Extrapulmonary Sarcoidosis

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ABSTRACT

Sarcoidosis can affect any organ in the body. Frequently extrapulmonary manifestations of the disease are the major cause of morbidity. Treatment of extrapulmonary sarcoidosis often requires consideration of alternative immunosuppressive agents, topical therapy, or therapy that is not specifically directed against the granulomatous inflammation of the disease. This article reviews the clinical presentation and therapy of extrapulmonary sarcoidosis.

KEYWORDS: Sarcoidosis, extrapulmonary, diagnosis, therapy

Sarcoidosis is a multisystem idiopathic granulomatous disease. Although the lung is most commonly involved, the granulomatous inflammation of sarcoidosis can involve any organ. Extrapulmonary sarcoidosis may be the major manifestation of the disease and on occasion may be life threatening. It may also affect the therapeutic approach. This article reviews the clinical presentation, sequelae, and treatment of extrapulmonary manifestations of sarcoidosis.

DEMOGRAPHICS

Extrapulmonary sarcoidosis is common, although it is almost always found with concomitant thoracic involvement. This was confirmed in A Case Control Etiologic Study of Sarcoidosis (ACCESS) where 736 sarcoidosis patients were evaluated.[1] Six-hundred and ninety-nine (95%) of 736 had thoracic involvement, and exactly half (368/736) had concomitant extrathoracic disease.[2] Isolated extrathoracic sarcoidosis was observed in only 2% (14/736) of subjects.[2]

The prevalence of extrapulmonary sarcoidosis varies among populations. ACCESS demonstrated that there was more extrathoracic sarcoidosis in African-Americans than in Caucasians.[2] In addition, a univariate analysis comparing sarcoidosis organ involvement versus race, sex, and age found that there was more frequent involvement of the eye, liver, bone marrow, extrathoracic lymph nodes, and skin in African-Americans than in Caucasians.[2] Caucasians more frequently had a disorder of calcium metabolism related to sarcoidosis.[2] A study comparing the phenotypic expression of sarcoidosis in Finnish and Japanese patients found much higher rates of cardiac and eye involvement in the Japanese [cardiac: Japanese—31/686 (5%), Finnish—2/600 (0.3%); eye: Japanese—344/686 (50%), Finnish—27/600 (4.5%)].[3] Lupus pernio skin lesions of sarcoidosis (vide infra) are common in Puerto Ricans, whereas erythema nodosum lesions are most frequent in Europeans.[4]

Extrapulmonary sarcoidosis may be more frequent in females. Although not subjected to a statistical analysis, a study of sarcoidosis prevalence in a health maintenance organization database found that extrathoracic sarcoidosis was more common in females than in males (36.7% vs 31.7% in Caucasian sarcoidosis cases and 50.5% vs 28.6% in African American sarcoidosis cases).[5] ACCESS found that females had a higher prevalence of eye (13.9% vs 8.2%, $p < .05$), erythema nodosum (10.5% vs 4.5%, $p < .01$), and neurological sarcoidosis (6.0% vs 2.2%, $p < .05$) than males.[2] Males had a higher rate of disordered calcium metabolism than females (6.3% vs 2.1%, $p < .01$).[2]

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There is a paucity of data concerning the prevalence of extrathoracic sarcoidosis in relation to age. In ACCESS, organ involvement was similar between those less than 40 years of age and those aged 40 years or greater with two exceptions. Peripheral lymph node involvement was more common in those less than 40 (20.0% vs 11.2%, $p < .005$), and disordered calcium metabolism was more common in those greater than or equal to 40 (5.5% vs 1.5%).[2]

Families with two or more first-degree relatives affected with sarcoidosis are a common occurrence.[6] Very few studies have analyzed whether extrapulmonary sarcoidosis is more common in affected family members than in a general sarcoidosis population. In one study of 340 affected sibling pairs, extrathoracic involvement was not found in both siblings more often than expected by chance alone.[7] A significant but weak concordance among siblings was found for ocular ($\kappa = .16$; $p < .05$) and liver involvement ($\kappa = .16$; $p < .05$.[7] No other concordance was demonstrated for five other extrathoracic organ systems evaluated.[7] Modeling phenotypic expression in sibling pairs using logistic regression did show that the presence of ocular and liver sarcoidosis in the sibling diagnosed first conferred a statistically significant increased risk to the second affected sibling for having those organs involved [odds ratio (OR) = 3; 95% confidence interval (CI) = 1.7 to 5.4 for ocular; OR = 3.3; 95% CI = 1.5 to 7.4 for liver].[7]

SPECIFIC ORGAN INVOLVEMENT

Skin

Skin lesions are divided into two categories: specific and nonspecific.[8] Specific lesions demonstrate granulomatous inflammation on biopsy. Nonspecific lesions are reactive inflammatory skin responses that show no granulomatous inflammation. Erythema nodosum is the predominant nonspecific cutaneous manifestation of sarcoidosis. It presents as tender nodules on the extremities. Erythema nodosum is not specific for sarcoidosis because it is associated with several other medical conditions, including infections, malignancies, and drugs.[9] However, the clinical findings of Löfgren's syndrome, including erythema nodosum coupled with bilateral hilar adenopathy on chest radiograph and often fever and ankle arthritis, strongly suggest the diagnosis of sarcoidosis.[4,10] This presentation is thought to be specific for the diagnosis unless an alternative explanation for these findings is clinically apparent; the diagnosis can then be made clinically without the need for histologic confirmation.[4,11] Erythema nodosum and other types of nonspecific skin lesions tend to be associated with an acute form of sarcoidosis with eventual resolution of the disease.[10]

Specific skin lesions are usually asymptomatic. Cosmetic disfigurement is the most common complaint.[8] Pruritus and pain are rare. Cutaneous lesions may occur before, coincident with, or after systemic involvement. Almost all morphologies have been reported, including macules, papules, plaques, hypopigmented patches, subcutaneous nodules, ichthyosis, ulcers, pustules, erythroderma, and localized alopecia.[8]

The most common presentation is the papular form. These lesions are usually firm 2 to 5 mm papules that often have a translucent red-brown or yellow-brown appearance.[8] These lesions occur most commonly on the face and neck, with a predilection for the periorbital skin.

