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Pulmonary sarcoidosis: New genetic clues and ongoing treatment controversies

ABSTRACT

The wide-ranging, multisystemic manifestations of sarcoidosis can make diagnosis and management difficult. Corticosteroid treatment is effective, but the optimal time to start, the dose, and the duration of treatment are controversial. We are just beginning to understand the genetic basis of sarcoidosis.

KEY POINTS

Patients with chronic sarcoidosis (10% to 30% of cases) are at high risk of extensive, irreversible pulmonary fibrosis; 75% have a relapse when corticosteroids are stopped.

Dermatologic manifestations of sarcoidosis are numerous, and one fourth of patients develop at least one.

Treatment is not appropriate in certain cases. For example, 90% of patients with stage 1 disease have a spontaneous remission, so corticosteroids are not likely to help.

In chronic sarcoidosis, the key to treatment is to find the lowest possible dose of corticosteroids to maintain stable lung function and symptoms without serious adverse effects; ≤10 mg/day works in 65%, and ≤15 mg works in 90%.

Current thinking holds that the sarcoid granuloma is probably the result of a stereotyped, chronic, dysregulated immune response to one or more environmental or shared agents (possibly infectious) in a susceptible host.

SARCOIDOSIS CONTINUES TO CHALLENGE our diagnostic and therapeutic capabilities. Its widely variable, multisystemic manifestations usually lead to the involvement of a subspecialist, but internists are often central in its ongoing management.

The distinguishing feature of sarcoidosis is the presence of noncaseating granulomas with associated lymphocytic inflammation in involved tissues. Fibrosis may ensue. The granulomatous inflammation can usually be reversed with corticosteroids, but the optimal timing for the start of steroid therapy, the dose, and the duration of treatment are not well defined.

In this article, we will review the major clinical features of sarcoidosis, recent research into its causes, and current issues of therapy, with a primary focus on management of pulmonary symptoms.

PREVALENCE AND IMPACT

Sarcoidosis affects people throughout the world, regardless of age, race, or sex, but it has a predilection for adults under age 40 and for certain ethnic groups, including African Americans, Scandinavians, and Irish.[1]

Worldwide, prevalence estimates range from fewer than 1 to as many as 40 cases per 100,000.[2] Age-adjusted prevalence rates in the United States are 10.9/100,000 for Caucasians and 35.5/100,000 for African Americans, conferring a lifetime risk of about 0.85% and 2.4%, respectively.[3]

Disease presentation and outcome vary markedly by race and ethnicity as well, with constitutional symptoms and chronic progres-

Genetic influences in sarcoidosis

Two broad lines of analysis underlie the hypothesis that genetic influences govern sarcoidosis: racial/ethnic disparities and familial case-clustering. For example, Irish immigrants in London are three times more likely to develop sarcoidosis than native Londoners.[17] Natives of Martinique living in France have a prevalence rate eight times that of the indigenous French population.[18] Prevalence in African Americans is 4 to 17 times greater than in Caucasians.[3,19]

Multiple reports have demonstrated familial case-clustering, termed "familial sarcoidosis."[20,21] The presence of an affected first-degree or second-degree relative amplifies risk by nearly fivefold.[21] In these families, monozygotic twins are affected more often than dizygotic twins.[20]

Environmental basis for familial clustering unlikely

Genetic simulation modeling suggests that an environmental basis for observed familial clustering is unlikely. Putative exposures would have to confer relative risks of 100 or greater to account for the frequency of clustering.[22] Such intense environmental risks would probably have been uncovered already by case-control studies.

Which genes might confer sarcoidosis risk?

Studies to identify specific genes conferring risk for sarcoidosis have concentrated on human leukocyte antigen (HLA) genes, which are important determinants of each individual's immune response. Studies worldwide have implicated a multitude of HLA genes, suggesting a large degree of heterogeneity in HLA-driven susceptibility across ethnic and racial lines.[23,24] Familial sarcoidosis is strongly linked to HLA genes of the major histocompatibility complex on chromosome 6p.[25] Other candidate gene polymorphisms include genes for the T-cell receptor, angiotensin-converting enzyme, immunoglobulins, and chemokines.[26] A number of these genes may also be important modulators of disease phenotype.

The mortality rate in chronic sarcoidosis is as high as 12%

sive disease far more likely in African Americans.[4] Extrathoracic manifestations are also more frequent in African Americans, Puerto Ricans, and Scandinavians.[2]

The overall mortality rate of sarcoidosis ranges from 1% to 5%,[2] but with chronic disease it rises to 12%.[5]

CAUSE UNKNOWN: IS IT ENVIRONMENTAL OR GENETIC OR BOTH?

