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Pulmonary Sarcoidosis: A Pictorial Review

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Sarcoidosis is a multisystem granulomatous process that most commonly involves the lungs. Radiographic findings consistent with sarcoidosis are important to the diagnosis of this disease, as no specific diagnostic test for sarcoidosis exists. The classic imaging manifestations of sarcoidosis are related to granulomatous involvement along the lymphatic pathways within the lungs, granulomatous involvement of lymph nodes, and fibrosis at the sites of previous inflammation. These findings sometimes take atypical forms. Additional manifestations of sarcoidosis are caused by involvement of the bronchi and bronchioles, the pulmonary arteries, and the heart. Fungal colonization may also occur. A range of thoracic imaging manifestations of sarcoidosis is illustrated to facilitate the diagnosis of this common, multifaceted disease.
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Sarcoidosis is defined as an idiopathic multisystem granulomatous process, and it may therefore present with involvement of almost any organ system. However, 90% of patients have thoracic involvement, and in the United States and Europe respiratory failure is the most common cause of mortality from sarcoidosis. Interstitial lung disease is common at presentation and contributes substantially to morbidity and mortality. There is no specific diagnostic test for sarcoidosis; instead, the diagnosis of sarcoidosis depends on the presence of compatible histologic and radiographic features in the setting of a concordant clinical presentation, and the exclusion of other etiologies. As imaging manifestations, commonly within the chest, represent one of the criteria for a diagnosis of sarcoidosis, it is necessary for the radiologist to be familiar with the range of its radiographic manifestations and its associated clinical features. This article will describe and illustrate a range of common and uncommon manifestations of sarcoidosis in the chest, in order to support clinical decision making in the diagnosis and treatment of patients with this disease.

Background

Although the etiology of sarcoidosis is by definition unclear, current research suggests that it is caused by an interaction of genetic susceptibility with an environmental antigen or antigens. A number of microbial and environmental antigens, including organic and inorganic antigens, have been suggested, although no definite link between any antigen and sarcoidosis has been established.[1] There is probably a range of different genetic factors that are involved in different cases of sarcoidosis, and each factor or group of factors may be associated with susceptibility to sarcoidosis in a different patient population. For example, 1 gene (butyrophilin-like 2, or BTNL2) that was discovered in a German population to be associated with sarcoidosis was later found to be associated with sarcoidosis in white Americans, but not in African-Americans.[2] Each genetic susceptibility may also be associated with different clinical manifestations of sarcoidosis; for example, in a Swedish population, the HLA-DRB1*03 subtype is associated with the development of Lofgren's syndrome.[2]

The relationship between sarcoidosis and both genetic and environmental risk factors makes it impossible to generalize about the epidemiology of sarcoidosis on a worldwide basis. The reported prevalence of sarcoidosis in national epidemiologic studies ranges from 160 per 100,000 population in Sweden[1] to only 5.89 per 100,000 population in Greece, with an even lower 3.7 per 100,000 reported on the Japanese island Hokkaido.[3] In the United States, the prevalence is reported to be 59.0-60.1 per 100,000 population overall, and 141.4 per 100,000 in African-Americans.[3]

It was once thought that sarcoidosis was primarily a disease of young adults between the ages of 30 and 50 years,

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but in the United States the distribution of the time of diagnosis may in fact be bimodal, with a substantial number of patients receiving the diagnosis later than age 50.[3] Sarcoidosis has also been described in children, usually between the ages of 9 and 15, and occasionally in even younger children, with an organ distribution similar to that seen in adults.[4,5] African-Americans not only have a higher incidence of sarcoidosis than white Americans, but they also are more frequently treated for pulmonary disease and have more organ involvement and higher mortality. The overall mortality of sarcoidosis in the United States appears to be increasing.[3] However, spontaneous remissions are not uncommon, occurring in 16%-39% of patients within the first 6-12 months after symptoms occur. If spontaneous remission occurs, late relapse is rare.[5]

Pathology

It has been argued that the imaging findings of sarcoidosis are sufficient to establish a diagnosis in the appropriate clinical setting even without tissue diagnosis,[6,7] but American Thoracic Society (ATS) guidelines suggest that histologic confirmation is required for a definitive diagnosis unless classic Lofgren symptoms are present and resolve quickly and spontaneously.[5] The classical description of sarcoidosis at pathology is "well-formed, tightly packed, non-necrotizing granulomas surrounded by lamellar hyaline collagen."[8] These are located along the pulmonary lymphatics, which are associated with centrilobular bronchovascular bundles and along the interlobular septa and the pleural surfaces (Fig. 1).[8] Despite the classical description of non-necrotizing granulomatous inflammation, some necrosis is present in approximately 20% of lung biopsies in patients with necrosis. The finding of extensive necrosis, however, should lead to careful investigation for infectious agents.[8]

Bronchoscopy is the mainstay of the histologic diagnosis of sarcoidosis except in patients with more easily accessible sites of involvement such as the skin or conjunctiva.[1] The approach to histologic diagnosis of sarcoidosis has changed over the past decades due to advances in bronchoscopic sampling techniques, and now the bronchoscopist may employ several different approaches to obtaining diagnostic material.[1,9] Bronchoscopic techniques include bronchioloalveolar lavage, transbronchial lung biopsy, endobronchial biopsy, ultrasound-guided transbronchial needle aspiration of lymph nodes, and transbronchial cryobiopsy.

Bronchioloalveolar lavage in sarcoidosis may yield lymphocytosis, a sensitive but not specific finding, and lymphocytosis with an elevated CD4/CD8 cell ratio at lavage favors a diagnosis of sarcoidosis over hypersensitivity pneumonitis.[10] A CD4/CD8 ratio greater than 3.5 has a sensitivity of 60% and a specificity of 90%-95% for sarcoidosis.[8] Lavage is also particularly useful in excluding infection. Transbronchial lung biopsy has the advantage of demonstrating granulomas directly. In patients with radiographic evidence of disease, transbronchial biopsy yields a result in 66%-95% of patients.[10] Endobronchial biopsy increases the

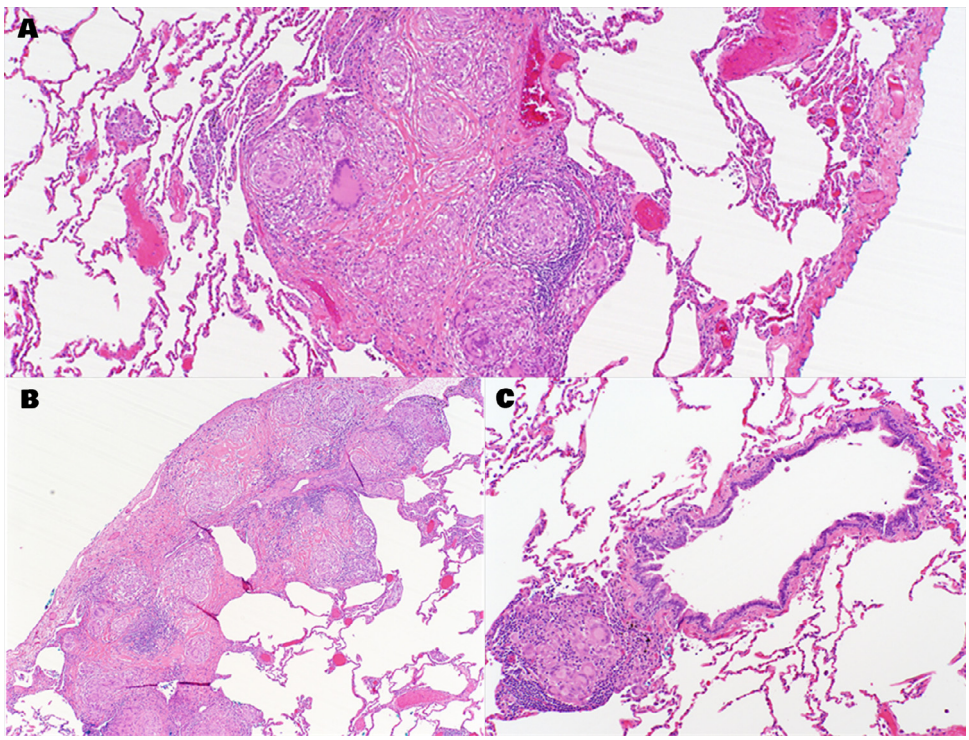

Figure 1 *Pathologic features of sarcoidosis.* (A) Sarcoid granulomas. Well-formed non-necrotizing granulomas composed largely of epithelioid cells/macrophages, giant cells, and lymphocytes surrounded by lamellar hyaline cartilage. The granulomas characteristically follow lymphatics and can be seen not only along interlobular septa (A), but also in subpleural (B), and peribronchovascular (C) locations.

