

## Pulmonary sarcoidosis

Robert P. Baughman, MD

*University of Cincinnati Medical Center, 1001 Holmes, Eden Avenue, Cincinnati, OH 45267-0565, USA*

Sarcoidosis is a multisystemic disease; however, it affects the lungs in more than 90% of patients [1]. Pulmonologists usually are involved in the initial evaluation of patients with sarcoidosis. Pulmonary symptoms are also the major reason for treatment. In this article we discuss the diagnosis and treatment of pulmonary sarcoidosis.

### Clinical presentation

Patients with sarcoidosis may have no symptoms at all and only are diagnosed by chest radiograph obtained for nonpulmonary reasons. Conversely, they can present with severe respiratory symptoms and even can die from this [2]. This wide range may lead to some delay in the diagnosis of sarcoidosis.

In the United States, a case-controlled etiologic study of sarcoidosis (ACCESS) recently was completed [3]. The study examined 736 patients with sarcoidosis within 6 months of their diagnosis. All cases were biopsy confirmed, and patients underwent a standard evaluation of pulmonary and extrapulmonary disease. ACCESS was performed at ten academic centers, mostly in the eastern portion of the United States. Because the study was performed at pulmonary subspecialty clinics, there were some limitations [4,5]; however, it does provide some insight into the initial presentation of sarcoidosis.

Table 1 lists the forced vital capacity and level of dyspnea for patients who present to ACCESS. More than 30% of the patients in this study had restrictive disease. In a large study of German and Swiss patients, more than 20% of patients at initial diagno-

sis had restrictive disease [6]. Obstructive defects also have been noted in most studies of patients with sarcoidosis [1,6,7]. In the ACCESS study, 14% of patients had a forced expiratory volume in one second/forced vital capacity (FEV<sub>1</sub>/FVC) ratio of less than 70%, with six patients having a ratio of less than 50%.

Dyspnea is a common complaint of patients with sarcoidosis, with half of the patients in ACCESS complaining of it (Table 1). The dyspnea score shown in Table 1 was modified from that developed for patients with pulmonary fibrosis [8]. Other studies have commented on dyspnea as a common complaint [6]; however, the results of a specific dyspnea questionnaire were not provided.

Other symptoms noted in patients with sarcoidosis include cough and chest pain. The mechanism of cough is multifactorial. In a study of 21 patients with symptomatic pulmonary sarcoidosis, all had cough [9]. There was no relationship between the results of methacholine challenge or the FEV<sub>1</sub>/FVC ratio and any aspect of the cough. Others have been able to demonstrate endobronchial lesions in some patients with cough [10]. Researchers also have observed that interstitial lung disease in general can cause a cough.

Chest pain is a frequent complaint of patients with sarcoidosis. The mechanism is unclear, although some researchers have related it to the mediastinal adenopathy of the disease. In a careful study that compared CT findings to chest symptoms, Highland et al [11] could not find a correlation between adenopathy or any other radiographic finding and chest pain in patients with sarcoidosis.

A staging system for the chest radiograph of sarcoidosis was independently developed by Wurm and Scadding more than 40 years ago [12]. The current system includes four stages: stage 1, adenopathy alone; stage 2, adenopathy plus infiltrates; stage 3,

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*E-mail address:* bob.baughman@uc.edu

Table 1  
Lung involvement on initial presentation for sarcoidosis

	Percent at initial evaluation
Forced vital capacity (%)	
>80	69%
70–79	18%
50–70	11%
<50	2%
Level of dyspnea	
Strenuous exercise (grade 0)	49%
Hurrying or hills (grade 1)	33%
Walking slower than others (grade 2)	12%
Stopping after 100 yards (grade 3)	4%
Cannot leave house (grade 4)	2%

Adapted from Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001;164:1885–9; with permission.

infiltrates alone; stage 4, fibrosis. Fig. 1 demonstrates the classic adenopathy of stage 1 sarcoidosis, whereas Fig. 2 demonstrates a case of stage 3 disease. Chest CT scanning can help identify the fibrotic phase of the disease. Fig. 3 demonstrates the chest radiograph and a high-resolution CT image in a patient with long-standing sarcoidosis. The bronchiectasis can be seen in the right upper lobe on CT scan.

