Pulmonary Sarcoidosis

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ABSTRACT

Sarcoidosis, a granulomatous disorder of unknown etiology, characteristically involves multiple organs. However, pulmonary manifestations typically dominate. Chest radiographs are abnormal in 85 to 95% of patients. Abnormalities in pulmonary function tests are common and may be associated with cough, dyspnea, and exercise limitation. However, one third or more of patients are asymptomatic, with incidental abnormalities on chest radiographs. The clinical course and expression of pulmonary sarcoidosis are variable. Spontaneous remissions occur in nearly two thirds of patients. The course is chronic in up to 30% of patients. Chronic pulmonary sarcoidosis may result in progressive (sometimes life-threatening) loss of lung function. Fatalities ascribed to sarcoidosis occur in 1 to 4% of patients. Although the impact of treatment is controversial, corticosteroids may be highly effective in some patients. Immunosuppressive, cytotoxic, or immunomodulatory agents are reserved for patients failing or experiencing adverse effects from corticosteroids. Lung transplantation is a viable option for patients with life-threatening disease failing medical therapy.

KEYWORDS: Pulmonary sarcoidosis, nonnecrotizing granuloma, necrotizing sarcoid angiitis

The spectrum of sarcoidosis is protean, and virtually any organ can be involved.[1–3] Multisystem involvement is characteristic, but pulmonary involvement usually dominates.[2–6] Skin, eyes, and peripheral lymph nodes are each involved in 15 to 30% of patients.[1–3,6] Clinically significant involvement of spleen, liver, heart, central nervous system (CNS), bone, or kidney occurs in 2 to 7% of patients.[1] Asymptomatic involvement of these organs is far more common. This article limits discussion to pulmonary manifestations of sarcoidosis.[5]

PULMONARY SARCOIDOSIS

Abnormalities on chest radiographs are detected in 85 to 95% of patients with sarcoidosis.[5–11] Cough, dyspnea, or bronchial hyperreactivity may be prominent in patients with significant endobronchial or pulmonary parenchymal involvement.[5,12] However, 30 to 60% of patients with sarcoidosis are asymptomatic, with incidental findings on chest radiographs.[5,10,13,14] The clinical course is heterogeneous. Spontaneous remissions (SRs) occur in nearly two thirds of patients but the course is chronic in 10 to 30%.[7–11,15] Chronic, progressive pulmonary

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Sarcoidosis: Evolving Concepts and Controversies; Guest Editors, Marc A. Judson, M.D., Michael C. Iannuzzi, M.D.

Semin Respir Crit Care Med 2007;28:1;53–74.
DOI 10.1055/s-2007-970333. ISSN 1069-3424.

sarcoidosis may cause inexorable loss of lung function and destruction of the lung architecture.[5,16] Fatality rates ascribed to sarcoidosis range from 1 to 5%.[7–11,13,14,17–19] British investigators retrospectively reviewed 818 patients with sarcoidosis (both treated and untreated).[7] Forty-eight patients (5%) died, usually because of chronic respiratory failure or cor pulmonale.[20] A recent epidemiological study in the United Kingdom identified 1019 cases of sarcoidosis between 1991 and 2003.[20] Mortality rates at 3 and 5 years for sarcoid patients were 5% and 7%, respectively, compared with 2% and 4% among age- and gender-matched controls without sarcoidosis. Causes of death were not reported. Swedish investigators followed 505 patients with sarcoidosis for up to 15 years.[10] Thirty patients died (6%), but only four deaths were directly attributed to sarcoidosis (< 1% mortality). Huang et al reported 2.8% mortality among 1090 sarcoid patients in Europe.[17] A review of 775 cases of sarcoidosis in Japan reported < 1% mortality as a direct result of sarcoidosis.[21] In the United States, mortality rates due to sarcoidosis were < 1% in nonreferral settings[11,13,14] but were higher in referral centers (likely reflecting a bias selecting for more severe cases).[4,19,22–25] In the United States, 87% of deaths attributed to sarcoidosis were secondary to pulmonary complications.[26] By contrast, in Japan, 77% of deaths resulted from cardiac involvement.[27]

CLINICAL FEATURES OF PULMONARY SARCOIDOSIS

In contrast to idiopathic pulmonary fibrosis (IPF), physical findings are usually minimal or absent in pulmonary sarcoidosis. Crackles are present in fewer than 20% of patients with sarcoidosis, even when radiographic infiltrates are extensive.[5] Clubbing, observed in 25 to 50% of patients with IPF,[28] is rare in sarcoidosis.[5] Fatigue[29] and impaired quality of life (QOL)[30] are far more common among patients with sarcoidosis compared with healthy controls. The impact of sarcoidosis on QOL is discussed in depth elsewhere in this issue by Drs. De Vries and Drent.

CHEST RADIOGRAPHIC FEATURES IN SARCOIDOSIS

Bilateral hilar lymphadenopathy (BHL), the classic radiographic feature of sarcoidosis, is present in nearly three quarters of patients; right paratracheal lymph nodes may be involved concomitantly.[5,7–11] Enlargement of left paratracheal, paraaortic, and subcarinal lymph node groups may be detected by computed tomographic (CT) scans[31,32] but are not usually evident on plain chest radiographs.[5] Unilateral hilar lymphadenopathy on CT is uncommon (< 10%).[33] Pulmonary parenchymal infiltrates (with or without BHL) are present in 20 to 50% of patients with sarcoidosis.[5,6,10] Infiltrates may be patchy or diffuse, but preferentially involve the upper and mid lung zones.[5,34] Reticulonodular infiltrates, macroscopic nodules, consolidation, or masslike lesions may be evident.[5] When pulmonary fibrosis occurs, volume loss, hilar retraction, and coarse linear bands may be observed on chest radiographs. With advanced fibrocystic sarcoidosis, large bullae,[35,36] cystic radiolucencies,[37,38] distortion,[34] mycetomas,[39,40] or bronchiectasis[41] may be observed.

RADIOGRAPHIC CLASSIFICATION SCHEMA

The chest radiographic staging system developed more than 4 decades ago continues to have prognostic value.[9] This classification schema defines the following stages: stage 0 (normal; Fig. 1); stage I (BHL without pulmonary infiltrates; Fig. 2); stage II (BHL plus pulmonary infiltrates; Fig. 3); stage III (parenchymal infiltrates without BHL; Fig. 4). Radiographic stage IV sarcoidosis, encompassing extensive fibrosis with distortion or bullae, is not universally accepted (see Table 1). The incidence of radiographic stages differs according to

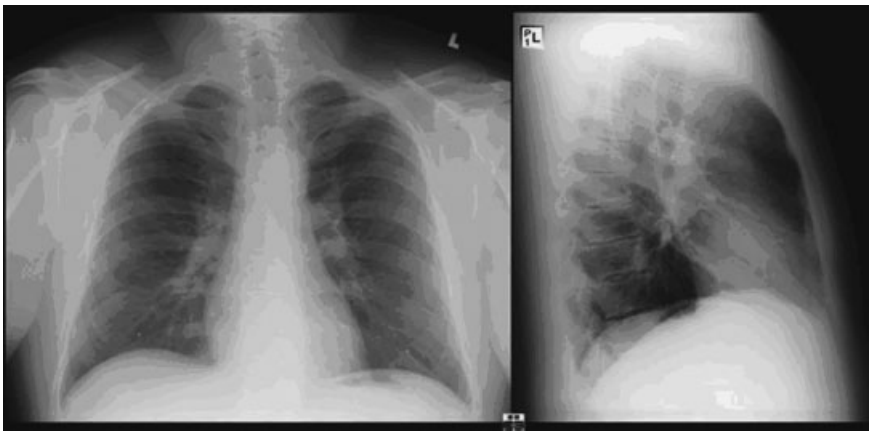

Figure 1 Stage 0 radiographic sarcoidosis. This normal chest x-ray may be observed in 5 to 15% of cases.

