. Lung transplantation is now an important therapeutic option for these patients [53].

Patients with “out of proportion” pulmonary hypertension (characterized by dyspnea insufficiently explained by lung mechanical disturbances and mean pulmonary artery pressure $\geq$ 40–45 mmHg at rest) should be referred to expert centers and enrolled in clinical trials of pulmonary artery hypertension-specific drugs [55]. Endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and intravenous epoprosterol, etc., have been tried, and some patients experienced a beneficial effect. However, large-scale prospective clinical trials are needed before these therapies can be universally adopted.

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