At the time of initial diagnosis, most patients present with stages 1 to 3 of their disease. Fig. 4 demonstrates the chest radiograph stage at time of presentation for three large study groups (>500 patients in each group) [1,7]. The patients from Japan were more likely to have stage 1 chest radiograph than either the Europeans or Americans. This is



Fig. 1. Posteroanterior chest radiograph of stage 1 sarcoidosis. Patient has hilar adenopathy and no evidence of parenchymal lung involvement.

probably because of the routine mass screening performed in Japan, which is not practiced in the United States or Europe. This is not the only cause for the differences, however, because there also were a significant number of patients in Japan with normal chest radiographs. There is a high incidence of eye disease in Japanese patients with sarcoidosis. In these studies, 50% of the Japanese patients had eye symptoms at the time of initial diagnosis, compared with 12% for Americans and 8% for Europeans.

Diagnostic features of the high-resolution CT scan in sarcoidosis include peribronchial thickening, subpleural nodularity, traction bronchiectasis, and upper lobe disease [13]. Fig. 5 demonstrates peribronchial thickening and traction bronchiectasis.

## Diagnosis

The diagnosis of sarcoidosis is based on the finding of a granuloma in a patient with a compatible clinical history and no other cause of granulomas identified [14]. Although pathologic tissue is a major part of the diagnosis, it is neither necessary nor sufficient for the diagnosis. There are several other causes of granulomas, including infections such as tuberculosis and fungal infections. Beryllium and other metals also have been found to cause granulomatous reactions [14]. Granulomas have been identified in reaction to cancer [15] or lymphoma [16].

Certain clinical features support the diagnosis of sarcoidosis [17]. Table 2 lists some of these findings. The clinician who obtains an initial history and performs physical examination should look for evi-



Fig. 2. Posteroanterior chest radiograph of stage 3 sarcoidosis. Patient has diffuse lung disease but no significant adenopathy.

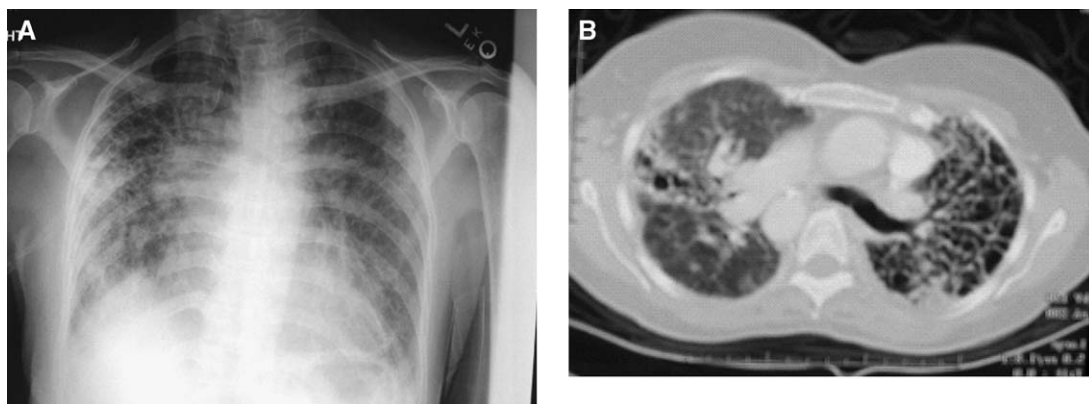


Fig. 3. (A) Posteroanterior chest radiograph of patient with stage-four sarcoidosis. (B) Fibrosis and upper lobe retraction are confirmed on high-resolution CT scan. The scan also demonstrates traction bronchiectasis.

dence of extrapulmonary disease. Because sarcoidosis is a multiorgan disease, the more organ involvement identified, the more comfortable one can be with the diagnosis. There also is an interaction between presentations. For example, the presence of uveitis is highly unusual for tuberculosis or lymphoma; conversely, multiple sclerosis and sarcoidosis can cause optic neuritis and uveitis. Multiple sclerosis does not cause mediastinal adenopathy, however.