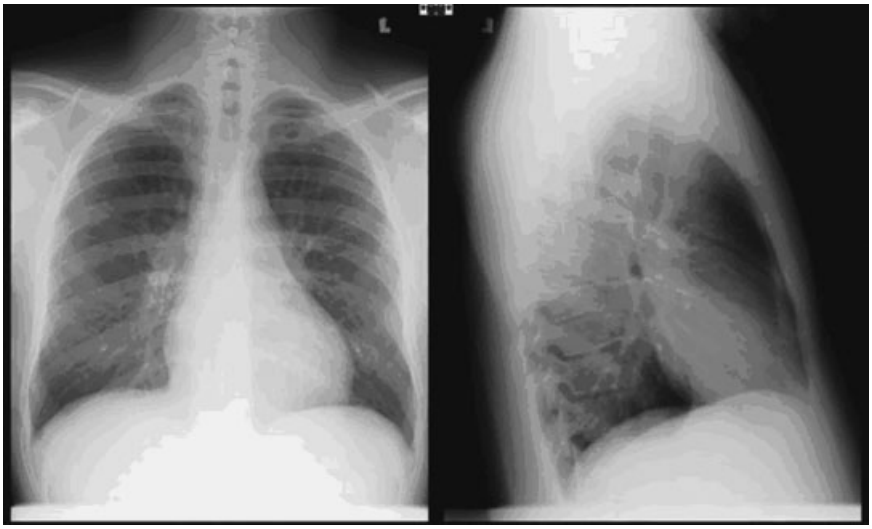

Figure 2 Stage I radiographic sarcoidosis. Bilateral hilar lymphadenopathy with clear lung fields.

geographic regions, ethnicity, and referral bias. Stage I is most common in most series, but significant variability exists (see Table 2). Most studies from Scandinavia cited a striking predominance of radiographic stage I and II disease,[8,10] whereas some studies from the United States and British Isles cite a disproportionate representation of radiographic stage III and IV disease.[23,25]

Although individual exceptions exist, the prognosis is best with radiographic stage I; intermediate with stage II; and worst with stage III or IV. SRs occur in 60 to 90% of patients with stage I disease; in 40 to 70% with stage II; 10 to 20% with stage III; and 0% with stage IV.[7–10,19,24,42] In a sentinel study in the United Kingdom, Scadding followed patients with sarcoidosis for 5 years.[9] At the end of follow-up, 31 of 32 patients (97%) with stage I disease were asymptomatic, whereas only 58% of stage II and 25% of stage III patients were asymptomatic.[9] In the United States, Siltzbach noted similar findings.[24] In his long-term follow-up of 244 patients with sarcoidosis (both treated and untreated), chest radiographs normalized in 54% of patients with stage I disease but in only 31% with stage II and 10% with stage III.[24] Importantly, none of 110 patients with stage I died, whereas mortality rates were 11% with stage II and 18% with stage III disease. British investigators followed 818 patients with sarcoidosis (both treated and untreated) and observed higher rates of radiographic resolution with stage I (59%) compared with stage II (39%) or stage III (38%) sarcoidosis.[7] Swedish investigators followed 505 patients with sarcoidosis (both treated and untreated) for up to 15 years.[10] At 5 year follow-up (both treated and untreated patients), chest radiographs had normalized in 82% of patients with stage I sarcoidosis; 68% with stage II; 37% with stage III.[10] Among 308 patients with stage I disease, 29 (9%) progressed to stage II and only five (1.6%) progressed to

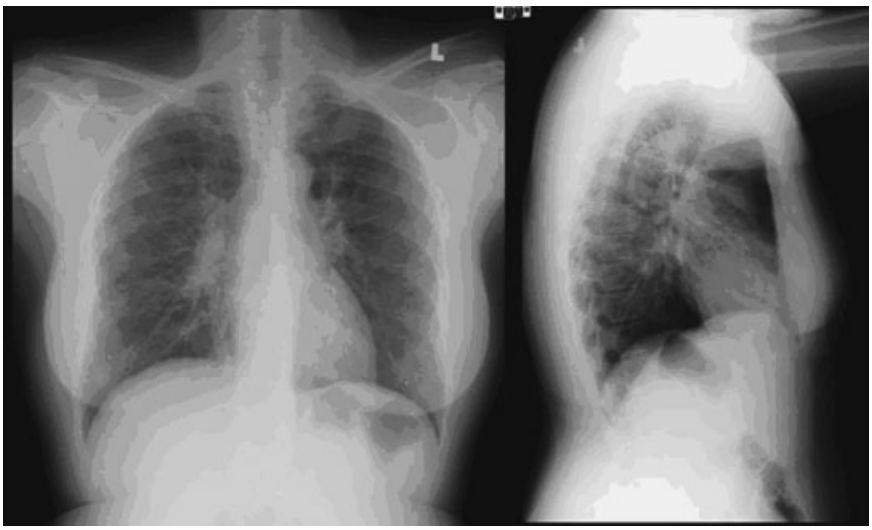

Figure 3 Stage II radiographic sarcoidosis. Combined hilar lymphadenopathy and upper lung zone predominant interstitial infiltrates.

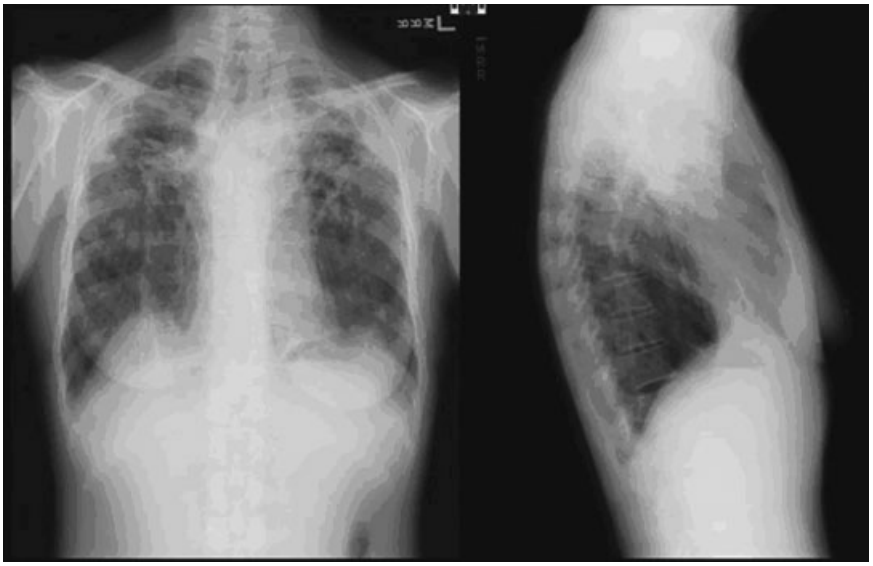

Figure 4 Stage III/IV radiographic sarcoidosis. Note the upper lung zone volume loss, upward retraction of the hilae, and tenting of the hemidiaphragms.

stage III or IV. Danish investigators followed 210 patients with sarcoidosis for 1 to 10 years (both treated and untreated).[8] Among 116 patients with stage I disease, chest radiographs normalized in 57%; only 10 progressed to stage II; none developed stage III. Among patients with stage II, chest radiographs normalized in 48%; only 12% worsened. By contrast, chest radiographs normalized in only one of 10 (10%) with stage III sarcoidosis. The investigators noted that the course of the disease was usually dictated within the first 1 to 2 years of presentation. The vast majority (85%) of all SRs occurred *within 2 years* of presentation.[8] Among patients who remained in stage II *after 2 years of observation*, chest radiographs eventually normalized in only 12% and worsened in 30%.[8] Late relapses were rare, however, in patients exhibiting stability for the first 2 years. Only one of 63 patients (1.6%) with stage I at presentation progressed *after* the second year.[8] Other studies noted that SR occurs in 16 to 39% of patients within 6 to 12 months from the onset of symptoms.[42–44] Further, among patients who are undergoing SR, the rate of late relapse is low (< 10%).[42–44] Genetic and demographic factors influence prognosis. In a study from New South Wales, chest radiographs normalized in 112 of 150 (75%) patients presenting with stage I or II sarcoidosis.[45] In a cohort of Japanese patients with sarcoidosis, chest radiographs cleared within 3 years in 68%.[46] In a cohort of 193 Spanish patients with sarcoidosis, chest radiographs had normalized in 78% within

Table 1 Chest Radiographic Staging System for Sarcoidosis*

Radiographic Stage	Radiographic Findings
Stage 0	Normal chest x-ray (Fig. 1)
Stage I	Bilateral hilar adenopathy (BHL)
Stage II	BHL plus parenchymal infiltrates
Stage III	Parenchymal infiltrates without BHL
Stage IV	Irreversible scarring and distortion

*Adapted from Scadding.[9]

Table 2 Distribution of Chest Radiographic Stages in Sarcoidosis

Country, Year, # patients	X-ray Stage				
	0(%)	I(%)	II(%)	III(%)	IV(%)*
Sweden, 1984 ($n=505$)[10]	3	61	25	10	1
Denmark, 1982 ($n=243$)[8]	0.4	55	40	4.5	ND
British Isles, 2000 ($n=212$)[45]	9	51	20	15	5
British Isles, 1983 ($n=818$)[7]	14	56	18	11	ND
Finland, 2000 ($n=437$)**	0	44	43	13	0.4
Japan, 2000 ($n=457$)**	0	67	27	5	0
USA 1967 ($n=244$)**	0	45	39	16	ND
USA 1997 ($n=337$)[24,25,48]	8	45	29	17	ND
USA, 1994 ($n=98$)[44]	20	18	27	10	25
USA 1985 ($n=86$)[13]	10	49	21	20	ND
USA 2001 ($n=736$)[6]	8	40	37	10	5

*Stage IV not universally adopted.
**Only included pulmonary sarcoidosis.
ND, not described.

