MAYO CLINIC

Pulmonary Sarcoidosis: Diagnosis and Treatment

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CME Activity

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Abstract

Sarcoidosis is a chronic granulomatous disease of unknown cause that is seen worldwide and occurs mainly in patients between the ages of 20 and 60 years. It can be difficult to diagnose because it can mimic many other diseases including lymphoproliferative disorders and granulomatous infections and because there is no specific test for diagnosis, which depends on correlation of clinicoradiologic and histopathologic features. This review will focus on recent discoveries regarding the pathogenesis of sarcoidosis, common clinical presentations, diagnostic evaluation, and indications for treatment. This review is aimed largely at general practitioners and emphasizes the importance of differentiating pulmonary sarcoidosis from its common imitators.

 ■ Mayo Clin Proc. 2016;91(7):946-954

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Sarcoidosis is a multisystem disease that predominantly affects individuals between the ages of 20 and 60 years. The incidence is about 10 per 100,000 in a predominantly white population but up to 3 to 4 times higher in African Americans. Sarcoidosis is frequently encountered first by primary care physicians when evaluating patients with nonspecific symptoms such as cough or dyspnea and not uncommonly also encountered incidentally during routine evaluations. Because its cause is unknown and there is no standard test for its diagnosis, sarcoidosis remains a diagnosis of exclusion. It can mimic many illnesses and therefore is included in the differential diagnosis of many pulmonary and systemic processes. Skilled clinical reasoning is required to

Mayo Clin Proc. ■ July 2016;91(7):946-954 ■ http://dx.doi.org/10.1016/j.mayocp.2016.03.004
www.mayoclinicproceedings.org ■

ensure that the correct diagnosis is made in a cost-effective and timely manner.

The etiology of sarcoidosis remains unknown despite decades of effort, including notably the ACCESS (A Case-Control Etiologic Sarcoidosis Study) project, a case-control study of over 700 matched case and control pairs. This study investigated occupational and environmental factors as well as infection and genetic associations, but a plausible cause could not be identified.[1] Despite the absence of a definitive cause, it is widely held that the pathogenesis of sarcoidosis involves exposure to an environmental or nonenvironmental agent(s) in a genetically susceptible individual. This combination triggers the activation of components of the immune system and the formation of nonnecrotizing granulomas, the hallmark lesions of sarcoidosis. Depending on unknown genetic aberrations or immune system defects, the granulomatous reaction either resolves or persists as chronic inflammation leading ultimately to fibrosis. Different combinations of exposures and host defects likely determine the multiple phenotypes seen in sarcoidosis.

This review summarizes the recent discoveries regarding the pathogenesis of sarcoidosis, most common clinical presentations, diagnosis, and indications for treatment of pulmonary sarcoidosis. This review is mainly aimed at general practitioners and emphasizes the importance of differentiating pulmonary sarcoidosis from its common imitators, particularly when treatment fails.

PATHOGENESIS

The pathogenesis of sarcoidosis still remains an enigma despite the first documented cases being described in the late 1800s by Hutchinson and Boeck. One of the largest efforts to identify a common causative agent was the ACCESS study, and although no unifying exposure was clearly identified, this study has been key in recognizing some occupations (raising birds, automobile manufacturing, teaching school, cotton ginning, and work involving radiation, organic dust, gardening, and building material exposure) and certain exposures (insecticides, molds and mildew, central air conditioning, and birds) that are more frequently associated with the development of sarcoidosis.[2] Interestingly, when infectious agents were sought, positive blood culture results and serologic test rates were similar in patients and controls. Nevertheless, given the pathologic resemblance of sarcoidosis to granulomatous infections, some of the most investigated environmental factors have been infectious agents. Among these factors, antigens from typical and atypical mycobacteria, *Propionibacterium*, viruses, and various fungi have been hypothesized as initial triggers of the granulomatous reaction.[3] Some of these microbial antigens, also known as pathogen-associated molecular patterns, are likely triggers of the innate immune response, leading to granuloma formation in the susceptible host.[4] Therefore, the absence of increased positive culture results in patients compared with controls does not completely exclude infectious organisms or associated antigens as potential triggers because it could be the exposure, and not necessarily the infection, that elicits the sarcoid reaction in the predisposed patient. Similarly, other pathogen-associated molecular patterns derived from toxins and chemical compounds as well as damage-associated molecular patterns such as human heat shock proteins could potentially trigger granuloma formation in the susceptible host.[5] Chen et al[4] also suggested that the acute phase response agent, serum amyloid A, triggered by mycobacterial infection can form insoluble aggregates with some of the mycobacterial antigens, which can then activate the immune response via toll-like receptors contributing to the granuloma formation.