diagnostic yield by 10%-20%, and may detect granulomas even in patients with normal appearing mucosa, but has a much higher yield in patients in whom a "cobblestone" appearance of the airways is identified.[1] Finally, endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes increases the diagnostic yield, particularly in those patients with lymph node enlargement on imaging. Non-necrotizing granulomas are seen in approximately 80% of patients with radiographic lymphadenopathy and, when accompanied by on-site interpretation, this technique may obviate transbronchial biopsy. Transbronchial cryobiopsy, a newer technique, has been used to increase the size of transbronchial biopsy specimens, but in the setting of sarcoidosis this seems to be most useful in identifying alternate diagnoses.[1]

Typical Manifestations of Sarcoidosis

The classic chest radiographic manifestations of sarcoidosis are divided into stages, commonly into Stages 0 through 4.[5,11] This system is based on a system devised by Scadding in 1961,[12] before the development of CT with its much greater sensitivity for subtle parenchymal abnormalities, and only refers to findings on chest radiographs. Because of the higher sensitivity of CT, the utility of a radiographic staging system for sarcoidosis has been questioned.[13] Interreader agreement for the radiographic stages is variable between different studies, adding to the uncertainty about using the staging system in clinical practice and in research.[14] Some authors have employed a modified Scadding system based on findings at CT.[15] The original system nevertheless remains a helpful framework for understanding the most likely imaging findings at presentation. Furthermore, the radiographic stage at presentation correlates with pulmonary function tests and remains a useful prognostic indicator.[16] The stages of sarcoidosis should not be considered necessarily a progression, as many patients do not proceed from earlier stages to the later stages of disease.

CT is not universally performed in patients with sarcoidosis. According to the ATS consensus statement, CT should be considered when clinical or radiographic findings are atypical, when complications of sarcoid or superimposed conditions (such as bronchiectasis, mycetoma, infection, or malignancy) are suspected, or when sarcoidosis is clinically suspected and the chest radiograph is normal.[5] Despite these relatively restrictive guidelines, in clinical practice in the United States, CT has become a common part of the workup of patients with suspected sarcoidosis.[1] CT is more sensitive for abnormalities, and therefore findings at CT do not correlate perfectly with the radiographic stages, but are described below in conjunction with those stages.

Stage 0

The Scadding sarcoidosis staging system has been modified to include Stage 0, defined as sarcoidosis without any chest radiographic manifestations. Approximately 5%-15% of patients diagnosed with sarcoidosis present with Stage 0 disease.[14] The diagnosis of Stage 0 sarcoidosis is commonly made in patients with extrathoracic findings suggesting sarcoidosis, in whom bronchoscopy may be safer or more likely to yield a diagnosis than biopsy of other organs. CT is more sensitive than radiography for abnormalities and may be performed to assess for subtle abnormalities when the radiograph is normal, but pathologic sarcoidosis may exist in the setting of completely normal CT as well. In fact, in a recent series of patients with imaging and clinical findings suggestive of cardiac sarcoidosis, 75% of patients with normal chest CT had positive findings at bronchoscopy.[15] The yield of bronchoscopy in these patients was much higher than that of endomyocardial biopsy.

Stage 1

Stage 1 sarcoidosis is defined as the presence of lymphadenopathy on a chest radiograph without parenchymal abnormalities. Between 15% and 65% of patients present with Stage 1 disease, depending on the series.[14] Many patients with Stage 1 sarcoidosis are asymptomatic at presentation, and the prevalence of Stage 1 sarcoidosis and the percentage of asymptomatic patients depend on the rate at which screening chest radiographs are obtained in a given population. As in Stage 0, a normal appearance to the lungs on radiography does not imply the absence of parenchymal findings at CT or on bronchoscopy. Approximately 20% of patients with Stage 1 disease have abnormal pulmonary function tests, most commonly an abnormal diffusion capacity or vital capacity.[5] Depending on the series, 12%-55% of patients with Stage 1 sarcoidosis have findings of pulmonary sarcoidosis at transbronchial biopsy.[10]

Lymphadenopathy in Stage 1 sarcoidosis is most commonly seen at radiography in the hila bilaterally. The classic Garland triad or "1-2-3" sign of sarcoidosis refers to bilateral hilar lymphadenopathy accompanied by right paratracheal lymphadenopathy (Fig. 2A,B).[17] However, right paratracheal lymphadenopathy on radiography is a more variable feature than hilar lymphadenopathy. In 1 historic series, more than 80% of patients had lymph node enlargement at presentation, and all of these patients had bilateral hilar lymphadenopathy, while approximately two thirds had right or bilateral paratracheal lymphadenopathy.[18] At CT, right paratracheal lymphadenopathy appears to be more common even than bilateral hilar lymphadenopathy, possibly because of the greater sensitivity of CT compared with radiography for mediastinal lymph node enlargement (Fig. 2C).[19] When lymphadenopathy is not bilaterally symmetrical, and when it involves the internal mammary, pericardial, paravertebral, or retrocrural regions, neoplasm should be considered in the differential diagnosis.[20]

Lymphadenopathy is commonly described as "noncompressive," implying that even when bulky it does not lead directly to narrowing of adjacent structures, although this finding is not universal. Airway narrowing may occur as a result of mass effect from adjacent lymph nodes.[21]

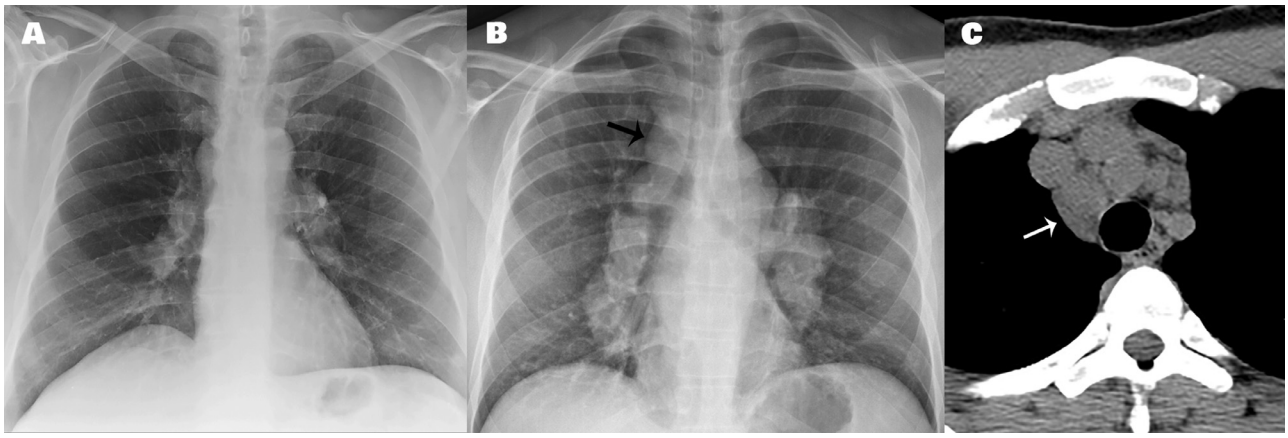

Figure 2 *Stage 1 sarcoidosis*. (A) Frontal radiograph demonstrates bilateral relatively symmetrical hilar and moderate right paratracheal lymph node enlargement. (B) Similar presentation with very bulky bilateral hilar and right paratracheal lymphadenopathy (arrow). Both of these images are characteristic. (C) Axial CT image with enlarged right paratracheal lymph node (arrow).