Lupus pernio refers to indolent, red-purple or violaceous sarcoidosis skin lesions that may affect the cheeks, nose, lips, and ears (Fig. 1).[10] These lesions are often disfiguring and can erode into cartilage and bone, especially around the nose. The lesions are more common in African-Americans than Caucasians.[12] Lupus pernio portends a poor prognosis of sarcoidosis and is associated with more severe pulmonary disease.[13]

Treatment of sarcoidosis skin lesions is not required if they are stable and not of cosmetic import. Localized lesions may be treated with topical corticosteroids in the form of creams or corticosteroid injections. Care must be taken when these agents are used on the face because they may cause skin atrophy. Topical tacrolimus has also been effective in some cases.[14]

If the skin lesions are diffuse or not responsive to topical agents, systemic therapy is required. In general, corticosteroids are the drug of choice for the treatment of skin sarcoidosis. The recommended initial dose is similar to that for pulmonary sarcoidosis: 20 to 40 mg of prednisone equivalent/day.[4,10] Corticosteroids should be weaned to the lowest effective dose over 3 to 9 months. Consideration should be given to alternative agents if corticosteroids cannot be weaned off or reduced to a low dose (< 10 mg daily prednisone equivalent). Effective alternative agents for skin sarcoidosis include methotrexate,[15] hydroxychloroquine,[16] chloroquine,[17] thalidomide,[18] tetracycline derivates

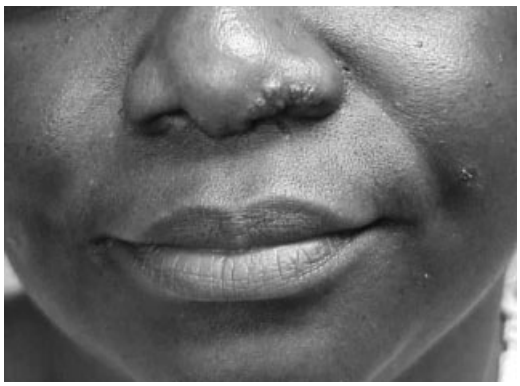

Figure 1 Characteristic lupus pernio lesions of sarcoidosis on the nose (the patient has given permission for use of this picture).

(minocycline, doxycycline),[19] monoclonal antibodies versus tumor necrosis factor α (TNF-α), such as infliximab,[20] leflunomide,[21] allopurinol,[22] isotretinion,[23] and fumaric acid esters[24] Resolution of sarcoidal skin manifestations after phototherapy has also been described.[25]

Eye

Sarcoidosis can affect any part of the eye and may be the major manifestation of the disease.[26] It can occur at any time during the course of sarcoidosis and even "predate" the disease because some patients initially diagnosed with idiopathic uveitis will eventually develop systemic signs of sarcoidosis.[27] Therefore, it is important that all sarcoidosis patients are evaluated for eye involvement and that sarcoidosis considered as the cause of abnormal eye findings.[26]

Ocular involvement occurs in 10 and 50% of American and European sarcoidosis patients and in 50 to 90% of Japanese patients with the disease.[26] It is more common in African-Americans than in Caucasians.[2,28] Sarcoidosis eye involvement is associated with the DRB1* 0401 human leukocyte antigen (HLA) polymorphism, which suggests that there is a genetic basis for this disease phenotype.[29]

Uveitis is the most common ocular manifestation of sarcoidosis.[27] Anterior uveitis occurs in the anterior chamber and may cause symptoms of blurred vision, red eye, painful eye, or photophobia.[27] However, up to one third of patients with anterior uveitis from sarcoidosis will have no symptoms (a "quiet eye").[30] The ocular examination via a slit lamp often reveals iris nodules at the papillary surface (Koeppe nodules), the iris surface (Busacca nodules), and "mutton fat" keratic precipitates, which represent globules composed of inflammatory cells at the posterior corneal surface (Fig. 2).[27] None of these findings is specific for sarcoidosis, although they are highly suggestive.[27]

Intermediate uveitis results in inflammation of the vitreous, pars plana (the anterior border of the retina), and the peripheral retina. Granulomatous inflammation in this area results in floaters, blurred vision, pain, photophobia, and red eye.[27] The funduscopic examination may reveal vitreous cell infiltrates and accumulation of inflammatory cells along the pars plana known as "snow banking."[26,27]

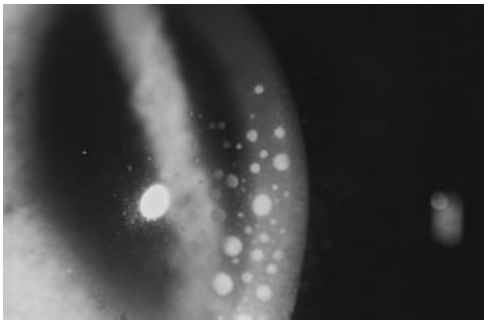

Figure 2 Keratic precipitates in a patient with anterior sarcoid uveitis.

Posterior uveitis results in a retinal perivasculitis.[26] This may result in a periphlebitis that often does not induce retinal exudation.[26] However, if the periphlebitis occludes the venous circulation, retinal hemorrhage develops.[31] This may result in neovascularization, vitreous hemorrhage, and proliferative retinopathy.[26] The patient may experience vision loss and blurred vision. Funduscopic examination may show patchy exudates. When the exudates appear along the vein and if the periphlebitis is extensive, their appearance resembles candle wax.[26,32]

There are many infectious and noninfectious causes of uveitis. Sarcoidosis is not the most common cause of uveitis in unselected patients. In two series, sarcoidosis was the cause of uveitis in 2.5 and 12% of cases, respectively.[33,34] In a third study, where all the subjects were from the southeastern United States, sarcoidosis was the cause of uveitis in 11%, and still only 25% in the African American subgroup.[35]