While the cause or causes of sarcoidosis are unknown, there have been significant recent advances in our understanding of its genetic and immunologic features.

Is it due to a transmissible agent?

Despite the long-standing perception that sarcoidosis is caused by a transmissible, possibly infectious agent, no single agent has been convincingly implicated as yet. A case-control study on the Isle of Man suggested person-to-person transmission or shared environmental exposure.[6] Increased incidence has been demonstrated in groups of firefighters and nurses in close contact.[7,8] Diagnosis of Löfgren syndrome (acute onset of bilateral hilar lymphadenopathy, erythema nodosum, fever, and polyarthralgias) varies by season.[9] All these findings are consistent with space-time clustering, as might be seen with a transmissible infectious agent. There have been reports of sarcoidosis transmission by lung, heart, and bone marrow transplantation.[10–12] Finally, the Kveim-Siltzbach reagent, an extract of human sarcoidosis tissue, is capable of inducing histologically indistinguishable cutaneous granulomas in 80% of sarcoidosis patients following intradermal injection.[13]

Agents that have been implicated

Mycobacteria, including deficient forms that lack a cell wall, have been implicated most often, but the data are contradictory and inconclusive.[14] A report from Japan strongly implicated *Propionibacterium* sp.[15] Other proposed agents have included fungi, viruses, *Tropheryma whippelii*, corynebacteria, *Borrelia burgdorferi*, and *Mycoplasma* sp.[16] Current thinking holds that the sarcoid granuloma is probably the result of a stereotyped, chronic, dysregulated immune response to one or more

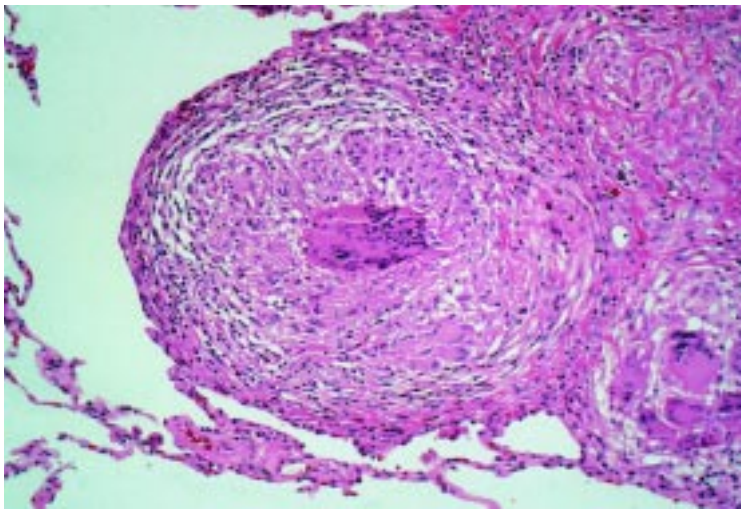

FIGURE 1. Non-necrotizing granuloma. The granuloma is composed mainly of epithelioid cells surrounded by a rim of lymphocytes. There is minimal central caseation, which may be seen in a small proportion of sarcoidosis granulomas. This specimen also contains several multinucleated giant cells. Hematoxylin and eosin × 100.

environmental or shared agents (possibly infectious) in a susceptible host.

GENETIC PREDISPOSITION APPEARS IMPORTANT

Granulomatous inflammation later either resolves or progresses to irreversible fibrosis

In conjunction with environmental exposure, genetic predisposition appears to be important in the development, presentation, and course of sarcoidosis. However, to date, no gene or set of genes has been identified that unilaterally confers risk of sufficient magnitude to explain the epidemiologic observations regarding the development, mode of presentation, or course of sarcoidosis across ethnic lines. Most likely, the propensity to develop the disease is a product of multiple genetic factors. Susceptibility could reside in polymorphisms governing immune regulation, T-cell function, or antigen processing and presentation.

For a more in-depth discussion of this topic, see "Genetic influences in sarcoidosis" on page 90.

PATHOGENESIS

In systemic sarcoidosis, disease development is related to the presence of predisposing genetic factors and exposure to an inciting antigen. Granuloma formation, central to our current understanding of pathogenesis, is necessary for recognition of the disease, although in some people the disease may in fact resolve before granuloma formation. The factors leading to ongoing granulomatous inflammation, fibrosis, or resolution are poorly understood. Also poorly understood is why organ involvement varies from person to person.

The histologic fingerprint of sarcoidosis is the epithelioid granuloma—a compact focus of epithelioid cells, lymphocytes, and, occasionally, multinucleated giant cells (FIGURE 1).