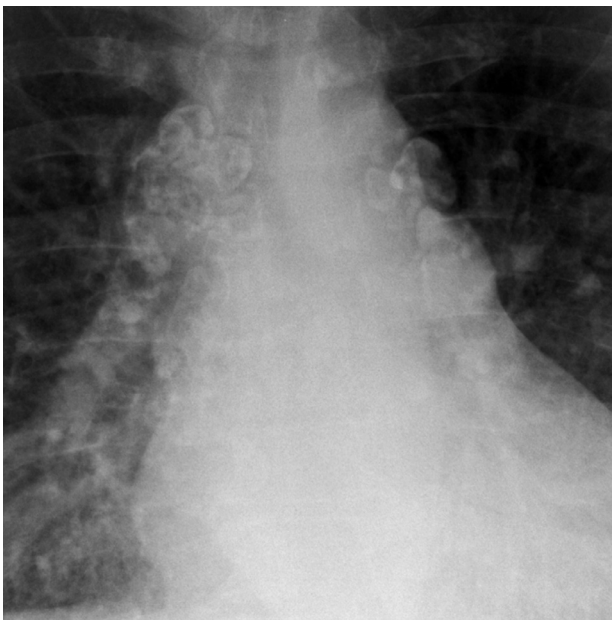

Figure 3 *Egg-shell calcifications*. Mediastinal and hilar lymph nodes on frontal radiograph with peripheral "egg-shell" pattern of nodal calcification.

Calcification may also occur in lymph nodes and increases over time. On radiography, calcification occurs in 3% of patients at 5 years and 20% at 10 years from diagnosis.[22] CT is much more sensitive for calcification and detects calcification in lymph nodes in approximately 20% of patients at presentation, and in 44% at 4 years.[14] A number of calcification patterns occur in sarcoidosis, including, occasionally, peripheral or "egg-shell" in calcifications (Fig. 3).

Lofgren syndrome is a particular clinical manifestation of sarcoid, in which patients present with a febrile illness with malaise and arthritis, occasionally accompanied by parotitis and uveitis, with hilar lymphadenopathy on imaging.[22] When this constellation of findings is present, a specific diagnosis of sarcoidosis may be diagnosed without histologic confirmation.[5] In the absence of this typical presentation, because the major differential consideration in patients with lymphadenopathy is neoplasm, the finding often forces histologic confirmation of a granulomatous process. However, once the diagnosis of Stage 1 sarcoid is confirmed, patients are rarely treated. Stage 1 disease is associated with only mild pulmonary function test abnormalities, and it has a favorable prognosis, with 60%-90% of patients going on to complete radiographic and symptom resolution.[14]

Stage 2

Stage 2 sarcoidosis is defined as having radiographically visible lymphadenopathy and simultaneous pulmonary involvement. At radiography, pulmonary findings in Stage 2 or 3 sarcoidosis include reticulonodular and fine nodular opacities as well as an "acinar" pattern of poorly marginated nodules of varying sizes (Fig. 4).[22] Only rarely are the opacities confined to a single focus.[22] Approximately 20%-40% of patients present with Stage 2 disease, and its prognosis is worse than that of Stage 1 disease although still fairly good, with 40%-70% of patients going on to resolution.[14]

CT provides more detailed evaluation of the interstitial lung disease of sarcoidosis. It is probably of relatively little value in cases in which the radiograph is abnormal and the radiographic findings and the clinical presentation are typical, but it is likely to be of much greater utility in less straightforward cases.[23] The CT hallmark of sarcoidosis is well defined, smooth or irregular nodules measuring 2-5 mm in diameter, which are seen at high resolution CT in 80%-100% of patients with sarcoidosis.[1,24] The nodules correspond to coalescent granulomas at pathology and tend to be clustered around airways, interlobular septa, and pleural surfaces, reflecting the anatomical distribution of granulomas,[25] in a CT pattern known as "perilymphatic" (Fig. 5). This can be distinguished from other nodule distributions at CT, such as the random distribution, associated with the hematogenous dissemination

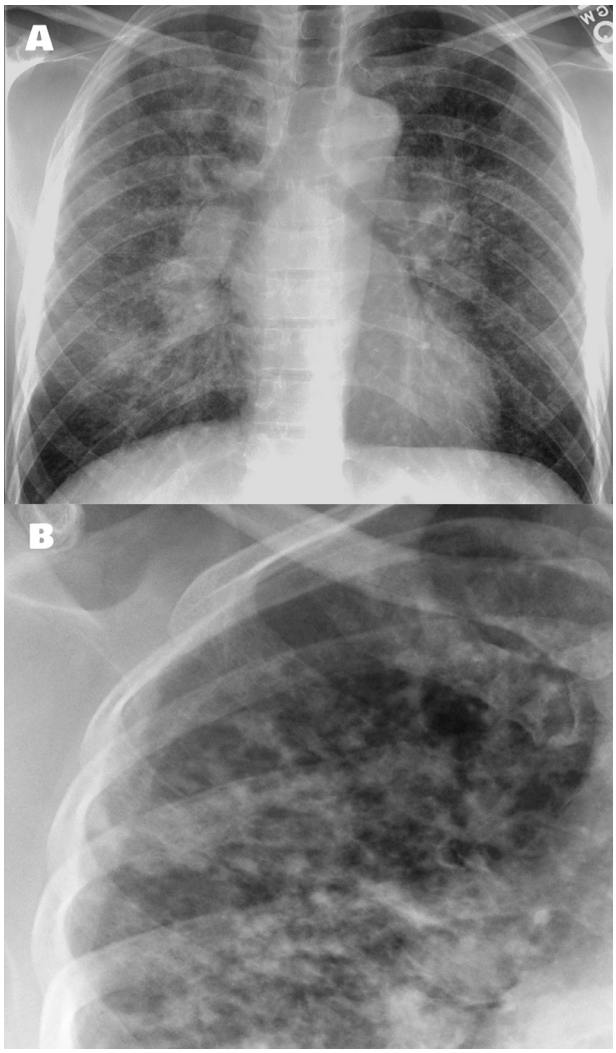

Figure 4 *Stage 2 sarcoidosis.* (A) Frontal radiograph demonstrating mediastinal and bilateral hilar lymphadenopathy as well as reticulonodular pulmonary opacities. (B) Magnified view of the right upper lobe in a second patient highlighting "acinar" pattern of parenchymal nodules of varying sizes.

of disease, and the centrilobular nodular distribution, which spares the pleural surfaces and is associated with airway-disseminated processes.[26] Ground-glass opacity is also seen at CT and reflects granulomatous infiltration interspersed with aerated lung (Fig. 5A).[25]

Stage 3

Stage 3 sarcoidosis is the stage in which patients have parenchymal lung disease without radiographic evidence of fibrosis or radiographically visible lymphadenopathy. Ten to 15% of patients have Stage 3 disease at diagnosis, and only 10%-20% of these patients go on to spontaneous resolution of their disease.[14] Pulmonary findings in Stage 3 disease are similar to those in Stage 2 disease. The absence of radiographic lymphadenopathy readily distinguishes Stage 3 from Stage 2 disease, but the distinction from Stage 4, fibrotic lung disease is more challenging, particularly at radiography.