Sarcoidosis of the conjunctiva occurs in 6 to 40% of cases.[26] In three quarters of cases, conjunctival involvement is present at diagnosis.[36] Patients with sarcoid conjunctivitis are usually asymptomatic but may have red eyes or dry eyes.[27] The yield of conjunctival biopsy for the diagnosis of sarcoidosis is ~33% in unselected sarcoidosis patients.[37,38] The diagnostic yield of biopsy may be as high as 67% if conjunctival nodules are present.[37] It is controversial whether blind biopsy of normal-appearing conjunctival tissue is of value, with one study reporting a yield of 30%, whereas others have found such biopsies to be fruitless.[39,40] Recently, in vivo confocal microscopy has been advocated for the diagnosis of conjunctival sarcoidosis based on a typical appearance.[41] This technique may also be useful to determine when a conjunctival biopsy will confirm the diagnosis of sarcoidosis.[41]

Lacrimal gland enlargement is clinically apparent in 15 to 28% of sarcoidosis patients,[36,42] but up to 88% of sarcoidosis patients may have lacrimal involvement detected on gallium-67 scanning.[43] Lacrimal gland involvement usually causes no symptoms.[26] On occasion, affected patients will develop a keratoconjunctivitis sicca syndrome.[44] Enlargement of the lacrimal gland may be palpable on physical examination and rarely so massive that it causes proptosis.[45]

Although optic neuropathy is a rare manifestation of sarcoidosis, it is a feared complication because it can result in rapid, permanent vision loss.[27,46] Patients usually present with rapid loss of vision or color vision in one eye.[26] Funduscopic exam shows papillitis, papilloedema, and neovascularization with ultimate optic atrophy. This condition is an

ophthalmologic emergency and requires immediate systemic therapy.[26]

Miscellaneous manifestations of ocular sarcoidosis include scleritis,[47] orbital mass lesions,[48] extraocular muscle involvement,[49] and involvement of the cornea.[26,46] Furthermore, glaucoma may occur from granulomatous inflammation of Schlemm's Canal.[50] Cataracts may occur from chronic inflammation of the eye.[42] It is often problematic to distinguish the development of glaucoma and cataracts from sarcoidosis as opposed to corticosteroid therapy used to treat the disease.[42]

Any degree of eye inflammation requires treatment. Corticosteroids are the mainstay of treatment.[26] Anterior uveitis can be treated with topical corticosteroid eye drops. When iritis is severe and does not respond to eyedrops, subconjunctival injections of corticosteroids may be efficacious.[26] Mydriatics should always be instilled to suppress inflammation and prevent the development of posterior synechia (adhesion of the iris to the lens).[26] Intraocular pressure should be closely monitored because both sarcoidosis and corticosteroids can induce a rise in intraocular pressure.

Systemic corticosteroids are indicated for anterior uveitis that fails to respond to topical steroids and for intermediate and posterior uveitis that is too deep to be reached with topical therapy.[26] The initial dose is usually 40 mg/day of prednisone or prednisolone that is tapered over 6 to 12 months.[26]

If sarcoid uveitis fails to respond to systemic corticosteroids or requires high doses, alternative medications should be considered. In these instances, corticosteroids are usually required but often the corticosteroid dose can be successfully reduced (the alternative medications act as "steroid sparing agents"). Alternative agents that have been reported to be of benefit for ocular sarcoidosis include methotrexate,[51] azathioprine,[52] leflunomide,[53] and infliximab.[54]

Liver

The reported frequency of hepatic sarcoidosis ranges widely depending on the method of detection. Fifty to 65% of sarcoidosis patients demonstrate granulomas on liver biopsy.[55] The frequency of liver function test abnormalities in sarcoidosis is as high as 35%,[56] which is lower than the frequency of histological hepatic involvement. The frequency of signs or symptoms of hepatic involvement is lower still at ~5 to 15%.[57–61] Therefore, sarcoidosis of the liver is often present histologically but usually does not cause liver blood test abnormalities or significant symptoms.

Hepatic sarcoidosis is at least twice as common in African Americans compared with Caucasians.[2,56,61] There is no increased prevalence based on age or gender.[2,61] No geographic area of high prevalence has been identified.[62]

Most patients with hepatic sarcoidosis are asymptomatic.[56,63] The disease is often discovered on liver biopsy as part of a workup for abnormal serum liver function tests or abnormalities on an abdominal chest computed tomographic (CT) scan. Abdominal pain and pruritus are two of the more common symptoms, with the former present in 15% (15/100) of cases.[61] Fever, weight loss, and jaundice are present in less than 5% of cases.[60,61] Hepatomegaly is found in 5 to 15% of patients with sarcoidosis.[57,59]

The most common liver function test abnormality in hepatic sarcoidosis is an elevated serum alkaline phosphatase, which is found in more than 90% of patients with signs or symptoms of hepatic sarcoidosis[56,64,65] but is present in as few as 15% (32/217) of patients with histological evidence of disease.[60] Occasionally, this elevation is five to 10 times the upper limits of normal or greater.[64,65] Fifty to 70% of patients with clinical evidence of hepatic sarcoidosis have elevations in serum transaminases,[61,64] which are usually less elevated than the serum alkaline phosphatase. Hyperbilirubinemia, hypoalbuminemia, and hepatic encephalopathy may rarely occur with chronic progressive disease.[65,66]

Although the abdominal CT radiographic features of hepatic sarcoidosis have been well described, the exact frequency of hepatic abnormalities is unknown because all series have involved a selection bias and/or have been retrospective. Hepatomegaly is the most common liver abnormality detected on CT[67–70] and is often associated with splenomegaly.[67] Hepatomegaly from sarcoidosis may occur in patients with normal (Scadding stage 0) radiographs.[67]

Hepatic nodules are found in less than 5% of patients in most series,[67,70] although frequencies as high as 53% (17/32) have been reported.[68] The nodules are usually discrete and of low attenuation, requiring intravenous contrast to be visualized.[67,68,71,72] They are always multiple and usually innumerable, with an average size of 0.6 to 0.75 cm in diameter but may be as large 2.0 cm and tend to become confluent as they enlarge.[67,68] Hepatic nodules are seen less frequently than splenic nodules.[67,68,73] The differential diagnosis of low-attenuation hepatic nodules includes various infections, metastatic disease, and lymphoma.[68]