Once the innate immune response has been activated, antigen-presenting cells process the antigen and present the peptide to HLA class II molecules, which can then be recognized by specific T-cell receptors. It is known that certain HLA alleles are associated with disease severity. For instance, patients with *HLA-DRB1*03* experience higher rates of disease resolution within 2 years than those without *HLA-DRB1*03*, while those with *HLA-DRB1*14* and *HLA-DRB1*15* tend to have a more chronic course.[6] Some HLAs may also predict disease pattern as illustrated by the association of *HLA-DRB1*0401* with eye involvement or *HLA-DPB1*0101* with abnormal calcium metabolism.[7] Furthermore, patients with sarcoidosis who have *HLA-DRB1*0301* and *HLA-DRB3*0101* have an accumulation of T cells expressing a specific T-cell receptor clone (AV2S3+), suggesting a clonal expansion of $CD4^+$ T cells to a particular

antigen.[8] Although these antigens are still unknown, vimentin-derived peptides have recently been suggested to be presented by *HLA-DRB1*03* to T cells expressing Va2.3/Vb22 receptors in patients with sarcoidosis.[9] Whereas the exact role of vimentin-derived peptides needs further investigation, it is possible that they can act as potential autoantigens that trigger granuloma formation in some patients. HLA is also important in other granulomatous diseases such as berylliosis, and individuals with *HLA-DP2* are a higher risk for development of the disease. In these patients, beryllium becomes associated with a self major histocompatibility-peptide complex binding internally within the peptide binding groove of DP2. Beryllium in the presence of the sodium cation causes structural and biophysical changes of the self peptide—major histocompatibility complex creating a "new antigen" that is now recognized by specific T cells.[10] This new and fascinating mechanism of granulomatous reaction may also apply to other yet unknown antigens. In addition to sarcoidosis susceptibility based on HLA alleles, recent genome-wide association studies have identified non-HLA—related genes (*BTNL2*, *ANXA11*, *RAB23*, and *Notch4*) that are also associated with sarcoidosis predisposition.

It is therefore plausible that sarcoidosis is expressed in its multiple forms depending on the type of trigger(s) and immunologic alteration(s). As we more fully understand these issues, we will likely be able to differentiate the disease into different immunologic subtypes based on underlying mechanisms and perhaps offer more specific and individualized treatments rather than treatment based on clinical phenotypes.

CLINICAL PRESENTATION

Sarcoidosis is often encountered incidentally on chest radiography that may reveal intrathoracic lymphadenopathy and/or pulmonary infiltrates (Figure, A). Intrathoracic involvement, especially mediastinal adenopathy, is present in up to 97% of patients with sarcoidosis, but less than half of them present with respiratory symptoms. Among those who do have symptoms, the most common are cough, dyspnea, and wheezing. Less commonly, some may have chest pain or discomfort, and hemoptysis is rare. General fatigue, malaise, weight loss, arthralgias, and fever are commonly seen alone or in association with respiratory symptoms. A classic and acute form of presentation is Lofgren syndrome, characterized by the presence of erythema nodosum, polyarthralgia, and bilateral hilar adenopathy. It usually has a good prognosis with complete resolution within 2 years of presentation.

In about 30% to 50% of cases, patients may also have extrapulmonary manifestations.[11,12] Cutaneous involvement is the most frequently encountered (15%-25%), followed by hepatic or gastrointestinal (11%-18%), ocular (12%), renal (1%-5%), neurologic (5%), cardiac (2%), and musculoskeletal (1%) involvement.[11,12] Therefore, every patient should be assessed for extrapulmonary involvement (Table). Cardiac sarcoidosis is a cause of serious morbidity and can be fatal because of severe arrhythmias or progressive cardiomyopathy. Unexplained syncope, presyncope, or palpitations should be considered highly suspicious for cardiac involvement and prompt further diagnostic evaluation.[13] Neurosarcoidosis can be similarly complex and present as seizures or stroke-like events or with neuropsychiatric manifestations.