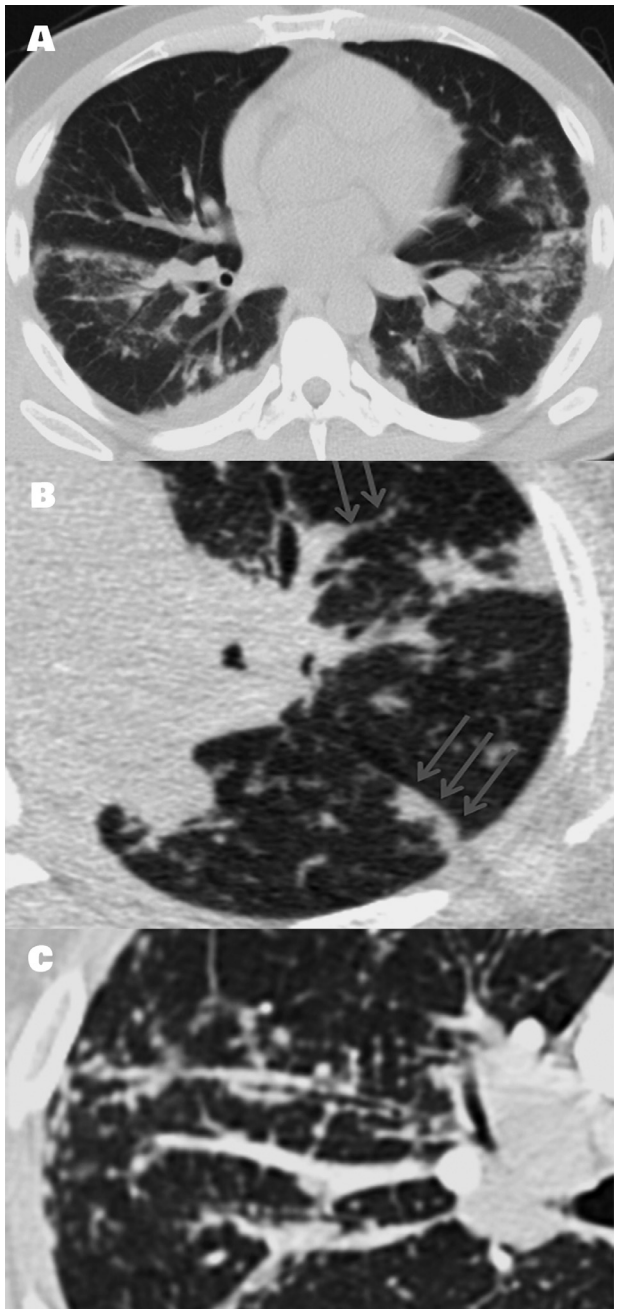

Figure 5 *CT Patterns of pulmonary sarcoidosis*. (A) Axial CT demonstrating perilymphatic distribution of nodules along the bronchovascular bundles, interlobular septa, and pleural surfaces. Note additional regions of bilateral ground-glass opacity, reflecting granulomatous infiltration interspersed with aerated lung. (B) Magnified axial CT image of the left lung of a different patient with confluent peribronchovascular (double arrow) and perifissural (triple arrow) nodules. (C) Magnified axial CT image of the right lung in a third patient with fine peribronchovascular and subpleural nodules.

Stage 4

Stage 4 sarcoidosis is defined as sarcoidosis with fibrotic abnormalities within the lungs. Approximately 5% of patients are considered to have Stage 4 disease at

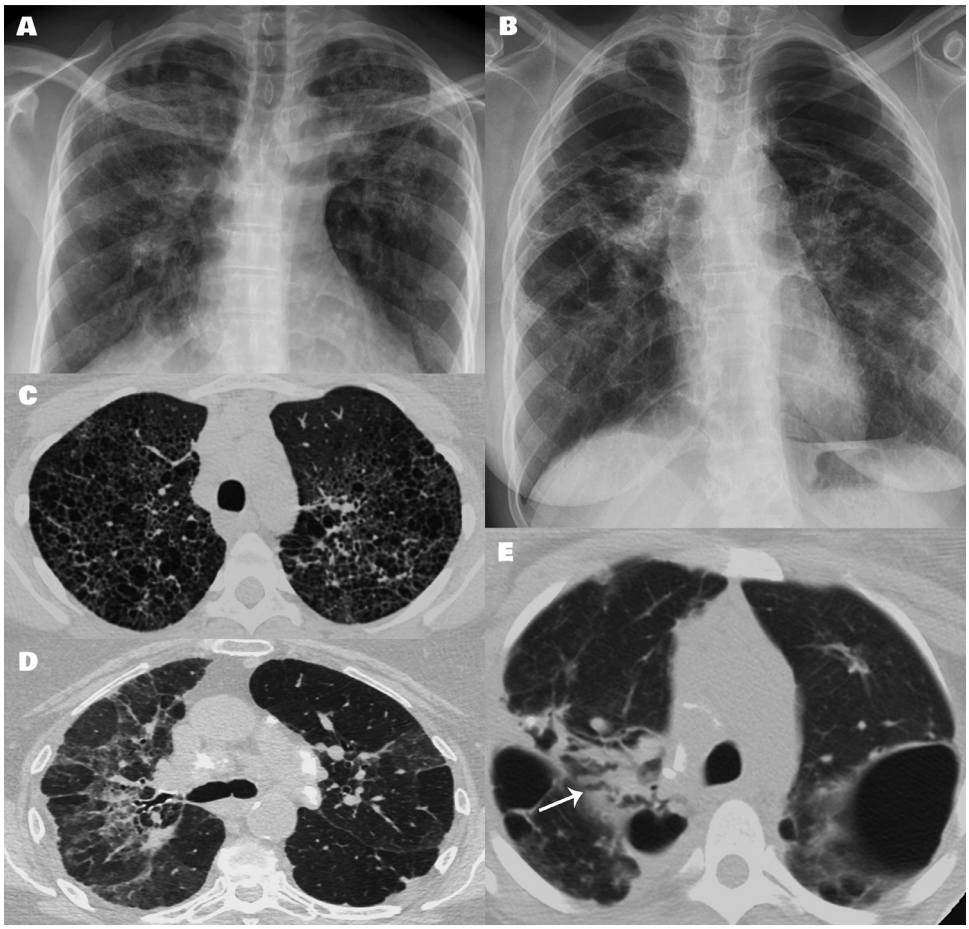

Figure 6 *Stage 4 sarcoidosis*. (A) Frontal radiograph demonstrating reduced lung volumes, coarse upper lung predominant reticular opacities, and upward retraction of the hila consistent with fibrosis in the setting of sarcoidosis. (B) Frontal radiograph of a different patient with similar findings but with associated large cysts. (C) Axial CT demonstrating upper-lobe honeycombing as a manifestation of fibrosis in sarcoidosis (D) Axial CT image with irregular interlobular septal thickening pattern of sarcoid fibrosis. Note the mosaic attenuation largely attributable to ground glass opacity, which may represent regions of fibrosis and/or active disease. (E) Axial CT image of peribronchial confluent fibrosis and large cysts. Note traction bronchiectasis in the right lung (arrow).

presentation, and, as fibrosis is an irreversible process, none of these patients have complete recovery.[14] Up to 20% of patients with sarcoidosis eventually develop pulmonary fibrosis.[27]

Fibrosis is, of course, a histologic diagnosis rather than a radiographic diagnosis, but there are clues on chest radiography to the presence of fibrosis. In 1 study, the most common chest radiographic finding of fibrosis in sarcoidosis was hilar retraction.[28] In theory, radiography should demonstrate lower lung volumes and relatively more reticular opacity and fewer nodular opacities than in earlier stages of the disease (Fig. 6).