Rarely, hepatic sarcoidosis will cause a chronic cholestasis syndrome featuring pruritus, jaundice, hepatomegaly, and marked elevations in serum alkaline phosphatase and cholesterol.[66,74–76] This syndrome is more common in African Americans.[75,77] The histological evolution of the disease suggests a slow, progressive destruction of the bile ducts by granulomas.[74] The histology may mimic primary biliary cirrhosis.[62] This granulomatous cholangitis leading to ductopenia seems to be the underlying mechanism causing chronic cholestasis.[66] Occlusion of intrahepatic portal vein branches by granulomatous inflammation may cause portal hypertension.[66]

An extremely rare cause of jaundice from sarcoidosis may occur from extrinsic compression of the biliary duct from porta hepaticus adenopathy.[78,79] In this situation, the jaundice usually responds to corticosteroid therapy with shrinkage of the lymph nodes.[78,79]

Cirrhosis has been reported in 6% (6/100) of patients with hepatic sarcoidosis.[61] Some of these patients also have cholestatic features, with loss of bile ducts indicating a pattern of primary biliary cirrhosis as previously described.[61] However, cirrhosis without a cholestatic pattern may also be seen.[61,66,80,81]

Portal hypertension has been estimated to occur in 3% of patients with hepatic sarcoidosis.[61] Although portal hypertension may occur via several mechanisms, the most common is from granulomas in the portal areas that restrict portal flow, causing a presinusoidal block.[80–82] Portal hypertension can lead to esophageal and gastric variceal bleeding and death.[83,84] Although all patients with portal hypertension from sarcoidosis have significant hepatocellular disease, portal hypertension is the primary clinical abnormality.[65]

Rarely, a patient with hepatic sarcoidosis may develop the Budd-Chiari syndrome.[85,86] Hepatic veins are narrowed by sarcoid granulomas, resulting in venous stasis and occlusion.

Most patients with hepatic sarcoidosis do not require treatment.[62] Although treatment with corticosteroids can improve liver function tests in approximately half of asymptomatic patients, three fourths of such patients who are not treated undergo spontaneous improvement in liver function tests and the remainder remain stable.[56] Furthermore there is evidence that corticosteroid treatment of hepatic sarcoidosis promotes relapse.[87] On the basis of these data, therapy for hepatic sarcoidosis is not indicated in asymptomatic patients with liver function test elevations. Such patients should be followed with serial liver function tests, although it is rare for liver failure to develop.[56]

Diffuse granulomatous hepatitis from sarcoidosis may require treatment when patients develop fever, nausea, vomiting, weight loss, or right upper quadrant abdominal pain.[88] Corticosteroids are usually effective in alleviating these symptoms and reducing liver function test elevations.[88,89] Many patients require a daily dose of prednisone in the 10 to 15 mg range. Therapy is often required for 1 to several years.[88] Despite the potential risk of hepatic toxicity from methotrexate, it has been shown to be effective and to reduce liver function test abnormalities and to be corticosteroid sparing.[88,90]

As mentioned previously, patients with hepatic sarcoidosis may develop a chronic cholestatic syndrome with jaundice, fever, malaise, weight loss, anorexia, pruritus, and a cholestatic pattern of abnormal liver function tests.[74–76] These symptoms are often severe and require treatment. Corticosteroids in doses of 30 to 60 mg/day of prednisone equivalent may improve symptoms, lower serum alkaline phosphatase levels, and improve hepatomegaly.[74,91] Often the cholestatic syndrome does not resolve and eventually progresses.[74,91] Ursodeoxycholic acid, which inhibits intestinal absorption and increases biliary secretion of cholic and chenodeoxycholic acids,[92] has been successfully used for the cholestatic syndrome of hepatic sarcoidosis.[93,94] A dose of 10 mg/kg/day has been shown to be effective in resolving symptoms and serum liver function test abnormalities.[93,94]

Portal hypertension often develops with hepatic sarcoidosis as a result of biliary fibrosis or cirrhosis.[80] Because these fibrotic changes are permanent, sarcoidosis-induced portal hypertension is usually unresponsive to corticosteroids or other therapy for sarcoid granulomas,[80,82,95] although hepatomegaly and serum liver function test abnormalities may improve.[81,82] Because on occasion portal hypertension is the result of granulomas in the portal areas that produce pressure that restricts portal flow, a therapeutic trial of corticosteroids is probably warranted. Otherwise, therapy for portal hypertension from sarcoidosis is treated in a similar fashion as portal hypertension from other causes, with intravenous octreotide or vasopressin and a Sengstaken-Blakemore tube for acute esophageal or gastric variceal bleeding, sclerotherapy of varices, β blockers, portocaval, splenorenal or transjugular intrahepatic portal-systemic shunt (TIPS), splenectomy, and liver transplantation as a last resort for refractory cases.[80–82,84,96,97]

Liver transplantation has been successfully performed for end-stage liver disease from sarcoidosis.[98] Survival is comparable to liver transplant recipients with other end-stage liver diseases.[98] It is prudent to give patients with end-stage liver disease from sarcoidosis a corticosteroid trial prior to considering liver transplantation, even though they are unlikely to respond to therapy.[62] Ideal candidates for liver transplantation should have minimal disease in extrahepatic organs. Even in these instances, worsening extrahepatic sarcoidosis may develop after liver transplantation.[99] In addition, sarcoidosis may recur in the allograft[100–102] similar to other organ transplants in sarcoidosis patients.[103]

Heart

Cardiac sarcoidosis is a potentially life-threatening complication of the disease. Although cardiac sarcoidosis is responsible for less than 10% of deaths from sarcoidosis in the United States,[104] death may occur suddenly, and failure to treat this condition may result in permanent injury.[105] Cardiac sarcoidosis is much more common in Japan than in Europe or North America.[4]