Symptoms of sarcoidosis often are present months before diagnosis. In one study, the median symptoms appeared 2.8 months before diagnosis, but the range was 1 to 72 months [6]. The authors of that study suggested that the delay was caused by slow onset of symptoms. In the ACCESS study, a subpopulation of 189 symptomatic patients was studied in detail [18].

Fig. 6 shows the percentage of patients diagnosed at each visit number. Approximately half of the patients were diagnosed within three physician visits. One fourth of the patients were diagnosed more than 6 months after their first physician visit. This number was more marked for patients with pulmonary symptoms, in whom 30% received diagnosis more than 6 months from the first physician visit. Conversely, only 1 of 22 patients (5%) with skin symptoms took more than 6 months to be diagnosed.

For patients with pulmonary symptoms, a major reason for delay in diagnosis may be the nonspecific nature of cough and dyspnea symptoms. Asthma may be the first consideration. Once a chest radiograph has been obtained, the presence of adenopathy may speed up the diagnosis process. The presence of

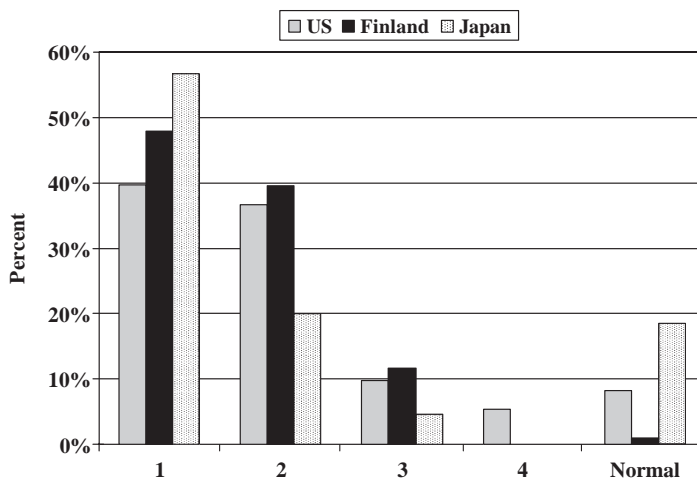


Fig. 4. Chest radiograph stage at time of initial diagnosis for patients evaluated in Finland, Japan, and the United States. (Data from references [1,12,90].)

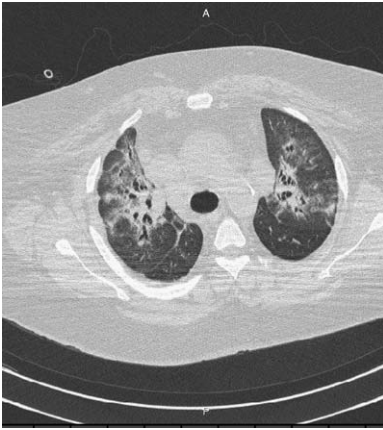


Fig. 5. High-resolution CT scan demonstrates peribronchial thickening and traction bronchiectasis of the upper lobes of a patient with pulmonary sarcoidosis.

interstitial lung disease alone (stage 3 or 4) is associated with a longer time until diagnosis [18]. In a patient aged 50 years or older, another diagnosis, such as idiopathic pulmonary fibrosis, may be considered more likely. Sarcoidosis is a disease that is increasingly diagnosed in patients over age 50 [19], with one-fourth of the patients in ACCESS diagnosed at age 50 or older. There seems to be a second peak of incidence of the disease in patients over age 60 [20].

For patients with pulmonary symptoms, clinicians have various techniques available to make the diagnosis, including needle aspiration, bronchoalveolar lavage (BAL), transbronchial biopsy, open-lung bi-

opsy, and mediastinoscopy. Each of these techniques has advantages and disadvantages.

The use of needle aspiration to diagnose sarcoidosis can include needle biopsy of extrathoracic adenopathy. Using rigid criteria, one can use this technique to distinguish from other causes of adenopathy, including lymphoma [21]. The bronchoscope allows one to aspirate lymph nodes within the mediastinum and hilum [22–24]. Use of ultrasound can improve the diagnostic yield [25]. One difficulty with needle aspiration is the limited sample, which may miss a granulomatous reaction to lymphoma [20]. The sample also may be insufficient for culture for fungus or mycobacteria.