CT findings of fibrosis in sarcoidosis have been more thoroughly studied. Follow-up studies of patients with sarcoidosis show that nodules and areas of consolidation often resolve, in keeping with the finding that they represent conglomerations of granulomas at pathology. Interlobular septal lines and other linear opacities, architectural distortion, and traction bronchiectasis (Fig. 6D) do not resolve and probably represent histologic fibrosis. There are findings, particularly ground-glass opacity, that resolve in some cases and persist in others, suggesting that they may represent either fibrosis or active disease.[29] In a series of patients with radiographic fibrosis, the most common CT findings were displacement and distortion of fissures, bronchial distortion, bronchovascular displacement, and large masses.[30] Findings were clustered into 3 patterns, of which the most common pattern was predominantly central, mid and upper lung abnormalities consisting of angulated or crossed bronchi, bronchovascular displacement, and bronchiectasis with peribronchial opacity (traction bronchiectasis). Large cysts were common in this pattern (Fig. 6B, D). Less common patterns included honeycombing, which also predominantly involved the upper and mid lung zones with stacked, subpleural cysts, and a linear pattern of diffuse interlobular septal thickening (Fig. 6C).[30]

Nuclear medicine techniques have been invoked in order help distinguish fibrotic sarcoidosis from Stage 3, active disease. These techniques also provide information about occult sites of active disease. Gallium-67 imaging was once utilized in this setting,[22] but more recent research has focused on the

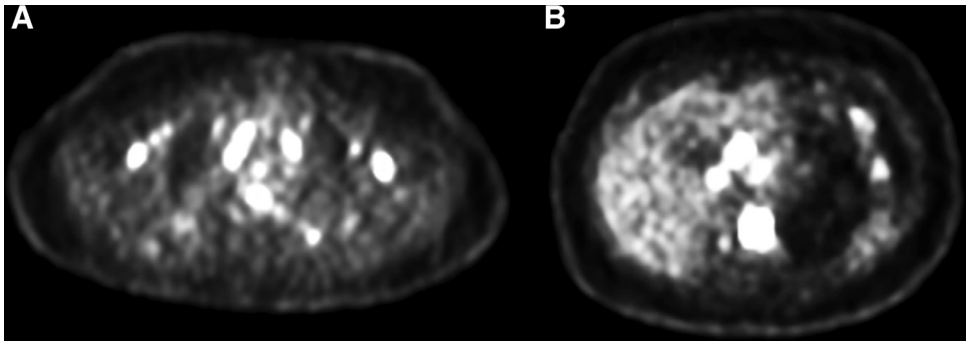

Figure 7 *FDG-PET in active sarcoidosis*. (A) Axial PET image near the level of the thoracic inlet with FDG avid mediastinal and axillary lymphadenopathy, suggestive (and useful for monitoring) of active disease. (B) Axial PET image of the upper abdomen (at the level of the porta hepatis) demonstrating extrathoracic disease including FDG avid retroperitoneal/periportal adenopathy and intense vertebral body radiotracer activity suggesting osseous involvement of sarcoidosis. This finding may mimic metastatic disease and may cause confusion in patients with neoplasm and concurrent or subsequent sarcoidosis.

use of 18-Fludeoxyglucose Positron Emission Tomography (FDG-PET).[31] FDG is taken up in areas of active granulomatous inflammation, in lymph nodes, lung, and extrathoracic sites (Fig. 7). FDG uptake decreases with treatment, and a decrease in FDG uptake is associated with durable treatment response, while persistent uptake may be an indication for changing therapy.[31,32] FDG-PET imaging may also demonstrate pulmonary metabolic activity in patients with radiographic and CT findings suggestive of fibrosis, suggesting that in many patients there is an active component to the disease even in the setting of irreversible pulmonary abnormalities. Some patients with radiographic fibrosis have clinical responses to treatment,[33] and it has been suggested that FDG uptake may be used to select patients for treatment.[27]

Masslike fibrosis is also a relatively common finding in sarcoidosis. It is radiographically similar to the masslike fibrosis that may be seen in patients with silicosis and coal-worker's pneumoconiosis, and may be seen in as many as 60% of patients with Stage 4 disease, generally in association with bronchial distortion (Fig. 8).[30] Calcifications are sometimes seen within the masslike opacities of sarcoid-related fibrosis.

Uncommon Manifestations of Sarcoidosis

Mycetoma formation

Fungal colonization is a somewhat uncommon finding in sarcoidosis, but it may occur in as many as 11% of patients with fibrotic lung disease.[33] This occurs when a mass, composed of fungal hyphae, mucus, fibrin, and cellular debris, forms within a pre-existing cavity or ectatic bronchus. The presence of cysts in association with fibrosis due to sarcoidosis is presumably at least one of the factors that place patients with fibrotic sarcoidosis at risk for mycetoma formation, and patients with sarcoidosis appear to be at higher risk for mycetoma formation than patients with other chronic lung disease.[34]

An early chest radiographic manifestation of fungal colonization is apical pleural thickening or thickening of the wall of a pre-existing cyst or cavity,[22] and the presence of new apical pleural thickening on the chest radiograph of a patient with fibrotic sarcoidosis should prompt CT to investigate for intracavitary nodules or masses (Fig. 9A). The more specific imaging manifestations of fungal colonization are well known: the presence of an intracavitary mass, or Monod sign, seen on chest radiography or on CT. On CT, these masses may appear calcified due to deposition of minerals within the fungal elements (Fig. 9B). Hemoptysis occurs in as many as 90% of patients with sarcoidosis complicated by mycetomas, and therefore the detection of mycetomas may prompt treatment with antifungal agents.[35]

Pulmonary Hypertension

Pulmonary hypertension was once thought to be rare but is now considered a relatively common complication of sarcoidosis, although its precise prevalence in this setting is not known.[36] Individual series report pulmonary hypertension occurring in 5%-15% of patients with sarcoidosis, and in up to 50% of patients with symptomatic sarcoidosis, with the highest prevalence in patients who are listed for lung transplantation.[2] Small case series have reported favorable results of vasodilating medications used for the treatment of pulmonary hypertension of other etiologies, but no prospective trials have yet been performed in this setting.[36]

Pulmonary hypertension in sarcoidosis is categorized in the Nice classification of pulmonary hypertension in Group V, "Unclear Multifactorial Mechanism."[37] A large number of mechanisms may lead to pulmonary hypertension in the setting of sarcoidosis, including myocardial involvement, granulomatous arterial and venous involvement, hypoxia with vasoconstriction, pulmonary vascular distortion, destruction of the capillary bed in fibrosis, and pulmonary emboli.[38]

Many patients with pulmonary hypertension in the setting of sarcoidosis have Stage 4, fibrotic-appearing lung disease, but pulmonary hypertension also may be found in patients with no evidence of parenchymal lung disease (Stage 0 or 1). The possibility of pulmonary hypertension should therefore be considered in a patient with significant dyspnea in the

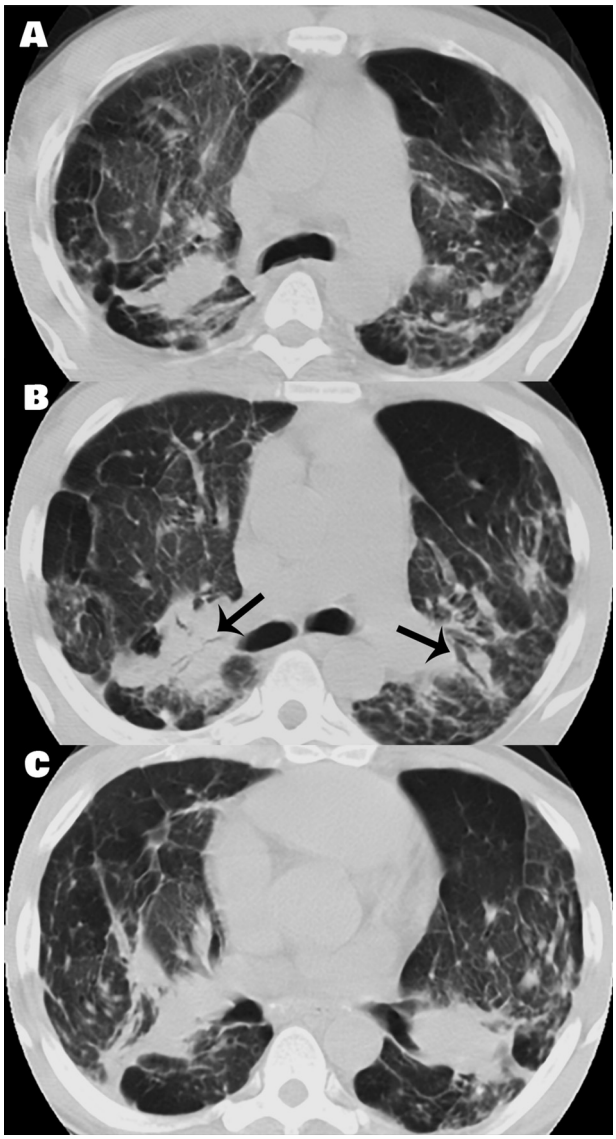

Figure 8 *Stage 4 sarcoidosis with masslike fibrosis.* (A, B, C) Sequential axial CT images at and below the level of the carina demonstrating perihilar coalescent masslike consolidation with associated architectural distortion mimicking progressive massive fibrosis (PMF) of coal worker's pneumoconiosis and silicosis. (B) Note air bronchograms (arrows) which are more common in masslike fibrosis of sarcoidosis than in PMF due to pneumoconiosis.