Alveolitis may be the first phase

Conceptually, tissue involvement can be divided into three phases or compartments: inflammation (eg, alveolitis), granuloma formation, and fibrosis. Bronchoalveolar lavage studies have suggested that alveolitis is the earliest pulmonary manifestation.[27] In a proportion of patients, the presence of a persistent or poorly degradable putative agent spurs granuloma development. Later, granulomatous inflammation either resolves spontaneously or progresses to irreversible fibrosis.

Progression vs resolution

The immunologic factors governing a shift to fibrosis or resolution are not well understood. It is clear, however, that regional heterogeneity may exist, with patchy alveolitis interspersed with fibrotic parenchyma.

In the context of $CD4^+$ T-lymphocyte activation, multiple chemokines are generated, stimulating monocyte and lymphocyte recruitment to the involved site. Later, immigrant monocytes differentiate into the epithelioid cells and multinucleated giant cells typical of granulomas. The ongoing gradient favoring transpulmonary lymphocyte chemotaxis may explain the paradoxical clinical finding of depressed delayed-type hypersensitivity reactions to recall antigens (eg, purified protein derivative) in 30% to 70% of patients: there are not enough circulating lymphocytes to produce the expected cutaneous response.[26,28,29]

CLINICAL FEATURES: SINGLE ORGAN TO WIDESPREAD DISEASE

The clinical manifestations of sarcoidosis are protean and may represent anything from

widespread disease to single-organ involvement. The presentation and course depend on disease duration, ethnic and racial background, sex, distribution of organ involvement, and intensity of inflammation and granuloma formation.[2,4]

In the United States, chronic disease with insidious onset of pulmonary symptoms is the most common mode of presentation, especially in African Americans.[30] Caucasians are affected more often by acute, self-limited disease.

Löfgren syndrome, a benign form of sarcoidosis characterized by bilateral hilar lymphadenopathy, fever, erythema nodosum, and polyarthralgias, accounts for 20% to 50% of patients with acute manifestations.[30] For these patients, with few exceptions, the prognosis is excellent.[31] For all other patients, 10% to 20% will develop significant morbidity or death.[2]

TABLE 1

Chest radiograph stratification (Scadding scale)

STAGE*	DESCRIPTION	RATE OF SPONTANEOUS RESOLUTION
Stage 0	Normal radiograph	?
Stage 1	Bilateral hilar lymphadenopathy (BHL)	60%–90%
Stage 2	Diffuse pulmonary infiltrates and BHL†	50%–60%
Stage 3	Diffuse infiltrates only	<30%
Stage 4	Fibrotic lung disease	0%

*Stages do not represent sequential steps in disease course and are based only on the posterior-anterior chest radiograph
†Usually reticular, reticulonodular, or focal alveolar opacities

Lungs

More than 90% of people with sarcoidosis have pulmonary involvement.[2] Even when extrathoracic manifestations dominate the clinical course, the lungs are usually involved.[30,32] Dyspnea on exertion, cough, and retrosternal chest discomfort similar to cardiac angina occur most frequently.

Auscultatory findings are uncommon (fewer than 20% of patients), even when radiography shows extensive infiltrates,[33] although inspiratory crackles have been classically associated with parenchymal disease. Airway involvement has been increasingly recognized, with granulomas present in up to 50% of airway mucosal biopsy specimens[34]; bronchial hyperreactivity or endobronchial stenosis may result, with attendant wheezing or stridor.[34,35]

Physiologic findings include reduced lung volumes and evidence of impaired gas exchange (low diffusing capacity or elevated A-a gradient).

Radiographic features. Sarcoidosis commonly presents first as an incidental finding on chest radiography. TABLE 1 describes the range of possible pulmonary findings on chest radiography, stratifying them into stages (the Scadding Scale):

- Normal radiograph (stage 0)
- Bilateral hilar lymphadenopathy (stage 1)
- Diffuse pulmonary infiltrates and bilateral hilar lymphadenopathy (stage 2)
- Diffuse infiltrates only (stage 3)
- Fibrotic lung disease (stage 4).

The Scadding Scale is a convenient, descriptive method to classify sarcoidosis. There is a loose correlation between the "stages" and the likelihood of resolution. When using the Scadding Scale, it is important to keep in mind that the stages do not represent sequential steps in the disease course, and that the changes listed are based only on those visible with posterior-anterior radiography.