2 years.[47] However, persistent infiltrates at 2 years predicted a chronic or persistent course.[47] In the United States, 215 patients with sarcoidosis were followed prospectively for 2 years.[15] In most patients, pulmonary function, x-ray stage, and dyspnea scale did not change during the 2 year period. Only 11 of 176 (6%) with stage 0, I, or II disease progressed to stage III or IV over the 2 year follow-up period. Spirometry worsened in 12%. Involvement of additional organs occurred in 50 patients (23%) during that time frame.[15]

Differing prognoses among studies may reflect ethnic, geographic, or referral biases.[48] Pietinalho et al followed a large cohort of 437 Finnish and 457 Japanese patients for 5 years.[48] Chest radiographs normalized within 1 year in 46% of Japanese but in only 16% of Finnish patients. After 5 years, the rates of radiographic resolution were 73% and 40%, respectively ($p < .001$). During the 5 year period, 43 of 309 (14%) Japanese patients and 28 of 142 (20%) Finnish patients with *initial stage I* lesions progressed to higher stages infiltrates. At 5 years, among patients with *initial stage II* disease, chest radiographs had normalized in 73% of Japanese and 36% of Finnish patients. Among patients with *initial stage III* disease, chest radiographs had normalized by 5 years in 35% of Japanese and 24% of Finnish patients, respectively.[48]

The prognosis of sarcoidosis is distinctly worse among African Americans.[4,23,25] Gottlieb et al studied 337 patients with sarcoidosis, 118 of whom achieved SR (36%). Interestingly, only 8% of patients who had SR experienced late relapse, whereas relapse rates were $>74\%$ among patients with corticosteroid-induced remissions.[25] Importantly, sustained remissions were achieved in 50% of Caucasians but only 20% of African Americans ($p = .01$).

These various studies emphasize that the course of sarcoidosis is heterogeneous and variable among ethnic groups. Identifying candidates for therapeutic intervention requires careful follow-up of clinical, radiographic, and physiological parameters. Treatment (discussed later) should be offered to patients with severe or progressive pulmonary or extrapulmonary dysfunction.

ADDITIONAL PROGNOSTIC FACTORS

As has been mentioned, the clinical course and prognosis of sarcoidosis is influenced by ethnic and genetic factors. Black race is associated with a higher rate of chronic progressive disease, worse long-term prognosis, extrapulmonary involvement, and higher risk of relapses.[4,7,15,22,23,25] Analysis of a cohort of 736 sarcoid patients in the United States noted that women were more likely to have eye and neurological involvement and erythema nodosum, whereas men were more likely to be hypercalcemic.[6] Black subjects were more likely to have eye, liver, bone marrow, extrathoracic lymph node, and skin involvement (other than erythema nodosum). Derangements in calcium metabolism were more common among white subjects.[6] The influence of human leukocyte antigen (HLA) markers and prognosis is controversial.[2,49–52] HLA-B8 is associated with acute inflammatory features and a favorable prognosis, whereas HLA-B13 is often associated with a progressive and protracted course.[52] Some HLA patterns are associated with a good prognosis in Japanese but a poor prognosis in Italians.[50,51] The influence of genetics on prevalence and clinical expression of sarcoidosis is discussed elsewhere in this issue by Dr. Iannuzzi.

Clinical features may have prognostic value. Löfgren's syndrome (i.e., BHL, erythema nodosum, polyarthritis, and fever) portends an excellent prognosis, with high rates ($>85\%$) of SR.[7,15,42,53] Löfgren's syndrome occurs in 30% of Caucasians with sarcoidosis, in 10% of Asians, but is rare in blacks.[7,22,25] Clinical factors associated with a worse prognosis in sarcoidosis include age onset >40 years[7,47]; hypercalcemia[7]; extrathoracic disease[7,22]; lupus pernio[7]; splenomegaly[47]; pulmonary infiltrates on chest radiograph[7,47]; chronic uveitis, cystic bone lesions, nasal mucosal sarcoidosis[7]; lower annual family income.[15]

COMPUTED TOMOGRAPHIC SCANS

High-resolution computed tomographic (HRCT) chest scans are superior to conventional chest radiographs in delineating parenchymal, mediastinal, and hilar structures, depicting parenchymal details, and discriminating inflammation from fibrosis.[31,34,54,55] Characteristic features of sarcoidosis on CT include mediastinal and/or hilar lymphadenopathy; nodular opacities and micronodules along bronchovascular bundles; predilection for mid and upper lung zones; an axial distribution; pleural or subpleural nodules; septal and nonseptal lines; confluent nodular opacities with air-bronchograms (i.e., consolidation); and ground-glass opacities (GGOs).[34,56] Architectural distortion, hilar retraction, fibrous bands, bronchiectasis, cystic radiolucencies, bullae, and enlarged pulmonary arteries may be observed with advanced disease.[32,34,57,58] Multiple CT patterns or features may be present in individual patients and may evolve over time.[34] Findings on *initial* CT scan have limited prognostic value, but certain CT features may discriminate active inflammation from fibrosis. Nodules, GGOs, consolidation, or alveolar opacities suggest granulomatous inflammation and may reverse with therapy.[59,60] By contrast, honeycomb change, cysts, coarse broad bands, distortion, or traction bronchiectasis indicate irreversible fibrosis.[57,61] Despite the enhanced accuracy of CT, *routine* CT is not necessary or cost-effective in the management of sarcoidosis.[62] Chest CT scans may be helpful in the following circumstances: atypical clinical or chest

radiographic findings; to detect specific complications of the lung disease (e.g., bronchiectasis, aspergilloma, pulmonary fibrosis, superimposed infection or malignancy); normal chest radiographs, but a clinical suspicion for sarcoidosis.[3,34] The salient features and role of CT in the management of sarcoidosis are addressed elsewhere in this issue by Dr. Wells and colleagues.

PULMONARY FUNCTION TESTS IN SARCOIDOSIS

Abnormalities in pulmonary function tests (PFTs) are present in ~20% of patients with radiographic stage I sarcoidosis and in 40 to 80% of patients with parenchymal infiltrates (stages II, III, or IV).[5,7,8,63–66] A restrictive defect with reduced lung volumes [e.g., vital capacity (VC) and total lung capacity (TLC)] is characteristic. The diffusing capacity for carbon monoxide (DL_{CO}) is the most sensitive of the PFT parameters,[66] but the degree of impairment is less severe in sarcoidosis than in IPF.[5,67] Even when chest radiographs are normal, forced vital capacity (FVC) or DL_{CO} is reduced in 15 to 25% and 25 to 50% of patients, respectively.[63,68] Oxygenation is preserved until late in the course of sarcoidosis.[5]

Airflow obstruction [e.g., reduced forced expiratory volume in 1 second (FEV_1) and expiratory flow rates] occurs in 30 to 50% of patients with pulmonary sarcoidosis.[64,66,68–70] Airflow obstruction may be caused by multiple mechanisms, including narrowing of bronchial walls (via granulomatous lesions or fibrotic scarring),[71–73] peribronchiolar fibrosis,[74] airway distortion caused by pulmonary fibrosis,[64,75] compression by enlarged lymph nodes,[5] small airways disease,[68,76,77] and bronchial hyperreactivity.[12,66] One study of 107 patients with newly diagnosed sarcoidosis noted a decreased FEV_1:FVC ratio in 61 patients (57%).[68] The DL_{CO} was reduced in 29 (27%); only seven (6%) manifested restriction.[68] Airflow obstruction was more frequent with worsening radiographic stage. Another study of 18 sarcoid patients (all of whom had reduced lung volumes or DL_{CO}) found that airways obstruction was present in all 18 when sensitive tests were employed (e.g., frequency dependence of compliance, airway resistance, closing volumes).[77] Airflow obstruction is suggested by CT showing bronchial mural thickening, small airway narrowing, or patchy air trapping (mosaic pattern of perfusion).[78–80] Patients with advanced pulmonary sarcoidosis (radiographic stages III or IV) may exhibit severe decrements in FEV_1:FVC.[64,81] Additionally, increased airway hyperreactivity in response to methacholine is common in patients with sarcoidosis.[82–84] Clinically, this may manifest as chronic, hacking cough. In one study, 50% of patients with stage I or II sarcoidosis exhibited bronchial hyperreactivity following methacholine challenge.[12] A more recent series cited bronchial hyperreactivity in 46 of 80 (58%) sarcoid patients.[84] Bronchial hyperreactivity likely reflects granulomatous inflammation involving the bronchial mucosa.[71] Clinical bronchiectasis is a rare complication of stage IV sarcoidosis.[85]