setting of sarcoidosis with no or minimal parenchymal lung disease on chest radiography or CT. Pulmonary artery enlargement may increase the suspicion of pulmonary hypertension in this setting and lead to further clinical workup. However, absolute pulmonary artery dilation is a less useful indicator in patients with pulmonary fibrosis, including fibrosis secondary to sarcoidosis. In the setting of pulmonary fibrosis it has been suggested that the ratio of pulmonary artery diameter to aortic diameter is a more reliable indicator of pulmonary hypertension (Fig. 10).[39] This finding is associated with a poor clinical prognosis even in patients with relatively good pulmonary function tests.[40]

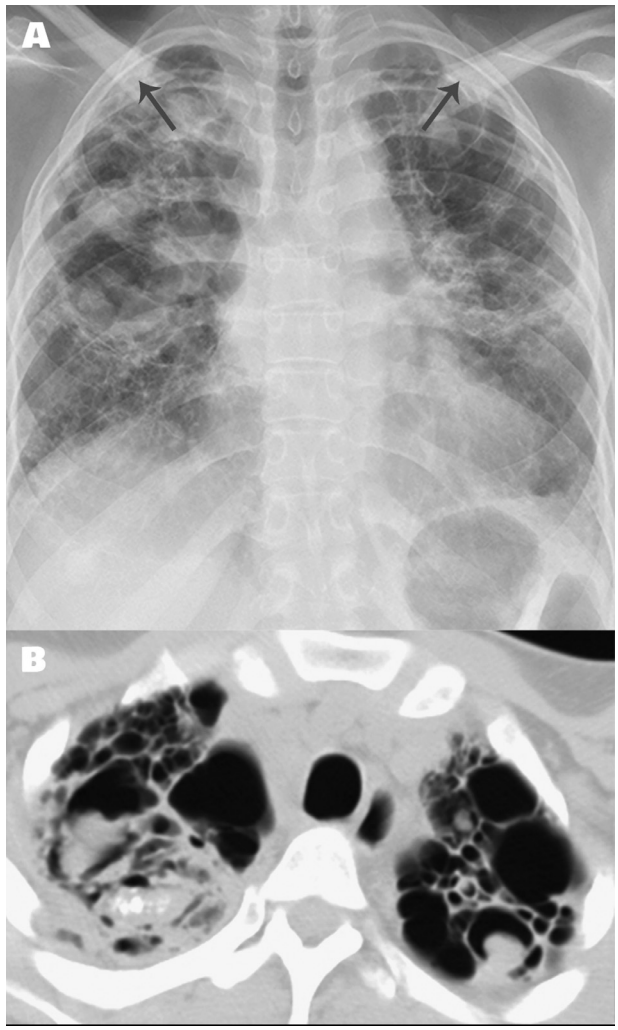

Figure 9 *Apical pleural thickening due to fungal colonization.* (A) Fibrotic (stage 4) sarcoidosis in a patient demonstrating new biapical pleural thickening (arrows) raising concern for fungal colonization (even in cases in which no discrete mass is readily apparent) in underlying cysts/cavities. (B) Axial CT of the upper lungs confirms fibrosis and intracavitary masses consistent with mycetomas. Note the intralesional coarse calcifications of the right apical mycetoma, caused by deposition of minerals within fungal elements.

"Alveolar" Sarcoidosis

The consolidative opacities seen in sarcoidosis are sometimes referred to as the "alveolar" pattern.[41] Radiographically and at CT, these opacities appear infiltrative, are not associated with architectural distortion, and may contain air bronchograms, in distinction from consolidation and masses in Stage 4 fibrotic sarcoidosis (Fig. 11). At histology, these are predominantly composed of areas in which granulomas fill and expand the interstitium obliterating the alveolar spaces, although a component of the abnormality may be caused by actual alveolar involvement by granulomatous inflammation.[41] In most series, this pattern is uncommon, occurring in fewer than 5% of patients with sarcoidosis.

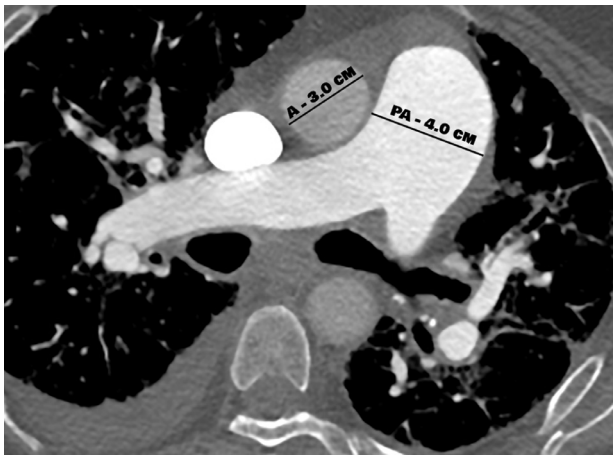

Figure 10 *Relative pulmonary artery enlargement*. Axial CT demonstrating increased caliber of the main pulmonary artery (PA) relative to the adjacent aorta (A). PA:A > 1, such as in this patient with sarcoid where PA:A = 1.3, may serve as an indicator of pulmonary hypertension. Note the presence of pleural fluid, which in the setting of sarcoid is most often secondary to causes other than direct pleural involvement by sarcoidosis (such as cardiovascular disease).

Large Nodules or Masses

Some of the large consolidative opacities in sarcoidosis may be nodular or masslike. Large nodules or masslike opacities are defined as rounded opacities of soft-tissue attenuation measuring greater than 1 cm in diameter (Fig. 11D). When they are seen in sarcoidosis, they are commonly multiple, and as a subset of the "alveolar" pattern of sarcoidosis, they are thought to be formed by the coalescence of multiple micronodules. Like other manifestations of "alveolar sarcoidosis," they may contain air bronchograms. In this context the sarcoid "galaxy sign" was first described, although it is also seen in other cases of "alveolar" sarcoidosis. The galaxy sign is described as the presence of micronodules in the periphery of larger nodules or masses (Fig. 11D).[42] Occasionally, these masses may contain areas of central cavitation. Masses in sarcoidosis may also occasionally be of ground-glass opacity or ground-glass opacity with peripheral consolidation (reverse halo sign).[43]

Miliary Opacities

Although small nodular opacities are a characteristic CT finding in sarcoidosis, a miliary pattern of diffuse micronodules, measuring 1 mm in diameter or less, is relatively rare, occurring in fewer than 1% of cases.[20,44] For this reason, care should be taken to exclude infection, particularly military tuberculosis, when this pattern is detected. In at least some of these patients, CT demonstrates that the distribution of the micronodules is perilymphatic, despite the otherwise miliary appearance, rather than the random distribution expected with miliary spread of granulomatous infection (Fig. 12).