Rare manifestations include clubbing, hemoptysis (which may occur in radiologic stage 4 disease with bronchiectasis), pleural effusions, pneumothorax, pleural thickening or calcification, unilateral lymphadenopathy, segmental infiltrates or mass lesions, diffuse ground-glass opacities, mycetomas, lymph node calcification, pulmonary nodules, and chylothorax.[33]

The course varies from self-limited, single-organ to chronic, progressive, multisystemic

Heart

Cardiac involvement in sarcoidosis is often occult, with only 40% to 50% of affected patients diagnosed during life.[36,37] The prevalence of cardiac disease among all patients with sarcoidosis ranges from 28% to 50%, but clinical disease manifests in only 5%.[36,38]

Early, aggressive treatment improves the prognosis in these patients, so a high index of suspicion is warranted.[38]

Manifestations of cardiac involvement may be due to active granulomatous inflammation or fibrosis, and any cardiac structure may be affected. The most frequent features are electrophysiologic abnormalities (heart block, dysrhythmias, sudden death), infiltrative cardiomyopathy with systolic or diastolic dysfunction, cor pulmonale, angina-like chest pain, and pericardial disease.[38] Ventricular aneurysm, papillary muscle dysfunction, valvular infiltration, and stenoses of intramural coronary arteries are uncommon or rare sequelae.

Thallium scintigraphy helps to identify areas of active or inactive myocardial involvement. Abnormal thallium uptake, with a characteristic pattern of improvement on redistribution scanning after dipyridamole (reverse distribution), may also be seen, suggesting microvascular insufficiency.[39] In a patient with known sarcoidosis in whom the coronary angiogram is normal, an abnormal thallium scan strongly suggests myocardial involvement. Asymptomatic patients with abnormal thallium scans are unlikely to have clinically bothersome long-term disease.[40]

Active granulomatous inflammation can affect any cardiac structure

Other diagnostic techniques such as technetium-99 single-photon emission computed tomography and gadolinium-enhanced magnetic resonance imaging (MRI) are promising tools for diagnosis and monitoring treatment response.[41,42] Electrocardiography, Holter monitoring, and event monitoring may identify patients with dysrhythmias, and baseline electrocardiography is recommended for all newly diagnosed patients.[2]

Endomyocardial biopsy, while helpful if positive, often fails to sample involved areas. Even with multiple samples, biopsy sensitivity may be as low as 19%.[43] Therefore, treatment should not be withheld on the basis of a nondiagnostic biopsy result.[2,43]

Liver

In patients with sarcoidosis, liver biopsy reveals granulomas in 50% to 80% of cases. Mild elevations of transaminases or alkaline phosphatase are common, but such findings are rarely of clinical importance[2,44,45] Occasionally, liver disease progresses to portal hypertension or cirrhosis.

Histopathologic findings include cholestasis, focal necroinflammatory lesions, vascular involvement, and widespread fibrosis.[46]

Treatment. Active inflammation usually responds to treatment with corticosteroids. Therapy is not indicated in asymptomatic patients or those with mild elevations of liver enzyme levels.

Nervous system

Clinically apparent neurologic disease occurs in 5% to 13% of patients with sarcoidosis, often in the absence of symptomatic disease in other organs.[47–49] Any neurologic structure may be involved, but there is a predilection for the base of the brain.

Cranial nerve VII palsy is the leading single manifestation in most case series.[48,49] However, a recent large series noted a higher frequency of optic nerve involvement.[50] In general, cranial nerve palsies, hypothalamic or pituitary infiltration, and aseptic meningitis are more commonly associated with acute or subacute sarcoidosis, a favorable course, and treatment responsiveness.[2]

Features of chronic sarcoidosis include space-occupying masses, peripheral nerve involvement, myelopathy, seizures, neuromuscular disease, and chronic meningitis. Peripheral nerve involvement may take the form of mononeuritis multiplex, symmetric polyneuropathy (sensory, motor, or mixed), Guillain-Barré syndrome, or polyradiculopathy.[51]

Diagnosis. MRI with gadolinium (especially with leptomeningeal enhancement) or gallium scanning is useful for suggesting the diagnosis but is nonspecific. However, enhancement after gadolinium has recently been shown to predict reversibility of sarcoid lesions.[52]

Lumbar puncture should be performed in the appropriate clinical context (eg, if it is uncertain whether the patient has nervous system sarcoidosis or tuberculous or fungal meningitis), especially since mycobacterial or fungal infections may be clinically similar. Cerebrospinal fluid analysis may reveal lymphocytosis, elevated protein, oligoclonal bands, and elevated levels of angiotensin-converting enzyme.[50]

Chest radiography aids diagnosis in patients with suspected neurologic disease, since asymptomatic intrathoracic disease is

present in up to 30% of cases.[50]

Treatment. Corticosteroids have been used most often, with mixed results.[48–50] In general, prolonged administration of relatively high steroid doses is necessary if treatment is required.