Impaired respiratory muscle function (RMF) may contribute to dyspnea or exercise limitation in patients with sarcoidosis.[66] In a cohort of 18 sarcoid patients with normal PFTs, inspiration muscle endurance (IME) was impaired compared with healthy controls, and correlated with symptoms and impaired QOL.[86] French investigators studied 34 sarcoid patients and 19 controls. Reductions in IME were noted in the sarcoid patients and correlated with impairments in health-related quality of life (HRQOL).[87] Baydur et al measured RMF by mouth inspiratory muscle pressure (PI_{max}) and expiratory muscle pressure (PE_{max}) in 36 sarcoid patients and 25 controls.[88] Significant linear relationships were found between increasing dyspnea and decreasing RMF. Interestingly, dyspnea did not correlate with lung volumes or DL_{CO}.

Alterations in cardiopulmonary exercise tests (CPETs) have been noted in 28 to 47% of patients with sarcoidosis.[75,89–91] Typical findings include ventilatory limitation or increased dead space volume/tidal volume (V_D/V_T) or widened alveolar-arterial O_2 (A-a O_2) gradient with exercise.[75,89] CPET may be abnormal when static PFTs are normal.[75,85] Miller et al performed CPET in 30 sarcoid patients with normal spirometry; DL_{CO} was normal in 13.[75] Maximal exercise testing elicited ventilatory abnormalities in 14 (47%)[75] Abnormal CPET (e.g., excessive ventilation to oxygen consumption and abnormal V_D/V_T) were noted in eight of nine with a low DL_{CO} compared with 11 of 21 with a normal DL_{CO}. Widened A-a O_2 gradient was observed primarily in patients with low DL_{CO}. Delobbe et al performed CPETs in 19 sarcoid patients with normal resting PFTs (including DL_{CO}). Compared with age- and sex-matched healthy sedentary controls, sarcoid patients displayed reductions in maximal workload, VO_2 max, tidal volume (V_T), heart rate, and increased V_D/V_T with exercise.[85] Another study of 20 patients with mild pulmonary sarcoidosis noted abnormalities on CPET in nine patients (45%).[89] VO_2 at the anaerobic threshold was low, and/or the rate of increase of VO_2 was abnormal relative to work rate or heart rate, suggesting a defect in cardiocirculatory function. Resting and exercise echocardiography revealed normal left ventricular function in all patients, but right ventricular dysfunction or hypertrophy was evident in five. Thus abnormal response of VO_2 during exercise may reflect subclinical right heart dysfunction[89] or an impaired heart rate response to exercise.[85]

Exercise-induced desaturation correlates with reductions in DL_{CO}.[75,90,92,93] In a series of 32 patients with pulmonary sarcoidosis, $DL_{CO} < 55\%$ had a high sensitivity (85%) and specificity (91%) in predicting exercise-induced desaturation.[90] Lamberto et al reported

that alveolar membrane diffusing capacity (Dm) and DL_{CO} were the strongest predictors of gas exchange abnormalities during exercise.[94] In contrast, lung volumes and expiratory flow rates did not correlate with exercise gas exchange.[94] Arterial desaturation with exercise is rare in patients with radiographic stage I disease or preserved DL_{CO}.[93] Arterial desaturation and DL_{CO} correlate with the extent and severity of sarcoidosis as assessed by CT.[92]

Although CPET is more sensitive than static PFTs in predicting work and exercise capacity, the *practical* value of CPET is limited. Spirometry and oximetry are usually adequate to follow the course of the disease. For patients with more severe disease, noninvasive 6 minute walk tests provide additional quantitative data.

Physiological aberrations correlate only roughly with histological severity of the disease.[74,95–98] Early studies employing quantitative morphometric analyses noted that physiological parameters failed to predict the histologic severity of the disease (on open-lung biopsy specimens).[74,96,97] Although PFTs were more seriously deranged among patients with advanced fibrosis, the degree of overlap was considerable. Further, physiological parameters cannot discriminate alveolitis (that might be amenable to therapy) from irreversible fibrosis.[97,98]

The extent of pulmonary physiological impairment correlates with severity of disease by chest radiographs[99–102] or CT scans,[31,32,101,103] but correlations are imprecise. Semiquantitative scoring systems improve the correlations between physiological parameters and HRCT.[101,103–105] In a seminal study, Bergin noted that semiquantitative scores on CT correlated inversely with FVC ($r = -0.81$) and to a lesser extent, with DL_{CO} ($r = -0.49$).[31] Drent and colleagues found that HRCT correlated with FEV_1, FVC, DL_{CO}, paO_{2max} (maximal partial pressure for oxygen), and was more sensitive than chest radiographs in detecting pulmonary disability or abnormal gas exchange.[106] However, given the imprecise correlations between CT and physiological parameters, direct measurement of PFTs is critical to assess the extent and degree of pulmonary functional impairment.

Specific CT findings (e.g., thickening or irregularity of bronchovascular bundles, intraparenchymal nodules, septal and nonseptal lines, and focal pleural thickening) correlate with *functional* impairment, whereas other features (e.g., focal consolidations, GGOs, or enlarged lymph nodes) are less important.[106] The *pattern* of CT may reflect underlying pathology. Hansell et al noted that a reticular pattern on HRCT correlated inversely with FVC, FEV_1, FEV_1:FVC, and DL_{CO}.[107] Others affirmed that reticular and fibrotic abnormalities on HRCT correlated modestly with physiological aberrations, whereas mass lesions or confluence did not.[104] Honeycomb change is most often associated with restriction and low DL_{CO}, whereas bronchial distortion is often associated with reduced expiratory flow rates.[58] CT patterns may evolve over time. A study of serial CT in 40 patients with pulmonary sarcoidosis found several distinctive evolutionary patterns.[108] Macroscopic nodules often disappeared or decreased in size at follow-up. In some patients, GGOs and consolidation resolved, but in others these patterns evolved into honeycombing and were associated with a decline in FVC. A conglomeration pattern shrank and evolved into bronchial distortion and a decline in FEV_1:FVC. The salient features and significance of CT are discussed in detail elsewhere in this issue by Dr. Wells and colleagues and will not be further addressed here.

INFLUENCE OF PULMONARY FUNCTION ON PROGNOSIS

Physiological parameters *at the onset* do not predict *long-term* outcome in patients with sarcoidosis,[63,109–111] but mortality is higher among patients with severe physiological impairment.[16] Sequential studies are important to follow the course of the disease and assess response to therapy. Several studies found that VC improves more frequently than DL_{CO},[63,112,113] TLC,[114] or arterial oxygenation.[98] Changes in VC and DL_{CO} are usually concordant; discordant changes occur in fewer than 5% of patients.[15,98] A prospective study in the United States of 193 sarcoid patients cited excellent concordance between changes in FVC and FEV_1.[15] Changes in FVC and FEV_1 were concordant (in the same direction) in 155 patients (80.3%) but were never discordant (opposite directions). In a previous study, measurement of oxygen saturation at rest or during exercise was no more sensitive than VC or DL_{CO} among patients with sarcoidosis.[98] Given the variability of DL_{CO},[63] and the expense of obtaining lung volumes, spirometry and flow-volume loops are the most useful and cost-effective parameters to follow the course of pulmonary sarcoidosis. Additional studies such as DL_{CO}, TLC, or gas exchange have a role in selected patients. Criteria for assessing "response" or improvement have not been validated. Most investigators define a change in FVC > 10 to 15% or $DL_{CO} > 20\%$ as significant.[98,115] Responses to therapy are usually evident within 6 to 12 weeks of initiation of therapy.[63,116]