Only 5% of patients with sarcoidosis have signs or symptoms of cardiac involvement,[106] although 25% of patients show evidence of granulomatous inflammation of the heart on autopsy.[107] Cardiac sarcoidosis may

become manifest several years after the initial diagnosis of sarcoidosis is established.[108] Sarcoidosis can affect any portion of the heart and produce a myriad of clinical problems that may simulate other more common disorders. Granulomas may massively infiltrate the myocardium and cause congestive heart failure[106,109,110] or deposit in papillary muscles resulting in mitral regurgitation.[111] Sarcoidosis may cause granulomatous pericarditis with or without pericardial effusion.[112,113] Long-term granulomatous inflammation may generate myocardial scarring with the formation of ventricular aneurysms.[114]

The myocardial conducting system is especially vulnerable to sarcoid granulomas, which may result in serious consequences that include complete atrioventricular block, premature ventricular contractions, ventricular arrhythmias, and sudden death.[106,109,112,113,115–117] The risks of sudden death and progressive congestive heart failure are the most feared complications of cardiac sarcoidosis and underscore why these patients must be diagnosed early and followed with extreme vigilance. It is for these reasons that all patients diagnosed with sarcoidosis are recommended to have a baseline electrocardiogram, and all unexplained electrocardiographic abnormalities should be investigated.[4]

Although a section of this manuscript concerning the diagnosis of extrapulmonary sarcoidosis is forthcoming, the diagnosis of cardiac sarcoidosis deserves special mention. Although an endomyocardial biopsy that reveals noncaseating granulomas is the gold standard for the diagnosis, it is positive in less than one quarter of cases because of the patchy distribution of the disease.[118] When cardiac sarcoidosis causes conduction disturbances, the diagnostic yield of endomyocardial biopsy is particularly low at less than 10%.[118] Even when sarcoidosis causes a cardiomyopathy, the yield from endomyocardial biopsy is approximately one third.[118]

Consequently, noninvasive tests are usually relied upon to establish the diagnosis of cardiac involvement with sarcoidosis. Available tests include the electrocardiogram (ECG),[108,113,115] echocardiogram,[108,113] thallium-201 perfusion scan,[119,120] gallium-67 scan,[119,121,122] gadolinium-enhanced magnetic resonance (MR) scan,[123–125] and positron emission tomography (PET).[126] The accuracy of thallium and gallium scans is enhanced by using a single-photon-emission CT (SPECT) technique.[121,122] Thallium defects from ischemic heart disease can often be differentiated from sarcoid heart disease in that the latter may decrease in size with exercise (reverse distribution).[106]

Each of these noninvasive tests has a different sensitivity and specificity. Unfortunately, an algorithm for the diagnosis of cardiac sarcoidosis has not been established because of the diagnostic shortcomings of the only available "gold standard," which is endomyocardial biopsy. Moreover, existing noninvasive tests have rarely been compared within the same clinical trials. When such comparisons are made, there is poor concordance, such that a negative result on any one test does not ensure the possibility of another test being positive.[108,113,125]

Nevertheless, guidelines for the application of noninvasive tests to the diagnosis of cardiac sarcoidosis have been developed by the Japanese Ministry of Health and Welfare[127] and the research group conducting ACCESS (Table 1).[128] Both of these guidelines combine the results of noninvasive tests with histological confirmation of noncaseating granulomatous inflammation in an extracardiac organ and evidence of unexplained arrhythmias, conduction system abnormalities, or ventricular dysfunction.

Because of the lack of controlled studies, the approach to the treatment of cardiac sarcoidosis remains unclear. Therapy often involves a combination of approaches, including antisarcoidosis medications, antiarrhythmic drugs, ionotropes, and pacemaker/defibrillator implantation. Early and long-term corticosteroid therapy has been shown to improve the prognosis of cardiac sarcoidosis.[109] In one of the largest studies of 95 Japanese patients with cardiac sarcoidosis,[109] survival rates were 85% at 1 year, 72% at 3 years, 60% at 5 years, and 44% at 10 years. Thirty percent died of congestive heart failure and 12% experienced sudden death. A multivariate analysis identified New York Heart Association (NYHA) function class (hazard ratio = 7.7 per NYHA class, $p = .0008$), sustained ventricular tachycardia (hazard ratio = 7.2, $p = .03$), and left ventricular end-diastolic diameter (hazard ratio = 2.6 per 10 mm increase, $p = .02$) as independent predictors of mortality.[109] Prognosis was excellent in those treated early with corticosteroids before the development of left ventricular dysfunction. Although some have recommended that high-dose corticosteroids be used for cardiac sarcoidosis, this study failed to reveal a difference in outcome between those receiving ≥ 40 of prednisone/day and those receiving < 30 mg/day. Some have advocated that lifelong low-dose (5 to 10 mg of prednisone equivalent/day) is beneficial for the long-term prognosis.[112]

These data suggest that suggest that symptomatic cardiac sarcoidosis be treated early and aggressively. Subjects should be monitored closely for the development of left ventricular dysfunction, which should suggest that the corticosteroid dose be increased, an alternate agent be added, or cardiac transplantation be considered if the patient fails to respond. There is minimal data concerning alternative medications to corticosteroids for the treatment of cardiac sarcoidosis. These medications have included methotrexate,[113] cyclophosphamide,[113] cyclosporine,[113] and infliximab.[129] The latter drug is problematic because infliximab has a black box warning for use in patients with congestive

Table 1 Clinical Criteria for Extrapulmonary Sarcoidosis Organ Involvement in Patients with Biopsy-Confirmed Sarcoidosis in Another Organ*