BAL has been proposed as a method to diagnose sarcoidosis. Some clinicians believe that BAL alone should be sufficient to diagnose sarcoidosis [26]. Others believe that the frequency of diagnostic features of the lavage is too low to warrant routine use of the test [27]. The value may be somewhere between these two extremes [28].

For many patients with sarcoidosis, BAL shows increased lymphocytes, which have an increase in the helper-to-suppressor ratio [29]. The elevated ratio has been found in a variable proportion of patients with sarcoidosis [27,30–32]. Some of this variability is caused by the presentation of a patient's sarcoidosis. Patients with erythema nodosum and hilar adenopathy (Lofgren's syndrome) have high CD4:CD8 ratios [33]. During the resolution of the disease, the CD4:CD8 ratio returns toward normal before the increased percentage of lymphocytes resolves [34]. The increase in lymphocytes may be a more useful

Table 2  
Features that support the diagnosis of sarcoidosis

	Feature	Comments
Physical findings	Cranial seventh nerve paralysis	Usually resolves within a few months
	Erythema nodosum and hilar adenopathy	Often associated with severe arthralgias of ankles and legs
	Lupus pernio	Erythema nodosum resolves within 1–2 months
	Uveo-parotid fever	Evidence for chronic disease Combination (Herefort's syndrome) is unusual but fairly specific for sarcoidosis; often has seventh nerve paralysis
Laboratory tests	Hilar adenopathy	In asymptomatic patient
	Gallium scan showing lambda and panda sign	Scan takes 3 days to complete
	BAL showing increased lymphocytes or CD4:CD8	Supportive of diagnosis; CD4:CD8 less sensitive
	Increased ACE level	Positive in 65% of patients with acute disease, less frequently elevated in chronic disease; up to 10% of elevated ACE caused by nonsarcoidosis conditions
	Elevated serum calcium	Supportive of the diagnosis

Abbreviation: ACE, angiotensin-converting enzyme.

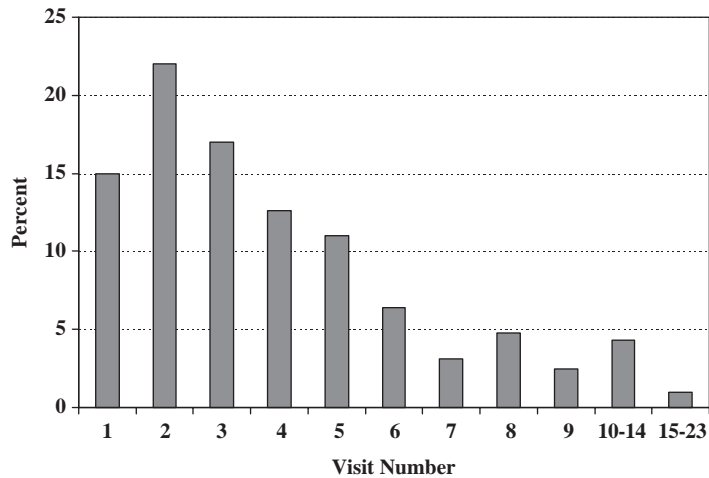


Fig. 6. The percentage of patients diagnosed with sarcoidosis versus their visit number. Approximately half of the patients required more than three physician visits until the diagnosis was made. (From Judson MA, Thompson BW, Rabin DL, et al. The diagnostic pathway to sarcoidosis. *Chest* 2003;123:406–12; with permission.)

indicator of a granulomatous process, such as sarcoidosis. Drent et al [35] have shown that lymphocytes alone in the BAL can be used as a predictor for sarcoidosis. As occurs so often in sarcoidosis, BAL findings are not definitive but supportive.

Bronchoscopic biopsy of the lung can demonstrate granulomas. Endobronchial biopsy can make the diagnosis, especially in patients with an irregular mucosa [36]. Transbronchial biopsy has been the standard method for diagnosing sarcoidosis by bronchoscopy for more than 25 years [37,38]. The yield is higher for patients with parenchymal lung disease (stage 2 or 3) than patients without parenchymal disease on chest radiograph (stage 1). CT scan can identify patients with parenchymal disease not seen on plain chest radiograph [39].