Eye

Sarcoidosis can affect any ocular structure.[2] The most striking presentation is acute anterior uveitis, characterized by the rapid onset of blurred vision, lacrimation, and photophobia. Treatment with topical steroids is usually efficacious, but the condition often resolves spontaneously.

Chronic uveitis (anterior, mixed, or posterior) is often clinically insidious, leading to glaucoma, cataracts, and blindness. Conjunctival follicles, keratoconjunctivitis sicca, dacrocystitis, and retinal vasculitis occur less frequently.

Treatment requires complete control of all ocular inflammation; a stepwise approach using topical corticosteroids, periocular steroid injections, and systemic corticosteroids is common. Methotrexate is often prescribed for maintenance therapy in patients with chronic disease.

Skin

Dermatologic manifestations of sarcoidosis are numerous. Ultimately, one of every four patients will develop at least one feature.[53]

Erythema nodosum is characterized by painful erythematous raised lesions, usually on the shins, often with associated regional arthritis or periarthritis. Erythema nodosum represents a nonspecific autoimmune phenomenon, so biopsy will not reveal granulomas.

Lupus pernio portends chronic, refractory sarcoidosis; it is more common in older African American or West Indian women. On examination, it appears as indurated plaques with violaceous discoloration of the cheeks, lips, nose, and ears, and it may be disfiguring.

Other chronic skin lesions include plaques, maculopapular eruptions, hypopigmented or hyperpigmented patches, subcutaneous nodules, and alopecia. Often, the lesions arise in scars or tattoos.

Localized skin lesions can be treated with topical corticosteroids or injections, but severe manifestations (eg, lupus pernio) or diffuse disease usually requires systemic treatment.

Kidney and endocrine system

Activated macrophages in granulomas may autonomously overproduce 1,25-dihydroxyvitamin D, leading to hypercalcemia in 2% to 10% of patients.[54,55] Hypercalciuria occurs up to three times as often.[55] Renal lithiasis, nephrocalcinosis, and renal failure may result. Hypercalcemia responds well to corticosteroids, but ketoconazole or antimalarials may be used as alternatives.[56,57] Granulomatous interstitial nephritis is rare.[2]

Reticuloendothelial system

In addition to the high frequency of intrathoracic lymphadenopathy (90% of cases), approximately one third of patients have palpable peripheral lymph nodes.[2] In the neck, posterior triangle glands are more commonly involved than anterior ones. The nodes are firm, nontender, and nonulcerating. Palpable splenomegaly, usually clinically silent, occurs in 14% of cases.[58]

Other organ involvement

Cytopenias may occur but are not usually of clinical significance. Rarely, the gastrointestinal tract, reproductive organs, muscles, bones, exocrine glands (parotitis), or upper airway may develop symptomatic disease.

Eye involvement is treated with topical steroids, then periocular injections, then systemic steroids

DIAGNOSIS IS BY EXCLUSION

Sarcoidosis is a diagnosis of exclusion. The noncaseating granuloma is the sine qua non of the disease, and demonstration of compact granulomas in biopsy specimens adds to diagnostic confidence. However, the differential diagnosis of noncaseating granulomas is broad, spanning infections (mycobacterial, fungal, parasitic, some bacterial), autoimmune disease (eg, Wegener granulomatosis), environmental exposures (chronic beryllium disease, hypersensitivity pneumonitis), medications (eg, methotrexate), and cancer-related granulomas.

Sarcoid granulomas are usually pathologically indistinguishable from other granulomas.[19] Thus, a complete physical examination and medical history including occupational,