Organ	Definite	Probable	Possible
SKIN	1. Lupus pernio 2. Annular lesion 3. Erythema nodosum	1. Macular/papular 2. New nodules	1. Keloids 2. Hypopigmentation
EYES	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis	1. Blindness	1. Glaucoma 2. Cataract
LIVER	1. Liver function tests > three times normal	1. Compatible computed tomography (CT) scan 2. Elevated alkaline phosphate	
HYPERCALCEMIA/ HYPERCALCIURIA/ NEPHROLITHIASIS	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis-no stone analysis 2. Nephrolithiasis with negative family history for stones
NEUROLOGICAL	1. Positive magnetic resonance imaging (MRI)with uptake in meninges or brainstem 2. Cerebrospinal fluid with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's palsy 5. Cranial nerve dysfunction 6. Peripheral nerve biopsy	1. Other abnormalities on magnetic resonance imaging (MRI) 2. Unexplained neuropathy 3. Positive electromyogram	1. Unexplained headaches 2. Peripheral nerve radiculopathy
RENAL	1. Treatment responsive renal failure	1. Steroid responsive renal failure in patient with diabetes and/or hypertension	1. Renal failure in absence of other disease
CARDIAC	1. Treatment responsive cardiomyopathy 2. Electrocardiogram showing intraventricular conduction defect or nodal block 3. Positive gallium scan of heart	1. No other cardiac problem and either: - Ventricular arrhythmias - Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: - Cardiomyopathy - Ventricular arrhythmias
NON-THORACIC LYMPH NODE		1. New palpable node above waist 2. Lymph node > 2 cm by computed tomographicy (CT) scan	1. New palpable femoral lymph node
BONE MARROW	1. Unexplained anemia 2. Leukopenia 3. Thrombocytopenia		1. Anemia with low mean corpuscular volume (MCV)
SPLEEN		1. Enlargement by: - Exam - Computed tomography (CT) scan - Radioisotope scan	
BONE/JOINTS	1. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
EAR/NOSE/THROAT		1. Unexplained hoarseness with exam consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness

Table 1 *(continued)*

Organ	Definite	Probable	Possible
PAROTID/SALIVARY GLANDS	1. Symmetrical parotitis with syndrome of mumps 2. Positive gallium scan (''Panda sign'')		1. Dry mouth
MUSCLES	1. Increased creatine phosphokinase (CK)/aldolase, which decreases with treatment	1. Increased creatine phosphokinase (CK)/aldolase	1. Myalgias responding to treatment

*There can be no other explanation for the clinical finding in this Table1 for these criteria to be valid. In addition, biopsy of each of these organs would constitute ''definite'' involvement. Adapted from Judson et al.[128]

heart failure. Some have advocated adding additional immunosuppressives, such as azathioprine or hydroxychloroquine to methotrexate plus low-dose corticosteroids for cardiac sarcoidosis.[130]

Arrhythmias, especially ventricular arrhythmias, should also be aggressively treated. Antiarrhythmic drug therapy is empirical.[105] Amiodarone is the preferred drug but appears to be less effective than in other cardiomyopathies[105] and may cause pulmonary toxicity in patients with concomitant pulmonary sarcoidosis. The value of electrophysiological examinations for choosing antiarrhythmic therapy, estimating the probability of cardiac events, and determining the need for placement of an automatic implantable cardioverter defibrillator (AICD) is extremely limited.[105,131] Indeed, cardiac sarcoidosis patients found noninducible with electrophysiological testing have experienced sudden death,[131] probably because the granulomatous lesions are not static and can worsen over time.

The treatment of asymptomatic cardiac sarcoidosis is controversial. One study demonstrated that sarcoidosis patients with asymptomatic cardiac involvement had an excellent long-term prognosis without therapy.[132] However, there were only three asymptomatic patients out of 82 patients screened, making this conclusion suspect.

Neurological

Clinically apparent involvement of the nervous system occurs in 5 to 15% of sarcoidosis patients.[133,134] However, as with other forms of sarcoidosis, subclinical neurological disease is much more frequent.[135,136] Neurosarcoidosis may appear as an acute explosive illness or as an indolent illness.[136] Neurosarcoidosis is responsible for ~15% of sarcoidosis deaths in the United States.[104] Any part of the nervous system may be affected, including the cranial nerves, hypothalamus, pituitary gland, meninges, parenchyma of the brain, brainstem, spinal cord, subependymal layer of the ventricular system, peripheral nerves, and blood vessels supplying the nervous structures.[136]

Cranial neuropathy is the most frequent neurological complication of sarcoidosis.[133,136] A peripheral seventh nerve palsy (Bell's palsy) is the single most common cranial nerve lesion and is the most common neurological manifestation of sarcoidosis overall.[1,136] It may be unilateral or bilateral and often predates the diagnosis of sarcoidosis.[136] The optic nerve is the second most likely cranial nerve involved.[136] Multiple sclerosis must also be considered when a young person presents with optic neuritis. In these cases, a chest radiograph showing typical features of sarcoidosis strongly suggests this diagnosis.[137] Any other cranial nerve may be affected, and in many series, the nerves supplying the extraocular muscles are commonly involved.[138,139]

Sarcoidosis may cause aseptic meningitis that may be acute or chronic.[136] Symptoms include stiff neck, fever, and headache. Cerebrospinal fluid (CSF) findings typically shows a pleocytosis of lymphocytes,[140] with a low CSF glucose in 20% of cases.[141] The basal meninges may be affected, resulting in cranial neuropathies.[136] Chronic meningitis is often recurrent and requires long-term therapy, whereas acute meningitis responds favorably to corticosteroids.[136]

Cerebral sarcoidosis lesions may develop in any portion of the brain and tend to be more common in supratentorial locations than in the cerebellum.[142] These lesions may cause symptoms consistent with any space-occupying lesions of the brain and therefore may be life threatening. There is a predilection for the hypothalamus and pituitary gland[133,138,139,142–144] that may result in diabetes insipidus,[145,146] hypogonadism,[146] or adenopituitary failure.[147]

Spinal sarcoidosis is underappreciated. Patients may present with transverse myelopathy, paresis, autonomic dysfunction, radicular syndrome, and cauda equina syndrome.[136,148,149] Sarcoidosis may cause a peripheral neuropathy.[133,139] It may manifest as a mononeuropathy, polyneuropathy, Guillain-Barré syndrome and symmetric distal polyneuropathy that may be sensorimotor, mostly sensory, or mostly motor.[136,139,150,151] Seizures may be the first manifestation of neurosarcoidosis,[139,152] and the presence of seizures portends a poor

prognosis.[136] Granulomatous infiltration of the central nervous system from sarcoidosis can result in cognitive decline to frank psychosis.[138,139,153] Sarcoidosis may also cause a small-fiber neuropathy that usually cannot be detected on routine nerve conduction testing.[154] Special testing of cold and heat discrimination is often needed to secure this diagnosis.[155] Small-muscle neuropathy may be responsible for disabling neuropathic pain and paresthesias, especially during sleep.[136] It may cause restless leg syndrome and periodic limb movement disorder.[156]