The bronchoscopist has multiple tests available to diagnose sarcoidosis, including transbronchial biopsy, endobronchial biopsy, BAL, and transbronchial needle aspiration [40]. For most patients, multiple biopsies and BAL are standard. In patients with significant adenopathy, the addition of needle aspiration may assist in the diagnosis. The culture of the bronchial washings can be useful for ruling out infections such as tuberculosis or fungus [41].

For patients in whom bronchoscopy has failed to make the diagnosis, clinicians may have to choose between open-lung biopsy and mediastinoscopy. Open-lung biopsy, usually performed by video-assisted thoracoscopy, is associated with significant morbidity. The major reason for performance of this procedure is clinician concern about other interstitial

lung diseases, such as idiopathic pulmonary fibrosis. In one prospective study of patients undergoing serial evaluations and eventual open-lung biopsy for idiopathic interstitial lung disease, 3 of 91 were found to have sarcoidosis [42].

Mediastinoscopy provides a good sample of the right paratracheal lymph nodes, which often are affected in patients with sarcoidosis. Mediastinoscopy is associated with significantly less morbidity than an open-lung biopsy, with most patients sent home the same day of the procedure [43]. Because it provides a large sample of a central lymph node, mediastinoscopy is particularly useful in distinguishing between sarcoidosis and lymphoma.

A CT scan is useful in determining which diagnostic procedure to perform. If there is significant adenopathy, I prefer a mediastinoscopy. If there is minimal adenopathy, I prefer a video-assisted thoroscopic surgery (VATS) procedure. Care must be taken to avoid obtaining a biopsy of only end-stage fibrotic and bronchiectatic areas of the lung. As with any interstitial lung disease, multiple biopsies are useful.

## Treatment

Therapy of sarcoidosis usually is based on symptoms [14]. There are a few absolute indications for therapy, including cardiac and neurologic involvement, hypercalcemia, and ocular disease that has not responded to topical therapy [17,44].

Pulmonary disease is a relative indication for therapy. Asymptomatic patients with parenchymal lung disease (stage 2 or 3) may not benefit from systemic therapy. In a study of 149 patients who presented with pulmonary sarcoidosis, 58 (39%) had spontaneous resolution over the next 6 months [45]. Conversely, 33 (22%) were placed on therapy because of worsening symptoms. Patients with persistent disease were randomly assigned to either therapy or observation. Of the treatment group, 25 of 27 patients were treated with 18 months of corticosteroids, and the other 2 patients declined therapy. In the observation group, 6 of 31 eventually received therapy because of deterioration. Although 20% of the observation group received therapy, there was a significant difference in the two groups more than 3 years after treatment stopped. The group assigned to long-term therapy had 8% more improvement of FVC than the observation group.

In a meta-analysis by the Cochrane group of corticosteroid therapy for sarcoidosis, the authors concluded that corticosteroids were of benefit for pulmonary disease [46]. The authors concluded that corticosteroid therapy would lead to resolution sar-

coidosis as shown on chest radiograph and improvement of the diffusion capacity for carbon monoxide.

Corticosteroid therapy often lasts for 2 or more years [47–49]. One study noted that half of the patients still required therapy after 2 years. Ninety percent of patients who stopped therapy required reinstitution of systemic therapy [48]. It is important to note that of the patients not placed on initial therapy, only 10% required therapy at a later date. The ACCESS trial also found that of patients who did not require therapy at the initial evaluation, only 10% required any therapy over the next 2 years.

The long-term use of corticosteroids is associated with significant toxicity. In a prospective study of toxicity associated with corticosteroid therapy, more than half of the patients complained most or all the time of one or more problem. Symptoms included weight gain, mood swings, heart burn [50].

The alternatives to corticosteroids are summarized in Table 3 [17]. Most agents have been studied in only a limited number of case series. Some of the agents have been studied in randomized trials, however.