Necrotizing Sarcoid Granulomatosis

In 1969, Liebow introduced the term "necrotizing sarcoid granulomatosis" to describe an entity comprising granulomas with necrosis and an accompanying vasculitis. The amount of necrosis and the severity of vasculitis in this entity separate it from more classic forms of sarcoidosis. However, at least small amounts of necrosis and some vascular involvement are now understood to be a finding in classical sarcoidosis and it therefore remains controversial whether necrotizing sarcoid granulomatosis should be considered an entirely separate entity or simply a variant of sarcoidosis. Findings in patients with necrotizing sarcoid granulomatosis tend to be radiographically similar to findings in patients with the large nodular form of sarcoidosis, although with lymphadenopathy a less prominent feature.[45] Cavitation may occur in both necrotizing sarcoid and in the large masslike form of sarcoidosis (Fig. 11E). While some pathologists continue to maintain that necrotizing sarcoid granulomatosis is a separate entity, others argue that the 2 are closely related, such that the term "sarcoidosis with necrotizing sarcoid granulomatosis pattern" should be used.[45]

Mosaic Attenuation

The perilymphatic distribution of granulomas includes clustering around distal airways, which accounts in part for the generally high yield of bronchoscopy in the diagnosis of sarcoidosis. Although sarcoidosis is commonly thought of as a restrictive lung disease, an obstructive pattern may also be seen on pulmonary function tests, as bronchiolar involvement by sarcoidosis commonly leads to small airways obstruction. Small airways involvement may cause mosaic attenuation on expiratory high resolution CT (Fig. 13A). Patchy pulmonary involvement by ground-glass opacity due to sarcoidosis may also lead to mosaic attenuation, and can be distinguished from small airways disease by the absence of air trapping on expiratory images.

Bronchial Involvement

The "cobblestone" appearance of the bronchi at bronchoscopy is a characteristic feature of sarcoidosis, which frequently involves the large airways. Bronchial wall thickening and luminal narrowing and irregularity may be seen in patients with large airway involvement.[46] Central bronchial involvement may lead to narrowing and even occlusion of airways, with secondary atelectasis or to bronchiectasis (Fig. 13).[20] Narrowing may be caused by granulomatous inflammation, in which case obstruction may be reversible with treatment, or by fibrosis in which case it is likely to be irreversible.[21]

Pleural Disease

Because sarcoidosis can involve any organ system, it is unsurprising that it can involve the pleura, and sarcoid involvement

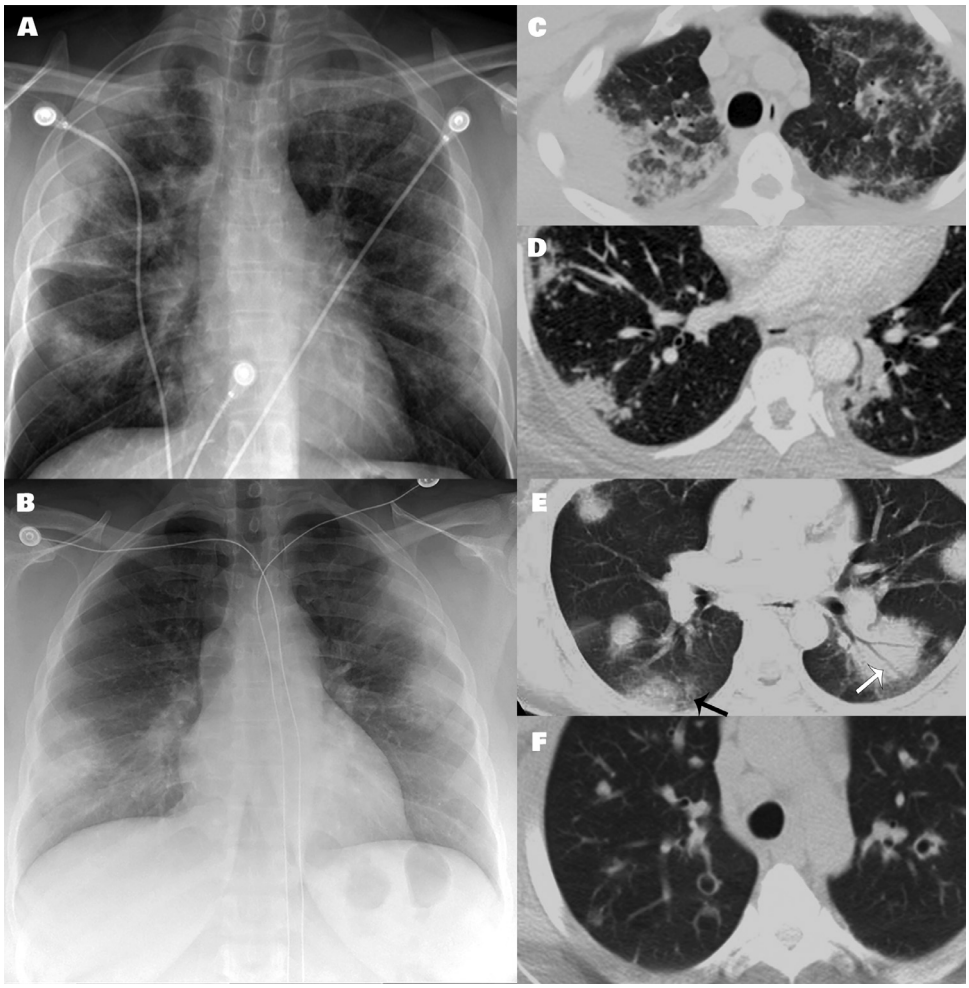

Figure 11 *"Alveolar" sarcoidosis*. (A, B) Frontal radiographs in 2 patients demonstrating peripheral airspace consolidative opacities. Note the lack of architectural distortion, distinguishing these opacities from the masslike confluent fibrosis that may occur with stage 4 sarcoidosis. (C) Axial CT correlate of the radiograph (A) demonstrating consolidation in the absence of significant fibrosis. Despite use of the word "alveolar" and the consolidative appearance, most granulomas histologically are found in the interstitum, expanding and obliterating adjacent alveolar spaces. (D) Axial CT correlate of the radiograph (B) which demonstrates confluent nodularity accounting for the consolidative opacities on the correlative radiograph. (E) Axial CT with large masses, which are also composed of confluent predominantly interstitial granulomas. Air bronchograms are present in the largest nodule of the left lung (white arrow), often a prominent sign in this manifestation of sarcoidosis. Note the micronodules ("galaxy sign") in the periphery of the large nodules (black arrow). (F) Axial CT of a patient with an uncommon (<0.8%) cavitary presentation of sarcoidosis. Again, note the larger size of the nodules, some of which demonstrate central cavitation.

of the pleura may rarely be associated with pleural effusion.[22,47] Nevertheless, pleural effusion is a sufficiently unusual manifestation of sarcoidosis that when pleural effusion is identified, other etiologies should be considered, including cardiac disease. More frequently, apparent pleural involvement by sarcoidosis is artifactual, caused by the clustering of subpleural nodules to form "pseudoplaques" (Fig. 14).[48]

Cardiac Disease

When sarcoidosis is suspected or known, interstitial opacities are usually assumed to represent sarcoid pulmonary involvement. However, if smooth interlobular septal thickening rather than nodular interstitial opacities are identified, the findings may reflect interstitial edema in the setting of cardiac sarcoidosis (Fig. 15A,B).

Cardiac involvement is often underappreciated clinically (approximately 10% of patients with other systemic manifestations receive the diagnosis), although autopsy studies demonstrate cardiac involvement in approximately 25% of patients.[49] Increased availability of cardiac MRI, utilizing segmented gradient echo inversion recovery delayed gadolinium enhancement sequences, provides a relatively sensitive means of evaluating for the presence of cardiac sarcoidosis. Although detailed discussion of cardiac MRI evaluation is beyond the scope of this review, in