The diagnosis of neurosarcoidosis is often problematic because biopsy of neural tissue is an invasive procedure. A tissue diagnosis of sarcoidosis can often be established in another location. In one series of neurosarcoidosis, other systemic manifestations were found in 97%, intrathoracic manifestations were found in 88%, and 82% had an abnormal chest radiograph.[133] Therefore, a search for extraneural locations should always be conducted, and this should involve a physical examination, chest radiograph, liver function tests, and complete blood count. An ophthalmic evaluation (searching for conjunctival or lacrimal gland involvement) should be performed. If the aforementioned tests are unrevealing, a whole-body gallium-67 or PET scan should be considered to identify a potential diagnostic biopsy site.[136,157] If a biopsy of an extraneural tissue demonstrates granulomatous inflammation of unknown cause, certain neurological findings have been established to make the diagnosis of neurosarcoidosis "definite" or "probable" (see Table 1).[128]

Corticosteroids are the cornerstone of treatment for neurosarcoidosis.[158,159] However, the response to corticosteroids is inconsistent, and high doses are often required.[138,139,158–160] Some have advocated a starting dose of 40 to 80 mg/day of prednisone equivalent.[158] Relapses are common when the prednisone dose is lowered to 20 to 25 mg/day.[138]

If the corticosteroid dose cannot be tapered to 10 mg/day of prednisone equivalent over the first several months, alternative agents should be considered. Most of these agents are not effective alone but may be corticosteroid-sparing. Such agents have included methotrexate,[160] chloroquine,[158,161] hydroxychloroquine,[158,161] azathioprine,[162] cyclophosphamide,[160,163] cyclosporine,[162,164] and infliximab.[165] Although reports of these drugs have been for the most part anecdotal and with a small number of patients, methotrexate and cyclophosphamide appear to be the most efficacious. Radiation therapy has been used in refractory cases.[166]

Calcium Metabolism

Calcium metabolism is disregulated in active sarcoidosis. This may result in hypercalciuria, hypercalcemia, and nephrolithiasis with possible renal insufficiency.[167] The primary abnormality in calcium metabolism stems from an increase in 1-α hydroxylase activity in sarcoid alveolar macrophages that converts 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D, the active form of the vitamin.[168–170]

The reported incidence of hypercalcemia in sarcoidosis is variable, having been reported from 2 to 63% in various series.[167] These disparate findings may be attributable to differences in sunlight exposure, skin color, dietary calcium, and genetic factors of the populations studied. Hypercalciuria is three times more common than hypercalcemia in sarcoidosis.[171] Undetected, persistent hypercalcemia and hypercalciuria can result in nephrocalcinosis, renal stones, and renal failure.[172] Therefore, it has been recommended that all patients diagnosed with sarcoidosis have serum calcium and creatinine measured and a urinalysis performed.[4] It should be noted that these screening tests will not detect hypercalciuria; therefore, renal complications may develop if these screening tests are normal. However, obtaining a 24 hour urine for calcium and creatinine on every sarcoidosis patient is too cumbersome to recommend routinely.

The treatment of hypercalcemia includes: (1) reduction of oral calcium supplements, dietary calcium, and vitamin D; (2) maintenance of an expanded intravascular volume; (3) reduction of the inappropriate production of 1, 25-dihydroxyvitamin D by sarcoid macrophages and granulomas; and (4) reduction of 1, 25-dihydroxyvitamin D–induced intestinal calcium absorption and bone resorption.[173]

Mild hypercalcemia can be treated initially with the first two approaches: restriction of dietary calcium and increased fluid intake. The patient should be advised to avoid sunlight, curtail intake of major sources of dietary calcium and vitamin D, and drink a large amount of fluids.[173]

If the serum calcium is greater than 11 mg/dL, the serum creatinine is elevated, or the patient has nephrolithiasis, drug therapy is usually required. The drug of choice is prednisone at an initial daily dose of 20 to 40 mg/day.[173] Corticosteroids cause a rapid decline in serum calcium in 3 to 5 days and in urinary calcium excretion in 7 to 10 days.[173] Failure of the serum calcium to normalize on this regimen in 2 weeks should alert the clinician to an alternate or coexisting disorder such as hyperparathyroidism, lymphoma, carcinoma, and myeloma.[173] Once the calcium disorder is brought under control, the corticosteroid dose can be lowered over 4 to 6 weeks.[173] Serum calcium and urinary calcium excretion rate should be closely monitored. If the patient develops unbearable corticosteroid side-effects or fails to respond, chloroquine,[174] hydroxychloroquine,[175] and ketoconazole[176] have been used successfully.

Sarcoidosis of the Upper Respiratory Tract

The incidence and prevalence of sarcoidosis of the upper respiratory tract (SURT) is unknown but probably

underrecognized.[177] The disease may affect any part of the upper airway, including the nose, sinuses, larynx, tonsils, and tongue.[177]

The nose is the most common upper airway structure to be affected by sarcoidosis.[177] The nasal mucous membrane is affected in a majority of cases. Common symptoms of sarcoidosis nasal involvement include crusting, dryness, nasal discharge, stuffiness, obstruction, and epistaxis. The diagnosis is often delayed because nasal symptoms are attributed to chronic sinusitis or allergies.[178] A confirmatory nasal biopsy should be done if this diagnosis is considered.[177] Sarcoidosis patients with disfiguring lupus pernio skin lesions of the nose often have nasal sarcoidosis, and such patients should always be asked about nasal symptoms.[179]

Sinus involvement, the second most common form of SURT,[177] is often associated with nasal disease.[177] Symptoms include periorbital pain, postnasal drip, nasal obstruction, and headache.[177] Laryngeal involvement usually occurs in patients with previously diagnosed disease.[177] The aryepiglottic folds, arytenoids, false cords, and subglottic areas are more commonly involved than the larynx.[177,180] Common symptoms include stridor, hoarseness, dysphonia, cough, dyspnea, and a sensation of a lump in the throat.[181,182] Hoarseness may also occur from cranial nerve involvement or from mediastinal adenopathy compressing the recurrent laryngeal nerve.[183] Tonsillar and tongue involvement with sarcoidosis is rare.