LABORATORY FEATURES

Serum angiotensin-converting enzyme (SACE) is increased in 30 to 80% of patients with sarcoidosis and may be a surrogate marker of total granuloma burden.[5,117] False-positives are noted in fewer than 20% of patients with other pulmonary disorders. However, SACE may be normal in patients with active disease. We believe SACE provides ancillary information when the activity of sarcoidosis is uncertain on clinical grounds. However, SACE should not be used in isolation to dictate therapeutic interventions. Historically, the

Kveim-Siltzbach skin test was used to diagnose sarcoidosis.[118] We see no current role for the routine use of the Kveim-Siltzbach skin test.[2]

PATHOGENESIS OF SARCOIDOSIS

Sarcoidosis is characterized by accumulations of activated T cells and macrophages at sites of disease activity (such as the lung). Sarcoid T lymphocytes belong to the helper CD_4 phenotype; rarely, CD_8+ lymphocytes predominate.[119,120] Interactions between alveolar macrophages, CD_4 T-helper (Th) cells, and a Th_1-cytokine network drive the granulomatous process.[2] Lung T cells from patients with sarcoidosis spontaneously release Th_1 cytokines such as interferon (IFN)-γ[121] and interleukin (IL)-2.[122] IL-12, a product of activated macrophages, upregulates the development of Th_1 cells and amplifies the Th_1 response (especially IFN-γ).[123] Interleukin-18 acts synergistically with IL-12 to induce release from Th1 cells and enhances cytotoxicity of T cells.[124] Increased serum and bronchoalveolar lavage fluid (BALF) levels of IL-18 were noted in patients with sarcoidosis and may be a surrogate marker of disease activity.[125] Sarcoid alveolar macrophages release other cytokines that drive the lymphocytic alveolitis, including tumor necrosis factor (TNF)-α,[126] IL-6,[127] IL-15,[128] monocyte chemotactic protein-1 (MCP-1),[120] RANTES (regulated upon activation normal T cell expressed and secreted),[129] and macrophage inflammatory protein (MIP)-1α and MIP-1β.[130] The CC chemokines MIP-1α and MIP-1β recognize CCR5 as a cellular receptor in activated T cells and alveolar macrophages.[130] MIP-1β may be important in the early (inflammatory) phases of sarcoidosis, whereas MIP-1α likely participates in later (fibrotic) phases.[130] CCR5 is expressed at high levels in CD_4 Th_1 lymphocytes and induces increased production and release of IL-1 and IFN-γ.[130] Downregulation of CCR5 in advanced (fibrotic) stages of sarcoidosis may indicate switch to Th_2 phenotype, which may enhance fibrosis.[131] Later stages of pulmonary sarcoidosis (stage III or IV) are associated with progressive increases in neutrophils and eosinophils.[130] Further, there is a relative reduction in CD_4 and increase in CD_8 lymphocytes in stage III as compared with stage I sarcoidosis.[130,132,133] Other chemokines that contribute to recruiting leukocytes in pulmonary sarcoidosis include RANTES (CCL5),[129] monocyte chemotactic protein-1 (MCP-1) (CCL2),[134] the novel chemokine single cysteine motif (SCM)-1α (XCL-1),[134] and interferon-γ inducible protein 10 (CXCL10).[135]

Factors that modulate or downregulate the granulomatous response have not been fully elucidated. Increased levels of TNF-receptors (TNF-R) have been noted in plasma and BALF in patients with sarcoidosis.[136,137] Increased expression of IL-13 (a Th_2 cytokine), by sarcoid alveolar macrophages[138] may attenuate or abrogate the granulomatous response. Increased expression of IL-10 in sarcoid bronchoalveolar lavage (BAL) cells has been noted in some,[139,140] but not all,[138] studies. Further, genetic polymorphisms may influence the clinical expression and evolution of the disease. In Scandinavian patients with pulmonary sarcoidosis, lung T cells express T cell receptor (TCR) AV2S3 and the human leukocyte antigen (HLA)-DR17 alleles.[141] These lung-restricted AV2S3 + T cells correlated with the CD_4:CD_8 ratio, acute disease onset, and a good prognosis.[141] These AV2S3 + T cells may have a protective role against a putative sarcoid antigen. In a cohort of Dutch patients, polymorphisms in C-C chemokine receptor 2 were associated with Löfgren's syndrome but were not observed in healthy controls or sarcoid patients without Löfgren's syndrome.[142] Other investigators found that certain HLA haplotypes were associated with acute onset and short duration of disease and were protected against pulmonary disease progression in Dutch and United Kingdom sarcoidosis patients.[143,144] The influence of genetics on disease susceptibility, clinical expression, and evolution of the sarcoid lesions is discussed in detail in this issue by Dr. Iannuzzi

BRONCHOALVEOLAR LAVAGE FLUID IN SARCOIDOSIS

BAL has provided significant insights into the pathogenesis of sarcoidosis.[145] BAL in sarcoidosis demonstrates increased numbers of activated lymphocytes (typically CD_4+ T cells), alveolar macrophages, and myriad proinflammatory cytokines and mediators.[145] BAL lymphocytosis is present in $>85\%$ of patients with pulmonary sarcoidosis; granulocytes are normal or low.[145–148] The CD_4:CD_8 ratio is increased in 50 to 60% of patients with sarcoidosis.[145] In late phases of sarcoidosis, neutrophils or mast cells or both may be increased.[82,100,149–151] BAL cell profiles are not specific for sarcoidosis, but they narrow the differential diagnosis.[145,146,148] Importantly, BAL cell profiles fail to predict prognosis or responsiveness to corticosteroid therapy.[2,132,145,147,152,153] Similarly, initial BAL CD_4:CD_8 ratios do not consistently predict outcome or responsiveness to therapy.[145] In fact, marked CD_4 lymphocytic alveolitis is characteristic of Lofgren's syndrome, which remits spontaneously in more than 85% of patients.[132,147,154] BAL is expensive and invasive, and we see no clinical role for BAL in determining the need for therapy or following response.

RADIONUCLIDE TECHNIQUES

Radionuclide techniques [e.g., ^{67}gallium citrate,[155,156] scintigraphy with somatostatin analogues (^{111}indium-penetreotide-)[157,158] or technetium^{99m}-labeled depreotide][159] or ^{18}fluoro-2-deoxyglucose (^{18}FDG) positron

emission tomography (PET) scans[160–162] have been employed to diagnose or assess disease activity in sarcoidosis. These techniques are expensive, and clinical value has not been established. HRCT scans are superior to radionuclide techniques to assess inflammatory and intrathoracic involvement in sarcoidosis.[103,10667]Gallium scans are inconvenient (scanning is performed 48 hours after injection of the radioisotope) and lack prognostic value.[163,164] However, ^{67}Ga scans may have a role in selected patients in whom the diagnosis is difficult, such as in cases with normal chest radiographs and features suggesting extrathoracic sarcoidosis [e.g., uveitis, involvement of the central nervous system (CNS), etc.].[163] Uptake of ^{67}Ga may identify appropriate sites to biopsy. PET scans may demonstrate increased metabolic activity in patients with pulmonary sarcoidosis,[163,165,166] but the clinical value of PET is uncertain. PET has a potential role in identifying sarcoid activity at extrapulmonary sites (e.g., bone,[167] cardiac,[168] or neural[169] sites. Currently, the value of radionuclide scans in assessing intrathoracic involvement remains to be established.

DIAGNOSIS OF PULMONARY SARCOIDOSIS

The histological hallmark of sarcoidosis is a necrotizing granulomatous process, typically distributing along bronchovascular bundles and lymphatics (Figs. 5–8) (discussed in depth elsewhere in this issue by Dr. Rosen). Flexible fiberoptic bronchoscopy (FFB) with transbronchial lung biopsy (TBLB) is the initial diagnostic procedure of choice in patients with suspected pulmonary sarcoidosis.[5] Sensitivity of TBLB ranges from 60 to 90%; yields are lower with radiographic stage 0 disease.[170,171] When mediastinal lymphadenopathy is present on chest CT, transbronchial needle aspiration (TBNA) biopsies with Wang 18, 19, or 22 gauge cytology needles are

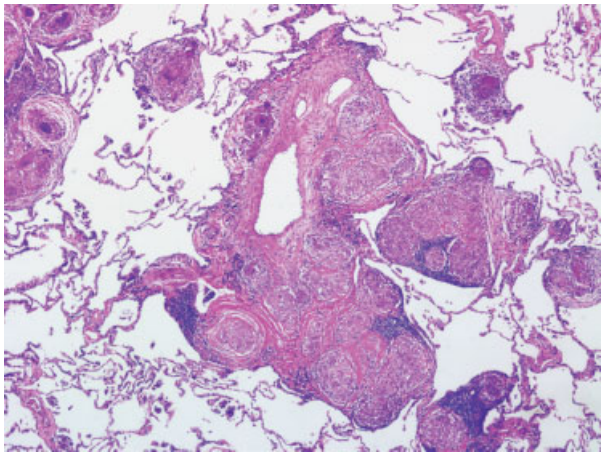

Figure 5 Pulmonary sarcoidosis. Low-power microscopic view shows the lymphangitic pattern of distribution of the granulomas so typical of sarcoid (hematoxylin and eosin (H&E), × 40).