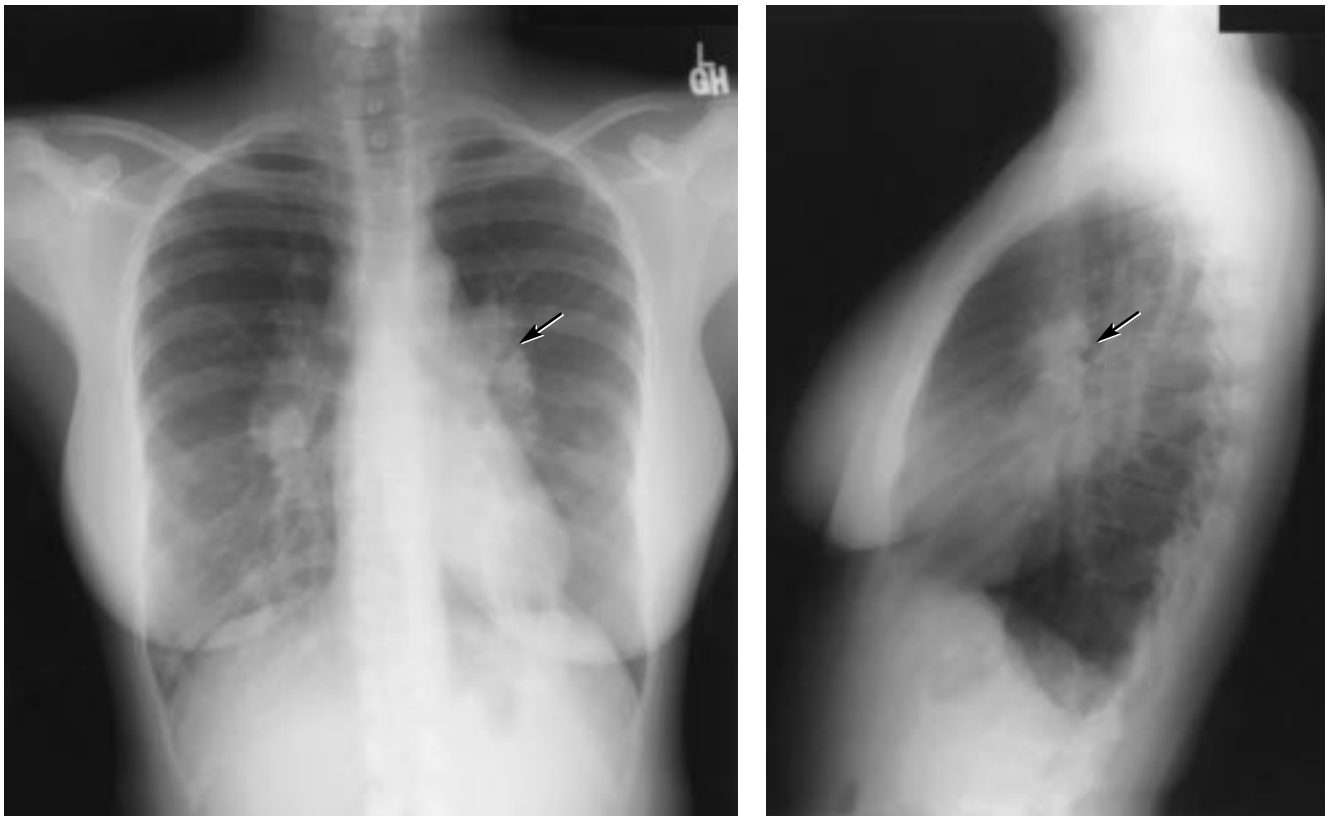

FIGURE 2. Posteroanterior (left) and lateral (right) chest radiographs demonstrate typical bilateral hilar lymph node enlargement (arrows). Ill-defined bilateral lower lung zone infiltrates are also present.

medication, and environmental exposures is mandatory prior to applying a label of sarcoidosis.

The role of biopsy

In an appropriate clinical context, the diagnosis may be presumptively made without biopsy, as in FIGURE 2, a chest radiograph of a young asymptomatic patient showing bilateral hilar adenopathy. Flexible fiberoptic bronchoscopy with biopsy is a safe, minimally invasive outpatient procedure that is the best way to establish a diagnosis and to exclude other diseases in the majority of patients with suspected sarcoidosis. We recommend obtaining a specific histologic diagnosis in symptomatic patients prior to treatment. Even in the absence of obvious pulmonary disease, bronchoscopic biopsy may facilitate diagnosis of systemic disease.[32,59]

Other sites easily amenable to biopsy include skin and cervical lymph nodes. Skin biopsy following intradermal injection of the Kveim-Siltzbach reagent (see earlier discussion) is diagnostic, but the assay is not standardized, not widely available, and not approved by the US Food and Drug Administration. For these reasons, we do not recommend it.

Laboratory testing

Serum angiotensin-converting enzyme activity and gallium-67 scanning may support a diagnosis but suffer from poor specificity and are rarely clinically useful.[30] We do not recommend the routine use of angiotensin-converting enzyme levels for the diagnosis of sarcoidosis or for routine follow-up.

STAGING DISEASE ACTIVITY: GUIDING TREATMENT AND PROGNOSIS

The clinical impact of sarcoidosis varies widely and depends on the distribution and intensity of granulomatous inflammation or fibrosis in the affected organs. TABLE 2 lists elements of the initial evaluation that help in the assessment of the extent of the disease.