Because sarcoidosis is the great imitator and there is no specific standard test for its diagnosis, a detailed history is needed not only to investigate extrapulmonary involvement but also to rule out alternative diagnoses such as infections (mycobacterial and fungal), lymphoproliferative disorders, or more rare conditions such as common variable immunodeficiency syndrome, which may be accompanied by sarcoid-like lung disease ("granulomatous lymphocytic interstitial lung disease"). It is also important to ascertain occupational exposures, especially long-term beryllium exposure, because berylliosis can be indistinguishable from sarcoidosis in many ways.

On physical examination, evidence of lymph node enlargement and skin, eye, and joint involvement should be routinely sought. Lung examination often underestimates parenchymal involvement because most patients have a paucity of physical signs, sometimes even in the presence of extensive parenchymal disease. Inspiratory crackles are generally absent unless advanced fibrosis has occurred. Occasionally, wheezing or squeaky sounds may be detected on auscultation. The presence of clubbing is rare and suggests an alternative diagnosis.

Mayo Clin Proc. ■ July 2016;91(7):946-954 ■ http://dx.doi.org/10.1016/j.mayocp.2016.03.004
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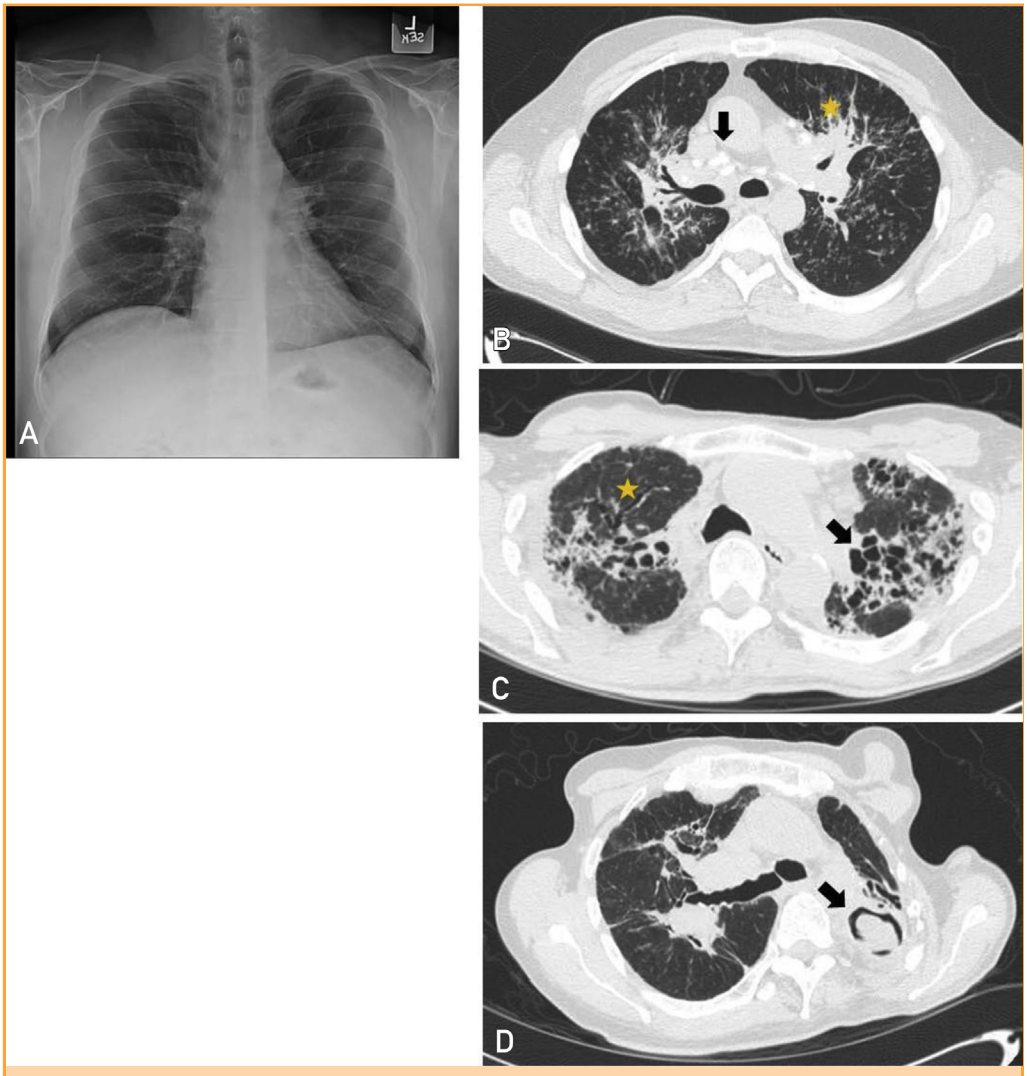