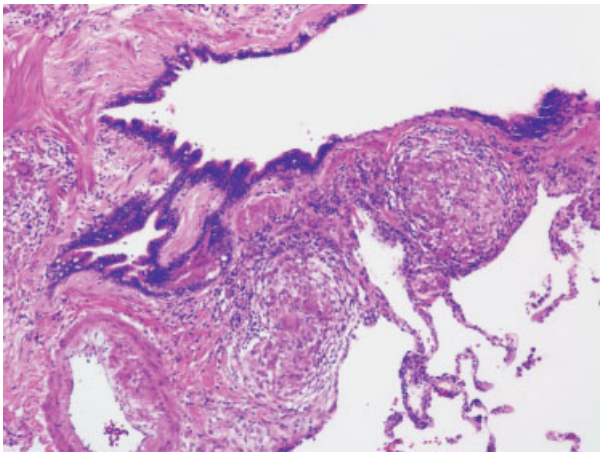

Figure 6 Pulmonary sarcoidosis showing airway involvement by nonnecrotizing epithelioid granulomas (H&E, × 100).

diagnostic in 63 to 90% of patients.[33,172–177] Typical features of sarcoidosis by cytological examination include lymphocytes, epithelioid cell granulomas, multinucleated giant cells with no or minimal necrosis, clusters of palisading epithelioid histiocytes, and negative stains for fungi and acid-fast bacteria (AFB).[33,176] In two recent studies, the combination of TBNA and TBLB had a higher yield than either procedure alone.[178,179] TBNA is much less expensive than mediastinoscopic lymph node biopsy[180] but requires skill. Damage to the bronchoscope may complicate TBNA, particularly when performed by individuals with limited experience.[181]

CT-guided transthoracic fine needle aspiration (FNA) with or without core needle biopsy may be useful to diagnose malignant or benign lesions involving mediastinal or subcarinal lymph nodes (yields up to 78%).[182] Complications of transthoracic FNA include pneumothoraces (10 to 60%) or hemoptysis (5 to 10%).[182] Endoscopic ultrasound (EUS)-guided FNA has been used to diagnose mediastinal masses or lymph nodes, with high yield (> 90%) in patients with malignancy,[179,183,184] but experience is limited in patients with sarcoidosis.[179,185] EUS allows visualization of mediastinal structures, including the paraesophageal space, aortopulmonary window, and subcarinal region.[179,186] The optimal approach to diagnosing mediastinal lymph nodes (i.e., TBNA or CT-guided FNA) depends upon the expertise and preference of the local institution.

Surgical biopsies are not usually required to diagnose sarcoidosis. However, when the foregoing procedures are not definitive, biopsy of either or both mediastinal lymph nodes and lung may be warranted. This can generally be done with minimally invasive procedures, such as cervical mediastinoscopy,[187,188] the Chamberlain procedure (a parasternal minithoracotomy to biopsy aortopulmonary window or para-aortic nodes), or video-assisted thoracoscopic surgical (VATS) biopsy.[189]

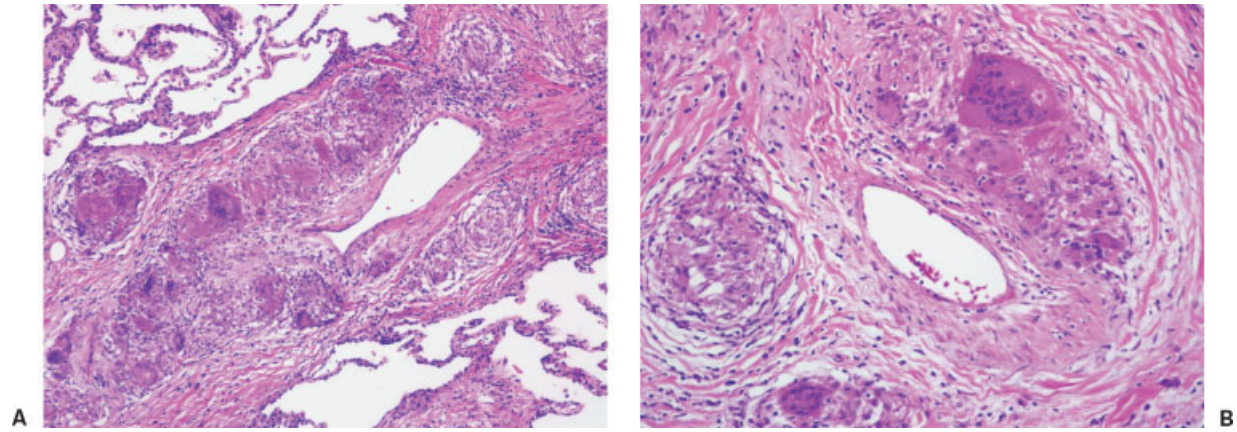

Figure 7 (A) Pulmonary sarcoidosis. There is intrusive involvement of the pulmonary vascular walls by granulomas, producing granulomatous vasculitis (H&E, × 100). (B) Pulmonary sarcoidosis. Higher magnification view of sclerosing nonnecrotizing granulomas intruding on the wall of a vessel. Note the asteroid body within a giant cell (H&E, × 200).

SPECIFIC COMPLICATIONS OF INTRATHORACIC SARCOIDOSIS

Pulmonary Vascular Involvement in Sarcoidosis

Clinically significant pulmonary vascular involvement is uncommon in sarcoidosis. However, sarcoid granulomatous lesions follow pulmonary vessels, and incidental histological involvement of vessels was noted in 42 to 89% of open-lung biopsies from patients with pulmonary sarcoidosis.[74,190] Pulmonary arterial hypertension (PAH) was reported in 1 to 5% of patients with sarcoidosis[191–195] but the incidence is much higher among patients with advanced fibrocystic sarcoidosis.[196–200] The United Network for Organ Sharing (UNOS) database identified 363 patients with sarcoidosis listed for lung transplantation (LT) in the United States between January 1995 and December 2002 who had undergone right heart catheterization (RHC).[200] This represented 73% of all listed sarcoid patients. PAH, defined as mean pulmonary arterial pressure (mPAP) > 25 mm Hg, was present in 74%; 36% had severe PAH, defined as mPAP > 40 mm Hg. Importantly, PFTs did not differ between those with or without PAH. However, patients with severe PAH were seven times more likely to require supplemental oxygen. Two previous studies found that PAH was an independent predictor of mortality among patients with sarcoidosis listed for LT.[197,199]

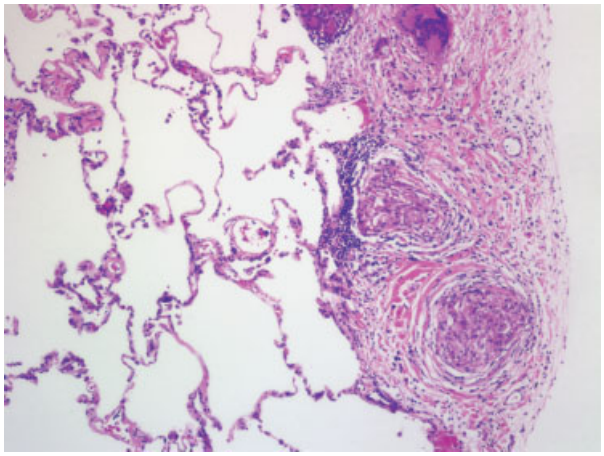

Figure 8 Pulmonary sarcoidosis. Pleural involvement by the granulomatous process is shown here. Note the rather sparse interstitial lymphocytic infiltrate, which is typical of the rather mild interstitial pneumonitis accompanying sarcoidosis (H&E, × 100).