TABLE 2

Suggested initial evaluation of sarcoidosis patients

Complete history with emphasis on occupational and environmental exposure
Physical examination
Complete blood count, comprehensive metabolic panel
Urinalysis
Posteroanterior chest radiography
Spirometry, test of diffusing capacity
Electrocardiography
Ophthalmologic examination (with slit lamp)
Purified protein derivative test for tuberculosis

The natural history of sarcoidosis is similarly variable. Features thought to predict poor prognosis vary among studies. Of all the putative risk factors, no study to date has comprehensively ascertained which factors are independently associated with disease chronicity or progression.

The staging of pulmonary disease based on chest radiography (TABLE 1) allows a general prediction of outcome. Computed tomography of the chest may delineate the extent of pulmonary fibrosis or uncover infiltrates not seen with radiography. However, there are no data to support an additive role for computed tomography in estimating the prognosis of sarcoidosis.

Patients with severe symptoms of active disease need aggressive steroid treatment

Other assays of disease "activity" have been the subject of intense investigation, including serum angiotensin-converting enzyme level, gallium-67 scanning, and bronchoalveolar lavage fluid analysis (eg, CD4/CD8 ratio, total lymphocyte count), but unfortunately, none has consistently predicted disease course.[60,61] For now, chest radiographic stage, demographic features, clinical involvement, and serial pulmonary function testing remain the best indicators for assessing prognosis and making therapeutic decisions.

THE CHALLENGES OF TREATING SARCOIDOSIS

Corticosteroids are the mainstay of treatment for patients with sarcoidosis. But deciding who should get them is often difficult. Factors that hamper any attempts to define specific populations likely to benefit substantially from corticosteroid therapy include:

- The high rate of spontaneous remission
- Intrastudy and interstudy heterogeneity among patients, treatment strategies, and outcome measures
- Lack of a validated marker of disease activity
- Difficulty distinguishing the effects of steroids from the natural history of the disease
- Ethical concerns about placebo controls in patients with significant symptoms.

There is no question that patients with severe systemic manifestations of active disease—eg, neurologic or cardiac symptoms, ophthalmic disease refractory to topical steroids, and significant hypercalcemia—warrant aggressive corticosteroid treatment.[2,30] However, in other cases the indications for treatment are less well defined.

Corticosteroids clearly down-regulate proinflammatory cytokines known to be important in pulmonary sarcoidosis, such as interleukin-2, interferon-gamma, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-alpha.[62] However, demonstrable immune modulation has not translated into consistent and persuasive evidence for broad clinical use.

PULMONARY SARCOIDOSIS: CURRENT ISSUES IN TREATMENT

Conceptually, treatment decisions for pulmonary sarcoidosis can be divided into the management of acute disease (<2 years) or chronic disease.[63] Ostensible goals of therapy for acute or chronic pulmonary sarcoidosis include palliation of symptoms and prevention of progression to irreversible fibrosis.

In some cases, treatment is clearly not appropriate. For example, 90% of patients with stage 1 disease have a spontaneous remission, so corticosteroid treatment is not likely to be of benefit. Also, patients with extensive fibrosis (radiographic stage 4) but no concomitant active inflammation (eg, end-stage disease) should not be treated, because the risk-benefit ratio is poor.[33]

Steroid treatment is most often started for

Multicenter study of infliximab in sarcoidosis

A multicenter, international, prospective, randomized phase 2 trial of infliximab (a TNF antagonist agent) for sarcoidosis is currently underway. A total of 120 patients will be enrolled, with a 2:1 drug:placebo ratio. Treatment will last 24 weeks, with follow-up for 1 year. The primary end point is change in pulmonary function.

Enrollment criteria

- Histologically proven disease of at least 1 year's duration
- Radiographic evidence (Scadding stage 2 or 3; TABLE 1)
- Forced vital capacity 50% to 85% of predicted value
- Current using prednisone ≥ 10 mg/day or other immunosuppressant (eg, methotrexate, azathioprine, antimalarials) for at least 3 months prior to enrollment

Enrollment of patients who also have extrapulmonary disease is strongly encouraged.

Exclusion criteria

- Evidence of mycobacterial or fungal infection
- History of anti-TNF medication use
- New York Heart Association class III or IV heart failure

To refer patients

To refer patients or for more information, readers should contact Nancy Ivansek, PAC, MA at (216) 445-8747 or toll-free at (866) 873-3679.

symptomatic patients with stage 2 or 3 disease.[2,30,33] It is clear that steroids usually temporarily improve symptoms, radiologic abnormalities, and lung function.[64,65] However, data to support a clinically significant beneficial effect on the natural course of disease, including prevention of fibrotic lung disease, have been inconsistent.[65–68] Consequently, steroids should be considered as suppressive, rather than curative, therapy.