Antimalarial agents have been studied for their use in pulmonary and cutaneous disease [51,52]. Chlo-

Table 3  
Therapies for sarcoidosis

Class	Drug	Usual initial dose	Maintenance dose	Toxicity
Anti-inflammatory	Prednisone	40 mg daily	5–10 mg daily to every other day	Weight gain, diabetes, hypertension, toxicity are cumulative
	Cyclosporine	25–200 mg	25–200 mg	Hypertension, renal failure, infection
Antimicrobial	Hydroxychloroquine	400 mg daily	400 mg daily	Ocular, nausea
	Chloroquine	500 mg daily	250 mg daily	Ocular, nausea
	Minocycline	200 mg daily	100–200 mg daily	Rash, hepatitis, dizziness
Cytotoxic	Methotrexate	10 mg once a week	2.5–15 mg once a week	Nausea, leukopenia, hepatitis, pneumonitis
	Leflunamide	10–20 mg daily	10–20 mg daily	Nausea, leukopenia, hepatitis
	Azathioprine	50–100 mg daily	Up to 3 mg/kg daily	Nausea, leukopenia
	Cyclophosphamide	500–800 mg intravenously every 2 weeks <b>or</b> 50–100 mg oral daily	1000–2000 mg intravenously every 2–8 weeks <b>or</b> 50–100 mg oral daily	Nausea, leukopenia, cystitis, bladder cancer
Cytokine modulators	Thalidomide	50 mg nightly	50–200 mg nightly	Somnolence, constipation, rash, teratogenicity
	Pentoxifylline	400 mg three times a day	400–1200 mg in divided doses	Nausea, diarrhea
	Infliximab	3–5 mg/kg initially and week 2	3–10 mg/kg every 4–8 weeks	Increased rate of infection, anaphylaxis
	Etanercept	25 mg sq twice a week	25 mg sq twice a week	Increased rate of infection, local reaction

Abbreviation: sq, subcutaneously.

Adapted from Baughman RP, du Bois RM, Lower EE. Sarcoidosis. Lancet 2003;361:1111–8; with permission.

roquine has been found to be effective for some patients with pulmonary sarcoidosis [52]. In a study of chronic pulmonary sarcoidosis, all patients initially received chloroquine. They were then randomized to maintenance on chloroquine or placebo [53]. The study found that chloroquine lowered the rate of relapses from the disease. Chloroquine has significant ocular toxicity, which appears much less frequently with hydroxychloroquine [54–56]. Because of this lower toxicity, hydroxychloroquine is used more frequently.

Methotrexate has been used widely as a steroid-sparing agent for sarcoidosis [57]. It has been found to be effective in various manifestations of sarcoidosis, including pulmonary [58], neurologic [59], cutaneous [58,60], juvenile-onset [61], and ocular disease [62]. A randomized, placebo-controlled trial demonstrated that methotrexate was steroid sparing for patients with acute disease [63]. That study and others have noted that there is a delay—up to 6 months—before methotrexate leads to objective improvement. The toxicities of methotrexate include nausea, mouth sores, bone marrow suppression, and hypersensitivity pneumonitis [64]. Hepatotoxicity has been noted with prolonged use of the drug, and surveillance biopsies every 2 to 3 years have been used by our group to avoid toxicity [65].

Other cytotoxic drugs have been used, including azathioprine [66], cyclophosphamide [59], chlorambucil [67], and leflunomide [68]. All of these drugs cause bone marrow suppression and nausea. Cyclophosphamide and chlorambucil are associated with an increased rate of cancer [69], whereas the risk as-

sociated with azathioprine is less clear [70,71]. Chlorambucil has been used less frequently because it has more toxicity than either methotrexate or azathioprine, but it does not seem more effective than those drugs. Conversely, cyclophosphamide has been effective in patients who have failed treatments with prednisone and methotrexate [59].