FIGURE. Characteristic chest radiographic and high-resolution computed tomographic (HRCT) findings of sarcoidosis. A, Chest radiograph showing bilateral hilar adenopathy. B, On HRCT of the chest, bilateral pulmonary nodules distributed along the fissures and bronchovascular bundles are evident. Some of the nodules form masslike lesions (yellow star). Calcified mediastinal lymph nodes can also be seen (black arrow). C, Chronic fibrotic changes with upper lobe predominance is seen on HRCT. Traction bronchiectasis (yellow star) and honeycombing (black arrow) are present. D, Left lower lobe mycetoma seen on HRCT. Fungus ball can be appreciated inside a cavitary lesion (black arrow).

DIAGNOSTIC EVALUATION

Initial evaluation of patients with suspected sarcoidosis should include blood cell counts, serum chemistry that includes creatinine, calcium, liver enzymes, and alkaline phosphatase levels, and urinalysis. Depending on the patient's background, geographic location, and travel history, tuberculosis testing or fungal serologies may be indicated. Other testing such as serum protein electrophoresis, tests for inflammatory markers (eg, C-reactive protein and erythrocyte sedimentation rate), and measurement of lactate dehydrogenase, vitamin D, and immunoglobulin levels should be tailored to the patient's history and clinical presentation and, in our opinion, should not be routinely ordered. Measurement of serum angiotensin-converting enzyme (ACE) level remains widely used, but

TABLE. Most Common Extrapulmonary Manifestations of Sarcoidosis

Site	Manifestation
Skin	Lupus pernio
	Subcutaneous nodules or plaques
	Erythema nodosum
	Inflammatory papules within a scar or tattoo
Liver	Hepatomegaly
	Hepatic nodules
Ocular	Uveitis
	Optic neuritis
	Mutton-fat keratic precipitates
	Iris nodules
	"Candle wax drippings"
	Retinitis
	Scleritis
Renal	Hypercalcemia
	Hypercalciuria
	Nephrolithiasis
Neurologic	Cranial mononeuropathy
	Neuroendocrine dysfunction
	Seizures, encephalopathy, or vasculopathy
	Myelopathy or radiculopathy
	Meningitis
	Peripheral neuropathy
	Small fiber neuropathy
Cardiac	Mobitz type II or third-degree heart block
	Ventricular arrhythmias
	Cardiomyopathy
	Sudden cardiac death
Musculoskeletal	Polyarthritis
	Diffuse granulomatous myositis
	Bone lesions
Generalized	Fatigue

a normal value does not exclude the diagnosis of sarcoidosis because of its poor sensitivity and insufficient specificity.[14] Its utility is further compromised by the fact that serum ACE levels vary depending on the different ACE genotypes (DD, DI, II) and by the use of ACE inhibitors.[15] Therefore, we do not recommend its routine use.

Some of the most frequently encountered laboratory abnormalities in patients with sarcoidosis are leukopenia with lymphopenia, hypercalcemia, and abnormal liver enzymes or abnormal liver function test. With the exception of hypercalcemia, which can cause renal failure, these conditions usually tend to resolve as the sarcoidosis improves and only rarely represent major complications.