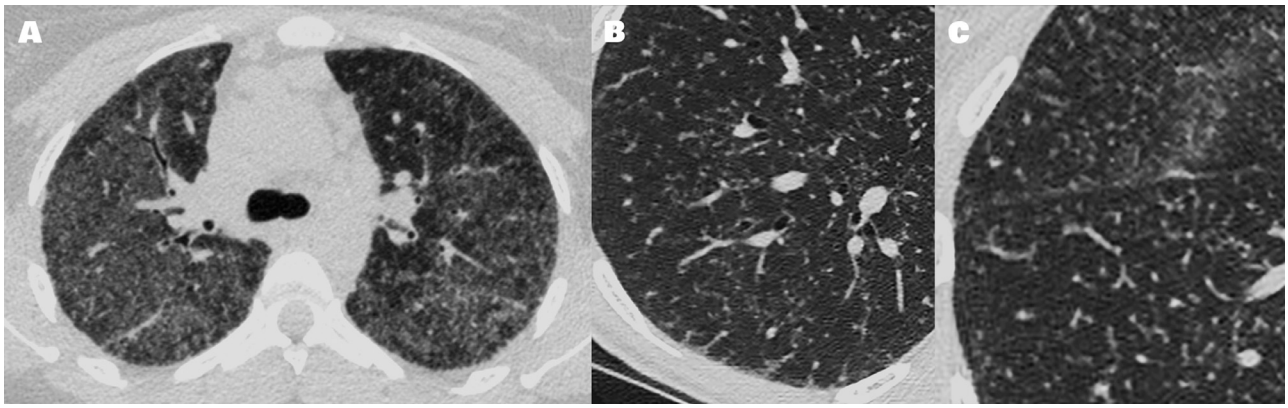

Figure 12 *Miliary pattern of sarcoidosis.* (A, B, C) Axial CT images demonstrate a relatively rare (<1%) miliary pattern of diffuse micronodules. Note the (B) interlobular septal and (C) perifissural nodules characteristic of distribution of granulomas along lymphatic channels. The "miliary" pattern is supported by small size (1 mm) of nodules in this case, rather than true random distribution.

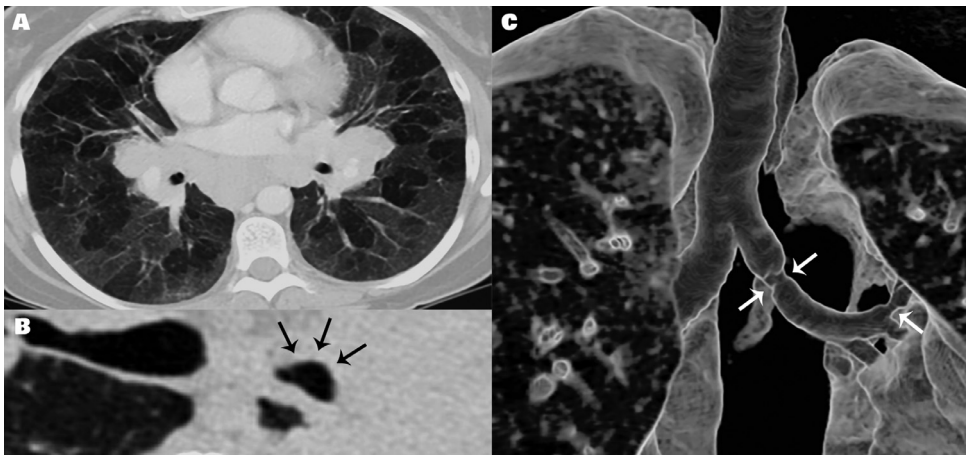

Figure 13 *Airway involvement*. (A) Although most often considered a restrictive lung disease, pulmonary function tests may show evidence of obstruction. Expiratory axial HRCT of a patient with bronchiolar involvement by sarcoidosis demonstrates mosaic attenuation characteristic of small airway obstruction. (B, C) Large airway involvement is a common finding at the time of bronchoscopy, with narrowing of airways sometimes evident on imaging. (B) Axial CT demonstrates partial effacement of the proximal left large airways with associated mural thickening (arrows). (C) Correlative volumetric rendering highlighting focal large airway strictures (arrows).

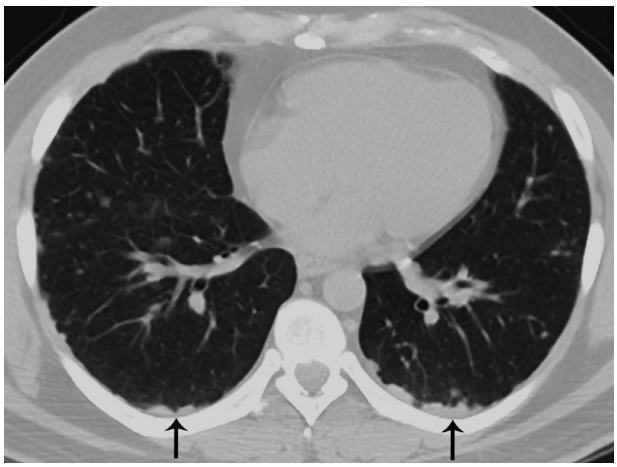

Figure 14 *Sarcoid pleural "pseudoplaques"*. This finding occurs when subpleural nodules become confluent and mimic the pleural plaques caused by asbestos exposure.

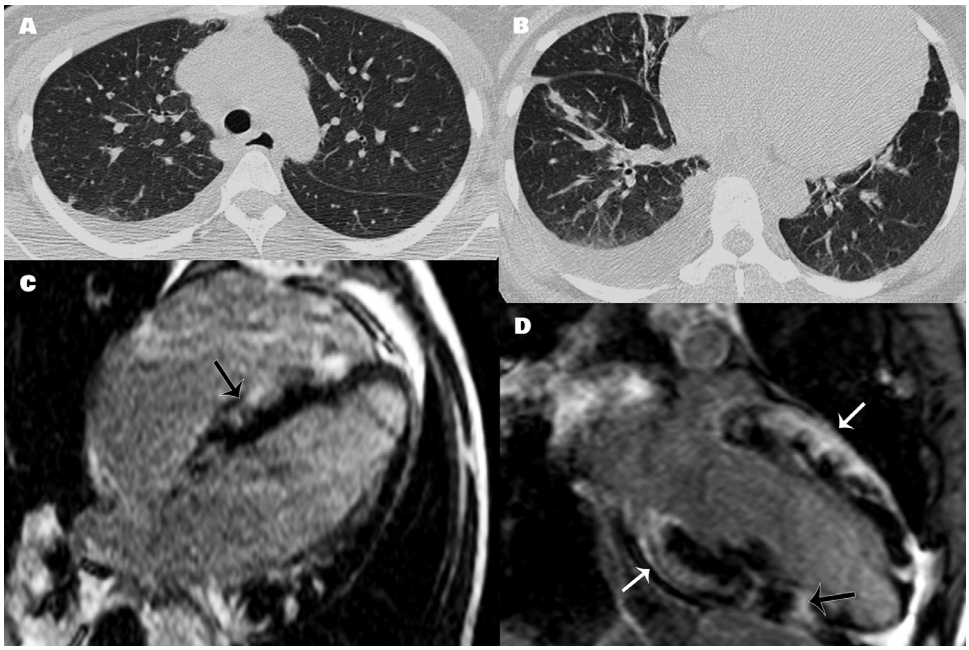

Figure 15 *Cardiac sarcoidosis*. (A, B) Axial CT images of demonstrating basilar predominant smooth interlobular septal thickening and associated small right pleural effusion consistent with edema in the setting of cardiac sarcoid. (C, D) Segmented gradient echo inversion recovery delayed gadolinium enhancement cardiac MRI in (C) 4-chamber and (D) 2-chamber views demonstrating patchy hyperenhancement predominantly involving the epicardium (white arrows) and mid-myocardium (black arrows) in a noncoronary artery distribution. (C) Note the basal and septal involvement (arrow), a relatively common finding.

brief, the classic presentation is that of delayed enhancement predominantly involving the epicardium and mid-myocardium in a noncoronary artery distribution (Fig. 15C,D).

Conclusion

Sarcoidosis is a common disease with numerous pulmonary clinical manifestations and a correspondingly large number of radiographic manifestations. Interstitial granulomatous involvement may resolve spontaneously or may progress to end-stage fibrosis with considerable morbidity. Pulmonary manifestations are sometimes atypical of interstitial lung disease, and the radiologist should be aware of both typical and atypical presentations as well as findings suggestive of potential complications, including sarcoidosis of the airways and heart, pulmonary hypertension, and fungal colonization. Appreciation of the many manifestations of sarcoidosis will allow the radiologist to assist in diagnosis where appropriate and to alert clinicians to possible complications, in order an effort to assist and optimize treatment decisions.

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