Mechanism(s) responsible for PAH in sarcoidosis include hypoxic vasoconstriction[192]; infiltration or obliteration of pulmonary vessels by the granulomatous, fibrotic response[201–203]; and extrinsic compression of major pulmonary arteries by enlarged lymph nodes.[191,202] A retrospective study of 22 patients with sarcoidosis and PAH found that mPAP correlated inversely with carbon monoxide transfer factor (T_{CO}) but not with spirometry (e.g., FVC, FEV_1).[202] In that study, five lung explants from sarcoid patients with PAH undergoing LT were examined. Granulomas were predominantly located within the veins, associated with occlusive venopathy and chronic hemosiderosis; arterial lesions were minor.[202]

The diagnosis of PAH may be difficult. Noninvasive techniques include chest CT[204] and Doppler echocardiography (DE).[197] Chest CT may be useful to predict PAH in patients with parenchymal lung disease.[204] CT features that suggest PAH include main pulmonary artery (PA) diameter > 29 mm; segmental artery to bronchus ratio > 1:1 in three of four lobes[204]; ratio of the diameter of the main PA and of the ascending aorta > 1.[205] Doppler echocardiography is superior to CT in estimating PAH but is less accurate than RHC.[197] In a cohort of 374 patients with end-stage lung disease who were being evaluated for LT, estimates of systolic PAP (sPAP) could be made by DE in 166 (44%).[197] However, sPAP estimates were inaccurate (> 10 mm Hg difference) compared with RHC measurements. In addition, 48% of patients were misclassified as having PAH by DE. Sensitivity, specificity, and

positive and negative predictive values of sPAP estimation for PAH were 85%, 55%, 52%, and 87%, respectively. DE was less accurate in patients with interstitial lung disease (ILD) compared with obstructive lung disease (OLD). The negative predictive value (NPV) of sPAP for DE was 96% among patients with OLD but only 44% for ILD. When right ventricular (RV) findings (e.g., RV dilatation, hypertrophy, or systolic dysfunction) were considered, NPV of DE was 96% for OLD and 74% for ILD. Thus a normal DE does not exclude PAH in patients with ILD. Further, an abnormal DE is not a reliable marker of PAH. When PAH is suspected in patients with sarcoidosis, a confirmatory RHC should be performed to assess the extent of PAP and responsiveness to vasodilators.

The presence of PAH in sarcoidosis markedly worsens survival. In one recent study of sarcoid patients with PAH, 2 and 5 year survival rates were 74% and 59%, respectively.[202] In sharp contrast, 5 year survival among sarcoid controls without PAH was 96.4%. Data regarding treatment of PAH complicating sarcoidosis are limited. Anecdotal successes were noted with corticosteroids in some patients. In a retrospective review, three of five sarcoid patients with PAH and no evidence for pulmonary fibrosis responded favorably to high-dose corticosteroids.[202] In contrast, none of five with radiographic evidence for pulmonary fibrosis improved.[202] The role of vasodilators[206] in sarcoid-associated PAH has not been elucidated, but short- and long-term responses were noted in case reports[192] or small series.[201,207] In the series of 22 patients with sarcoidosis and PAH reported by Nunes et al, none received long-term vasodilator therapy.[202] The authors urged caution in using vasodilator therapy because of the potential for precipitating pulmonary edema in patients with veno-occlusive disease.[202]

Other rare vascular complications of sarcoidosis (limited to a few case reports) include pulmonary arterial stenoses from granulomatous involvement of the vessels,[203,208] extrinsic compression of pulmonary arteries by enlarged hilar lymph nodes or fibrosing mediastinitis,[209,210] and pulmonary veno-occlusive disease (resulting from obstruction of interlobular septa veins by granulomata or perivascular fibrosis).[211,212] Extensive fibrosis of mediastinal or vascular structures may result in narrowing or obstruction of innominate veins[213] or superior vena cava (SVC).[208,214–220]

Necrotizing Sarcoid Angiitis

Necrotizing sarcoid angiitis and granulomatosis (NSG), initially described by Liebow in 1973,[221] is a rare disorder characterized by pulmonary vasculitis, granulomas, and pulmonary nodules on chest radiographs.[222–227] Hilar adenopathy has been cited in 10% to 60% of patients.[224–227] Lung biopsies in NSG demonstrate a granulomatous vasculitis involving arteries and veins, confluent nonnecrotizing granulomata involving bronchi, bronchioles, and lung, and foci of parenchymal necrosis.[222,225] Vascular involvement (angiitis) typically consists of intramural granulomata or lymphocytic and plasma cell infiltrates confined to vessels walls.[227] Systemic vasculitis does *not* occur. Since the original description, seven series of NSG,[222,223,225–229] as well as case reports[224,230–234] have been published, for a total of ~100 cases. In a recent review of 14 cases of NSG, 12 had extrapulmonary symptoms; pulmonary function was normal in 13, but DL_{CO} was decreased in eight of 11 patients tested.[227] Chest radiographs demonstrated alveolar infiltrates in seven; nodules in seven; cavitation in two.[227] Clinical and radiographic features of NSG are similar to "nodular sarcoid" or "nummular sarcoidosis"[235–238]. Nodular sarcoidosis demonstrates focal nodules composed of masses of granulomas and hyalinized connective tissue.[235] We believe that NSG and nodular sarcoid are simply variants of sarcoidosis. Prognosis of these entities is usually excellent. The disease resolves in most patients (either spontaneously or in response to therapy). In one recent series, favorable responses to corticosteroids were noted in five of five treated patients with NSG.[227]

Bronchostenosis

Stenosis or compression of bronchi may result from granulomatous inflammation of the bronchial wall, extrinsic compression from enlarged hilar nodes, or distortion of major bronchi caused by parenchymal fibrosis.[72,73,239–241] Proximal endobronchial stenosis is typically associated with dyspnea, cough, wheezing, and extrapulmonary manifestations.[72,73] Atelectasis of involved lobes or segments may result.[239,240,242–244] The right middle lobe is most often affected because of the small orifice, sharp angulation from the bronchus intermedius, and large number of local lymph nodes.[34] The incidence of bronchostenosis (by bronchoscopic assessment) in patients with sarcoidosis ranged from 2 to 26% in two studies,[72,241] but severe bronchostenosis is rare. In a retrospective study of 2500 patients with sarcoidosis, French investigators identified 18 patients with $>50\%$ stenosis of proximal bronchi.[73] Bronchoscopic patterns included single focal stenosis, multiple focal stenoses, and diffuse narrowing of the bronchial tree.[73] Edema and inflammation of the mucosa at sites of stenosis were a universal finding. Endobronchial biopsies revealed nonnecrotizing granulomata in 77% of patients.[73] Wheezing, high-pitched inspiratory "squeaks," or stridor may be evident on chest auscultation in patients with symptomatic bronchostenosis.[72] Helical CT scans are useful to determine the extent and nature of stenotic lesions in the lower respiratory tract,[78] but CT overestimates the degree of stenosis.[78,245] Early initiation of corticosteroid therapy

may be efficacious.[73] Conversely, delay in therapy may result in acquired fixed stenoses and persistent ventilatory defects.[73] Dilatation of endobronchial stenoses should be considered for patients refractory to medical therapy.[246]

Mycetomas

Mycetomas (typically due to *Aspergillus* species) may develop in cystic spaces (typically in the upper lobes) in patients with advanced (stage III or IV) sarcoidosis.[39,40,247,248] Ipsilateral pleural thickening usually precedes the fungus ball or air-crescent sign.[249] Mycetomas are often asymptomatic, but fatal hemorrhage can occur due to invasion of vessel walls.[243,247,250] Prognosis of aspergilloma is poor (fatality rates $>50\%$); most fatalities reflect progression of the underlying disease rather than a direct complication of mycetoma.[39,40] Surgical resection is advised for localized lesions in patients able to tolerate surgery[39,40,247] but the risk of surgery may be prohibitive in patients with severe parenchymal disease or extensive pleural adhesions.[39,247] Anecdotal success has been cited with topical or intracavitary therapy, but experience is limited.[251,252] Systemic antifungal therapy is of unproven value. Bronchial embolization may control intractable bleeding.[40]