Complete pulmonary function tests (PFTs) including diffusing capacity should be obtained in patients who have respiratory symptoms or lung parenchymal abnormalities on imaging studies. Pulmonary function tests may yield restrictive abnormalities, particularly in the fibrotic stages, as well as varying degrees of airflow obstruction, often pointing to airway involvement that might otherwise be overlooked. At times, PFT results may appear normal. A disproportionate reduction in the diffusing capacity for carbon monoxide could signal the presence of pulmonary hypertension, a rare but frequently missed complication.[16]

Baseline chest radiography (CXR) is indicated particularly if there are any respiratory symptoms or PFT abnormalities. The classic staging of CXR abnormalities was proposed by Scadding,[17] who distinguished 4 disease stages with implied prognostic implications: stage 0, normal; stage I, hilar lymphadenopathy; stage II, hilar lymphadenopathy and parenchymal involvement; stage III, parenchymal lung disease; and stage IV, fibrosis. Patients with stage I disease have an excellent prognosis with spontaneous resolution expected to occur in 60% to 90% within 5 years compared with 10% to 20% of patients at stage III.[18]

If CXR reveals abnormalities and the patient has respiratory symptoms or abnormal PFT results, high-resolution computed tomography (HRCT) of the chest is usually obtained. Although HRCT may not be necessary if patients are asymptomatic and have classic findings on CXR, it can be very useful in determining the pattern and severity of parenchymal involvement, particularly in the presence of atypical radiographic findings. Additionally, HRCT may help identify supraclavicular, hilar, and mediastinal adenopathy that could be potential targets for tissue sampling. The most common parenchymal finding is the presence of nodules in a lymphatic and peribronchovascular distribution, usually bilateral and with an upper or mid lung distribution. The nodules can coalesce and form focal consolidative masses with mid zone predominance. Often, there is also bilateral hilar and mediastinal lymphadenopathy that may calcify with time (Figure, B). Some patients may have airway involvement that can be associated with bronchial stenosis, atelectasis, and mosaic attenuation (due to air trapping). In the fibrotic stages, classic HRCT findings are reticular opacities, volume loss, traction

Mayo Clin Proc. ■ July 2016;91(7):946-954 ■ http://dx.doi.org/10.1016/j.mayocp.2016.03.004
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bronchiectasis, fibrotic masses, and even honeycombing (Figure, C).[19] Mycetomas can also be seen, and although rare, they should be monitored closely because of the risk of bleeding (Figure, D). Spleen and liver granulomas may also be identified on HRCT. High-resolution computed tomography is not needed for standard follow-up assessments, which can generally be performed with clinical evaluation, CXR, and PFT in patients with pulmonary sarcoidosis. Reserving the use of repeated HRCT for specific indications, eg, unexplained new findings on CXR, minimizes both cumulative radiation exposure to patients and costs.

Baseline electrocardiography should be obtained in all newly diagnosed patients. If findings are abnormal or if there are any cardiac symptoms, further evaluation with echocardiography, Holter monitoring, or cardiac imaging studies such as cardiac positron emission tomography or magnetic resonance imaging should be considered. In such cases, referral to a cardiac sarcoidosis specialist is recommended. We do not recommend routine echocardiography as a screening test, although this remains a controversial issue.[13] If pulmonary hypertension is suspected, echocardiography or right-sided heart catheterization should be considered. Other imaging studies such as fludeoxyglucose F 18—positron emission tomography have been used to identify extrathoracic involvement and identify targets for biopsy, especially in cases in which conventional evaluation has not yielded a clear diagnosis. Additionally, all patients with a confirmed diagnosis of sarcoidosis should undergo ophthalmologic evaluation to assess eye involvement.[3]

After the initial evaluation, most cases require tissue confirmation of the presence of nonnecrotizing granulomas, especially if treatment of sarcoidosis is contemplated. Exceptions may be those with Lofgren syndrome, typical chest imaging patterns, or high risk for biopsy complications or those who prefer not to undergo tissue confirmation. To obtain tissue, the most safe and accessible site is always favored. If skin biopsy is not an option, bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration biopsy (EBUS-TBNA) is a minimally invasive method to obtain tissue samples from enlarged intrathoracic lymph nodes.[20,21] The diagnostic yield of EBUS-TBNA for patients with suspected sarcoidosis and mediastinal adenopathy ranges from 80% to 90%.[22,23] Transbronchial biopsies of lung parenchyma can also be performed and have a diagnostic yield of 50% to 75% but are associated with a higher risk of pneumothorax and bleeding when compared with EBUS-TBNA. The use of rapid on-site evaluation (often called ROSE) of cytological specimens can increase the yield of EBUS-TBNA by helping the bronchoscopist determine the diagnostic adequacy of obtained samples and reducing the performance of redundant biopsies.[24]