Table 3 lists some other agents used for sarcoidosis in limited case series, including cyclosporine, a potent immunosuppressive agent. Studies have demonstrated that cyclosporine effectively inhibits T-cell activation in patients with active pulmonary sarcoidosis [72]; however, this was not associated with any objective clinical improvement [72,73]. Pentoxifylline was reported in one trial to be useful for acute pulmonary sarcoidosis [74]. The gastrointestinal toxicity of the drug at high doses has limited its application, however. Minocycline has been reported useful for cutaneous sarcoidosis [75]. The possible mechanism of action would be the effect of the drug on *Propionibacter acne*, a putative agent for sarcoidosis [76]. The drug simply may work as an immunosuppressive agent as it seems to work in other diseases [77]. Given the relatively low toxicity of minocycline, further studies of this drug seem warranted.

Thalidomide has been used for many chronic inflammatory cutaneous diseases, including sarcoidosis [78]. A dose escalation trial established that a usual effective dose for lupus pernio, a chronic facial rash from sarcoidosis, was 100 mg given once at night [79]. The drug is an effective hypnotic agent, but sedation is dose limiting. Other side effects include constipation and peripheral neuropathy. Thalidomide

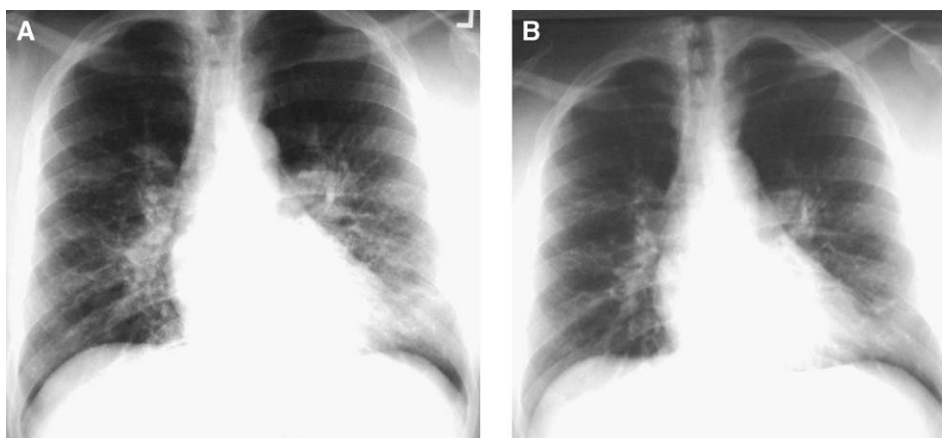


Fig. 7. (A) Posteroanterior chest radiograph of patient with chronic sarcoidosis who had persistent disease despite high doses of corticosteroids. (B) There is a marked improvement of adenopathy and parenchymal infiltrates after four treatments with infliximab. (From Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2001;18:70–4; with permission.)

was responsible for a large number of congenital malformations, and current prescription of the drug is under strict control in the United States.

Alveolar macrophages retrieved by BAL from patients with active sarcoidosis release elevated levels of tumor necrosis factor [80,81]. This finding has led to the hypothesis that anti-tumor necrosis factor agents may be useful for treatment of sarcoidosis [82]. Infliximab is a chimeric antibody to tumor necrosis factor and has been found effective in treating rheumatoid arthritis and Crohn's disease [83,84]. Etanercept is a tumor necrosis factor receptor antagonist that has been effective for rheumatoid arthritis [85]. Infliximab has been reported as effective in a small number of patients with sarcoidosis who were treated with the drug [86,87]. Fig. 7 demonstrates the chest radiograph of a patient before and 3 months after therapy with infliximab. In a carefully controlled case series, Utz et al [88] were not able to demonstrate benefit for etanercept for pulmonary sarcoidosis. There are differences between etanercept and infliximab, including their target of action. Infliximab is associated with a much higher risk of reactivation for tuberculosis than etanercept [89]. Because sarcoidosis is a granulomatous disease similar to tuberculosis, this observation supports the difference in activities for these two agents.

## Summary

Sarcoidosis is a common pulmonary interstitial lung disease. Extrathoracic involvement may support the diagnosis. A final diagnosis is usually made based on the finding of granulomas in patients with a compatible clinical history. The treatment of sarcoidosis ranges from none to complex immunosuppressive agents. Given the range of effective therapies for sarcoidosis, it is important to make the diagnosis and prescribe treatment appropriately.

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