Most authors do not recommend treating asymptomatic or mildly symptomatic patients unless serial pulmonary function testing reveals a progressive decline in the forced vital capacity or the diffusing capacity for carbon monoxide. However, untreated patients should be periodically monitored, especially for the first 2 years after presentation. Delaying treatment does not appear to compromise the later effectiveness of steroids.[69]

Dosing not yet standardized

Dosing of corticosteroids for sarcoidosis is not standardized, since the optimal dose and duration have not been prospectively studied. Most authors suggest daily prednisolone-equivalent doses of 30 to 40 mg, though others have employed initial doses of 1 mg/kg/day.[69]

Equivalent-dosage, alternate-day regimens minimize side effects. At least one study found comparable responses with this approach.[70]

Gauging treatment response

If no improvement is seen by 3 months after the start of therapy, the condition should be considered unresponsive.[2] The proportion of responders is unclear, since most studies have included a large proportion of patients with high expected rates of spontaneous remission. Reported objective response rates range from 61% to 100%.[60,71] Once a response is established, the dosage can be tapered to 10 to 15 mg/day. However, treatment should continue for 6 to 12 months before attempting to wean the patient.

The condition is considered unresponsive if no improvement is seen by 3 months after therapy starts

Risk of relapse

Interestingly, race and chest radiographic stage have not been shown to correlate with the risk of relapse, a problem that affects 22% to 74% of treated patients.[72,73] The effect of long-term preemptive corticosteroid treatment on the progression of sarcoidosis is controversial.[68,71] Overall, current opinion still supports a period of observation with demonstration of deterioration prior to the use of corticosteroids.

Managing chronic pulmonary sarcoidosis

Ten percent to 30% of patients with sarcoidosis have the chronic form, with long-standing symptom progression or treatment required for more than 2 years.[2] The greatest hazard for these patients is the development of extensive and irreversible pulmonary fibrosis, the leading cause of sarcoidosis-related death in the United States. More than 75% of these patients relapse almost immediately when steroid therapy is stopped.[74] In this population, the goal of therapy is to carefully delineate the lowest dose necessary to maintain stable lung function and symptoms.[63] Most of these patients can be maintained on low doses of prednisone: 15 mg or less in 90% of patients, and 10 mg or less in 65%.[74]

Managing asthma-like symptoms

For patients with predominant cough or airflow obstruction, inhaled corticosteroids may alleviate symptoms. One study found good efficacy for maintenance therapy of stage 2 and 3 disease compared with oral steroids.[75] Most investigations have revealed either no benefit or only very limited benefit.[76–78] Given the lower toxicity profile of inhaled corticosteroids, however, a trial may be warranted for patients with symptoms predominantly referable to endobronchial disease.

Nonsteroid treatments

When steroids are ineffective, contraindicated, or cause unacceptable adverse effects, or when a steroid-sparing agent is needed for maintenance therapy, a second-line medication is indicated.

Methotrexate and azathioprine have the highest level of evidentiary support in pulmonary sarcoidosis, and they have tolerable safety profiles.[79,80] They have been used in place of or in conjunction with ongoing corticosteroid therapy.

Chloroquine. A recent report has reinvigorated interest in the antimalarial drug chloroquine as an additional viable agent, and its side-effect profile compares favorably with the other options.[81]

Cyclophosphamide and chlorambucil are more toxic agents, and their use is limited to severe disease refractory to combinations of the aforementioned agents.[33]

Other treatments. Recent small case series have suggested salutary effects of pentoxifylline, thalidomide, and infliximab on refractory lupus pernio or pulmonary sarcoidosis.[82–84] All have physiologic appeal on the basis of tumor necrosis factor-alpha inhibition. Interestingly, cyclosporine appears to be ineffective, despite its theoretic attractiveness as an inhibitor of interleukin-2-mediated T-cell proliferation and function.[85] For end-stage disease of the lung, organ transplantation may be considered.

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CME 1.5 CREDIT HOURS

CME ANSWERS

Answers to the credit test on page 167 of this issue

1 **A** 2 **D** 3 **B** 4 **B** 5 **D** 6 **C** 7 **D** 8 **E** 9 **E**
10 **E** 11 **B** 12 **E** 13 **E** 14 **D** 15 **D**