Bronchoscopy may provide additional information during the airway inspection, such as the presence of mucosal cobblestoning (often seen in sarcoidosis), airway distortion, and findings that may suggest an alternative diagnosis. Bronchoalveolar lavage fluid (BALF) may be obtained to assess for infections and malignant cells. Total and differential cell counts on BALF can provide further supportive data for the diagnosis of sarcoidosis, particularly in challenging cases. A BALF $CD4^+/CD8^+$ lymphocyte ratio greater than 3.5 has a specificity of 94% and a sensitivity of 53% for diagnosis of sarcoidosis, and a lymphocyte differential count of more than 15% has a sensitivity as high as 90%.[25] If lymphoma is suspected, BALF flow cytometry can be also performed. Although bronchoscopy can be very helpful, it should not be used as a routine diagnostic procedure and instead be individualized depending on clinical presentation.

Additional diagnostic testing may be indicated depending on the clinical presentation, laboratory data, and results from the aforementioned tests. If clinical symptoms and imaging findings are compatible, biopsy has identified nonnecrotizing granulomas, and other potential causes have been reasonably excluded, the diagnosis of sarcoidosis can be established.

In most cases, patients with sarcoidosis are encountered by primary care physicians who initiate the diagnostic evaluation. Referral to a pulmonologist should be considered when biopsy confirmation is needed to establish the diagnosis, when patients are symptomatic and may require treatment, when complex multiorgan features or progressive disease is

present, and other situations in which the diagnosis remains uncertain or the physician believes that specialized evaluation and management are needed.

DIFFERENTIAL DIAGNOSIS

Although the presence of nonnecrotizing granulomas is a hallmark of sarcoidosis, it is not pathognomonic and can also occur in other diseases including malignant neoplasms ("sarcoid-like reaction"), infections (fungal, tuberculosis and atypical mycobacteria), common variable immunodeficiency syndrome, inhalational exposure–related diseases (eg, berylliosis, hypersensitivity pneumonitis), drug-induced lung diseases, and vasculitis. It is therefore important to exclude these identifiable causes of granulomatous inflammation in establishing a diagnosis of sarcoidosis.[3] Although necrotizing granulomas have been described in sarcoidosis, they are unusual in sarcoidosis and should lead to careful consideration of an alternative diagnosis. Data from our institution revealed that the most common causes of necrotizing granulomas were histoplasmosis, nontuberculous mycobacterial infections, rheumatoid nodules, and granulomatosis with polyangiitis (Wegener granulomatosis).[26] In particular, histoplasmosis can present with bilateral adenopathy and pulmonary infiltrates along with nonnecrotizing and necrotizing granulomas in the tissues. Tuberculosis also should be considered in patients who live in or have traveled to endemic regions.

Lymphoproliferative disorders can be misdiagnosed as sarcoidosis. Sarcoidosis is highly likely in certain clinical settings, such as in patients with asymptomatic bilateral hilar adenopathy and normal physical examination findings.[27] However, if suspicion for lymphoma is high, an excisional rather than an aspiration lymph node biopsy may be needed to ensure a correct diagnosis. The presence of prominent constitutional symptoms should raise suspicion for alternative diagnoses, especially lymphoproliferative disorders or infections.

TREATMENT

The decision to treat should be based on the presence of specific symptoms and disease progression evidenced by worsening functional status and imaging abnormalities.[28] Patients with severe symptoms or end-organ damage affecting the heart, eyes, or central nervous system will need treatment. However, many patients with pulmonary disease (the main focus of this review) can be monitored over a period of time because spontaneous resolution or stability without treatment may occur. Studies have found that up to half of the patients with pulmonary sarcoidosis have spontaneous improvement within the first 6 months.[29-31]

Once initiation of treatment is decided, the recommended drug of choice is an oral corticosteroid unless there are specific contraindications.[3] For patients with mainly pulmonary disease, studies have revealed that between 50% and 90% have a favorable response to corticosteroids, although sarcoidosis tends to relapse after discontinuation of treatment in about 20% to 74% of the cases.[30] For patients with severe end-organ damage, a corticosteroid-sparing agent may have to be initiated simultaneously because of the likelihood of prolonged duration of treatment (treatment recommendations for these patients will not be reviewed in this article because our focus is pulmonary disease).