Pleural Involvement in Sarcoidosis

Clinically significant pleural manifestations (e.g., pneumothorax, pleural effusions, chylothorax) occur in 2 to 4% of patients with sarcoidosis.[253–259] Pleural thickening may be observed when sensitive techniques are applied but is usually not associated with clinical symptoms. Two studies using HRCT cited pleural thickening in 9%[32] and 11%[260] of sarcoid patients, respectively. The incidence is higher in patients with chronic fibrocystic sarcoidosis. A study of 61 patients with chronic sarcoidosis (>2 years duration) cited pleural involvement on chest CT in 25 (41%); this included 20 cases of pleural thickening and five effusions.[261] Pleural thickening was more common among patients with parenchymal fibrosis (stage IV), restrictive PFTs, and low DL_{CO}. Earlier reports noted that pleural involvement in sarcoidosis was typically associated with widespread parenchymal lung disease.[262,263] Subpleural or pleural nodules[264,265] may be observed by HRCT in 22 to 76% of sarcoidosis cases,[101,266,267] but rarely cause symptoms. Pleural effusions complicate sarcoidosis in $<3\%$ of patients and, when present, are usually asymptomatic.[259] Kostina et al detected only three pleural effusions among 2775 patients with pulmonary sarcoidosis.[268] The incidence is more common when more sensitive tests are used. In a recent prospective study, thoracic ultrasonograms were performed in 181 consecutive outpatients with sarcoidosis.[257] Pleural effusions were detected in five (2.8%) but only three were attributed to sarcoidosis; two were a manifestation of congestive heart failure. Sarcoid pleural effusions may be either transudative or exudative; lymphocytosis occurs in two thirds of cases,[253,254,257,259] with predominance of CD_4 lymphocytes.[259,269,270] A few cases of eosinophilic pleural effusions were described.[271,272] Although exceedingly rare, cases of massive pleural effusions have been described.[273–277] In one case, pleural sarcoidosis with "trapped lung" required decortication for relief of symptoms.[278] Pneumothorax may complicate sarcoidosis,[255,259,268,279–282] due to rupture of bullae or necrosis of subpleural granulomas.[259] Only a few cases of chylothorax complicating sarcoidosis have been reported.[283–287]

Sarcoidosis in HIV-Infected Patients

Sarcoid-like granulomatous response is a rare complication of infection due to human immunodeficiency virus (HIV).[288–293] Chest radiographic[288] and histological[292] findings are similar to sarcoidosis in non-HIV infected patients. Most cases occur after beginning highly active antiretroviral therapy (HAART),[288,291–295] but sarcoidosis can precede institution of HAART.[288,296] The sarcoid-like granulomas following HAART likely reflect immune reconstitution, with influx of naive and IL-2 receptor-positive CD_4 cells.[292,297,298] However, CD_8 alveolitis was noted in one case.[299] Administration of exogenous IL-2, which leads to a sustained increase in CD_4 T cells,[300] may precipitate sarcoid-like lesions in HIV-infected patients. In one HIV-infected patient with undetectable viral load under HAART, sarcoidosis developed 2 months after initiation of IL-2 treatment.[293] Symptoms resolved following discontinuation of IL-2. Treatment of sarcoid-like reaction in HIV-infected patients is controversial, but favorable responses to corticosteroids have been noted.[290,298]

Sarcoidosis Complicating Type 1 Interferon Therapy

Type 1 interferons (e.g., IFN-α or IFN-β), used to treat viral hepatitis, multiple sclerosis, and diverse autoimmune and malignant disorders, may increase IFN-γ and IL-2 levels, evoking a Th_1 lymphocyte bias and granulomatous inflammation.[301–303] Sarcoidosis is a rare complication of IFN-α or IFN-β, therapy.[301,302,304–311] In a review of 60 cases of sarcoidosis following recombinant IFN-α (rIFN-α) therapy; 52 (87%) were receiving pegylated α-INF for hepatitis C virus (HCV) infection.[303] The remaining cases were associated with hepatitis B infection,[309] lymphoproliferative malignancies,[312,313] and other hematologic conditions. The incidence of sarcoidosis among patients with HCV infection treated with rIFN-α was $<0.5\%$ in most studies[302–304] but one study cited an incidence of 5%.[314] Ramos-Casals et al reported 68 cases of sarcoidosis associated with chronic HCV

infection; 76% had lung involvement; 30%, skin involvement.[304] Sarcoidosis developed within 6 months of antiviral therapy in two thirds of patients. HCV-positive patients with sarcoidosis had a lower incidence of lymphadenopathy (hilar or extrapulmonary) and a higher frequency of cutaneous and articular involvement compared with HCV-negative sarcoid patients.[304] Most cases of sarcoidosis resolve with withdrawal of rIFN-α or dose reduction[303,304] but corticosteroids are required in some patients.[302,315] However, corticosteroids or immunosuppressive agents may increase the viral load[304] and should be reserved for highly selected patients.

Treatment of Sarcoidosis

Treatment of sarcoidosis remains controversial. Corticosteroids (CSs) are the cornerstone of therapy for severe or progressive sarcoidosis (pulmonary or extrapulmonary), and often produce dramatic resolution of disease.[65,316,317] The long-term benefit of CS therapy has not been established because relapses may occur upon taper or cessation of therapy.[4,23,25] The decision to treat requires a careful assessment of acuity and severity of disease, likelihood of SR, and risks associated with therapy. Treatment should be circumscribed and focused. Treatment is rarely appropriate for stage I disease unless extrapulmonary symptoms are prominent. In *symptomatic* patients with stage II or III disease, a trial of CSs should be considered *after an initial observation period* (6 to 12 months). Immediate treatment, however, is appropriate for patients with severe symptoms or pulmonary dysfunction and presumed active alveolitis. Therapy is rarely efficacious, however, and may be associated with significant toxicities in patients with far-advanced fibrosis, honeycombing, or bullae (radiographic stage IV).

The appropriate dose and duration of CS therapy has not been evaluated in controlled, randomized trials. For most patients, initial daily dose of prednisone 40 mg/day (or equivalent) for 4 weeks, tapered to 40 mg alternate days by 3 months, is sufficient. Higher doses may be appropriate for patients with cardiac or central nervous system involvement, or selected patients with severe pulmonary sarcoidosis. Responses to CSs are usually evident within 4 to 8 weeks. Failure to respond to CSs may reflect inadequate dose or duration of therapy, presence of irreversible fibrotic or cystic disease, noncompliance, or intrinsic CS resistance. Among CS-responders, we continue prednisone, albeit in a tapering fashion. The rate of taper is individualized according to response and adverse effects. A minimum of 12 months of therapy (among responders) is recommended. In selected patients, long-term (often years) of low-dose, alternate-day prednisone may be required to prevent relapses.

Inhaled CSs suppress endobronchial or alveolar inflammation but have limited efficacy.[318–323] Inhaled CSs are expensive, and we do not employ these agents for patients with symptomatic pulmonary sarcoidosis. However, inhaled CSs may have an adjunctive role among patients manifesting bronchial hyperreactivity or cough.

Alternatives to Corticosteroids

Immunosuppressive, cytotoxic, and immunomodulatory agents have been used to treat patients failing or experiencing adverse effects from CSs.[324] The optimal agent(s) has not been determined because controlled studies comparing various agents are lacking. Favorable responses have been cited with methotrexate,[325–327] azathioprine,[328–330]; leflunamide,[331,332] cyclophosphamide,[333–335] chlorambucil,[336] cyclosporine A,[337] antimalarials (chloroquine or hydroxychloroquine),[338–340] pentoxyfylline,[341,342] thalidomide,[343–345] and TNF-α inhibitors[346] (particularly infliximab).[347–349] Because of potential serious toxicities (including oncogenesis) associated with cyclophosphamide and chlorambucil,[350] we do not use these agents to treat pulmonary sarcoidosis. We reserve the use of thalidomide and pentoxyfyline for research trials. For patients with progressive pulmonary sarcoidosis refractory to CSs, we initiate treatment with azathioprine (dose 100 to 150 mg/d PO) or methotrexate (dose 15–25 mg once weekly PO). These agents can be used in lieu of or in addition to CSs. Hydroxychloroquine (dose 200 mg twice daily) has minimal toxicity and may have modest benefit as adjunctive therapy in selected patients with pulmonary or extrapulmonary sarcoidosis. Infliximab is reserved for severe cases refractory to CSs and these alternative agents. Novel medical therapies for sarcoidosis are discussed in detail by Drs. Baughman and Lower in this issue.

Lung Transplantation for Sarcoidosis

LT (either single or bilateral) is a viable option for patients with end-stage pulmonary sarcoidosis refractory to medical therapy.[198,351] Dr. Shah discusses LT for sarcoidosis in depth elsewhere in this issue.

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