There is no standard protocol for corticosteroid dose or duration of treatment. However, a 6-phase treatment regimen has been proposed by some experts in the field—initial dosing, taper to maintenance dose, maintenance dosing, taper off corticosteroids, monitor off treatment, and treatment of relapse.[32,33] The recommended initial dose of corticosteroid varies between 20 and 40 mg/d of prednisone or equivalent for 2 to 6 weeks. This initial treatment has also included alternate-day administration.[34] For patients whose disease responds to the initial dose, taper to a maintenance dose should be achieved between 6 weeks and 6 months after initiation of treatment.[35] The recommended maintenance dose is generally between 5 and 15 mg/d but should be tailored to the individual patient's response to therapy and treatment goals. Achieving a dose of 10 mg/d or less is ideal to minimize adverse effects from corticosteroid therapy, although this goal is not always possible. In general, patients require treatment for about 5 to 9 months before tapering off the corticosteroids, which can then take between 1 and 6 additional months. If taper is achieved, monitoring is necessary to identify relapses promptly.

Mayo Clin Proc. ■ July 2016;91(7):946-954 ■ http://dx.doi.org/10.1016/j.mayocp.2016.03.004
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When corticosteroids cannot be tapered to 10 mg/d or less, use of a corticosteroid-sparing agent should be considered. Most experts recommend once-weekly methotrexate as the first choice unless contraindicated.[35] Other second-line agents, with limited supporting data, are azathioprine and leflunomide. If these agents do not produce a response, then other drugs such as infliximab, mycophenolate mofetil, rituximab, cyclophosphamide, or corticotropin can be considered. Antimalarial agents, such as chloroquine and hydroxychloroquine, have also been used, particularly for patients with skin disease and hypercalcemia. For patients receiving prolonged courses of corticosteroids (more than 20 mg/d of prednisone or equivalent for more than 4 weeks or additional immunosuppressive therapy), we recommend *Pneumocystis jirovecii* pneumonia prophylaxis, although a consensus on this issue is lacking.[36,37] Osteoporosis precautions should be considered, but the presence of hypercalcemia may occasionally be an obstacle to conventional preventive measures.

Failure to respond to corticosteroid therapy should raise concerns about the possibility of nonadherence to treatment, comorbidities, superimposed complications (eg, infection, pulmonary hypertension), or incorrect diagnosis. Some patients who present with advanced fibrosis complicating sarcoidosis may not respond to even aggressive immunosuppressive therapy. The presence of fibrosis alone without evidence of progression should not be an indication for treatment per se. In those advanced cases, referral for lung transplant evaluation may be indicated.

CONCLUSION

Although pulmonary sarcoidosis can be a chronic granulomatous disease that progresses to fibrosis in some, most patients have a favorable prognosis including spontaneous resolution. It is critically important that the clinicoradiologic features and the results of diagnostic evaluation are consistent with sarcoidosis and that alternative diagnoses have been rigorously excluded. For patients with symptomatic pulmonary disease, it is important to establish functional and radiographic progression of disease along with treatment goals to ensure that the potential benefits of planned treatment outweigh the risk of adverse effects. As a corollary, close monitoring is recommended to avoid both undertreatment and overtreatment.

Abbreviations and Acronyms: **ACE** = angiotensin-converting enzyme; **BALF** = bronchoalveolar lavage fluid; **CXR** = chest radiography; **EBUS-TBNA** = endobronchial ultrasound-guided transbronchial needle aspiration biopsy; **HRCT** = high-resolution computed tomography; **PFT** = pulmonary function test

Potential Competing Interests: Dr Carmona is a coinvestigator in a RESAPH study, a registry for patients with sarcoidosis and pulmonary hypertension.

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