Corticosteroids are the drug of choice for SURT.[177] High doses are often required. It is recommended to start at 20 to 40 mg/day of prednisone equivalent with or without a concomitant immunosuppressive agent.[177] Intralesional injections can be useful if the lesions are localized. Nasal corticosteroid inhalation may diminish nasal inflammation and obstruction.[184] Methotrexate,[90] azathioprine,[185] chloroquine, hydroxychloroquine,[161] cyclophosphamide,[186] and infliximab[187] have all been reported to be useful in case reports and series.

Surgical resection should be avoided whenever possible because lesions may recur, and perforation of the nasal septum is a common complication after submucosal resection.[188,189] Chemotherapy should be tried first whenever possible. Surgery is indicated in cases of acute respiratory distress, expanding mass lesions, mass lesions causing airway obstruction, and mass lesions encroaching on the central nervous system that fail to respond to chemotherapy.[177]

Bone/Joint

Arthritis is present in 14 to 38% of sarcoidosis patients.[190] Up to 70% of patients will complain of arthralgias.[190,191] Sarcoid rheumatic involvement can be divided into acute and chronic types, and their characteristics are so widely different that it has been questioned whether they are separate forms of the disease.[190,192]

Acute sarcoid arthritis may be migratory, intermittent, and can precede other manifestations of sarcoidosis by several months.[190] Fever and other constitutional symptoms often accompany acute sarcoid arthritis.[190] Acute sarcoid arthritis is very common with Lofgren's syndrome where a periarthritis of large joints, especially the ankles and knees, often occurs.[193] In fact, the primary symptom of Lofgren's syndrome is often difficulty walking related to joint pain. Lofgren's syndrome is not recurrent in the vast majority of cases, and the arthritis is usually self-limiting, averaging 11 weeks in duration.[193]

Chronic sarcoid arthritis is rare, affecting only 0.2% of sarcoidosis patients.[194,195] It is usually found in patients with cutaneous sarcoidosis and African American patients.[192,196] The arthropathy may be destructive.[197] Synovial biopsy shows noncaseating granulomas.[190]

Sarcoid bone involvement occurs in 1 to 13% of patients.[190] It is most common in patients between the ages of 30 to 50 and in African-Americans.[190] Bone lesions are most common in the bones of the hands and feet; however, the skull, nasal bones, and vertebrae may be affected (Fig. 3).[190] The lesions may be painful, especially if adjacent joints are involved.[196] The lesions are often asymptomatic and routinely found on radiographic or MR studies. Radiological findings usually show cystic or punched-out lesions (Fig. 4).[198]

Sarcoidal arthritis is usually treated with nonsteroidal anti-inflammatory agents,[192] which is especially useful for acute sarcoid arthritis, typically a self-limiting disease. Chronic destructive synovitis may require intra-articular or systemic corticosteroids.[190] The addition of methotrexate or azathioprine may improve results and be corticosteroid sparing.[190]

Figure 3 Deforming sarcoid arthritis of the fingers.

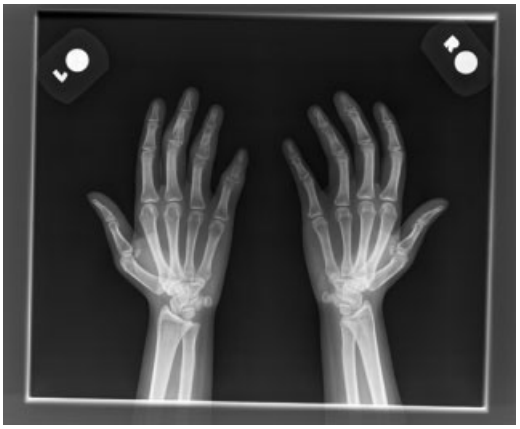

Figure 4 Punched-out bone lesion of sarcoidosis at the proximal end of the left third metacarpal. Cystic bone lesions and erosive arthritis from sarcoidosis are also present at several middle interphalangeal joints of the left hand.

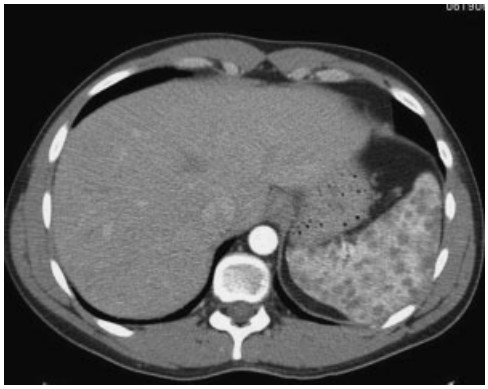

Figure 5 Abdominal computed tomographic scan of a patient with splenic sarcoidosis. Splenomegaly and numerous low-attenuation nodules are seen. These findings are typical, although not pathognomonic, of splenic sarcoidosis because they may be seen with lymphoma and other granulomatous diseases.

Spleen

The frequency of splenic involvement in sarcoidosis has been reported to be 10 to 50%, depending on whether it is detected on physical examination (5 to 14%), a radiographic test (33 to 53%), or a tissue biopsy (24 to 59%).[62,199–204] Patients with splenic sarcoidosis are usually asymptomatic.[205] Left upper quadrant pain is occasionally present.[199,205] Constitutional symptoms such as night sweats, fever, and malaise may occur.[199] Massive splenomegaly is found in ~3% of patients with splenic involvement.[62,206] Splenic sarcoidosis may cause hypersplenism resulting in anemia, leukopenia, thrombocytopenia, or any combination including pancytopenia.[62,206,207]

The frequency of radiographic abnormalities of the spleen is unknown in sarcoidosis because all series reported have involved significant selection biases.[62] Splenomegaly is more common than hepatomegaly on abdominal CT.[203,204,208] Splenic nodules are usually multiple and of low attenuation and more common than hepatic nodules[203,204,208,209] (Fig. 5).

Most patients with splenic sarcoidosis do not require treatment. The natural course of splenic sarcoidosis is unknown, but splenomegaly, including giant splenomegaly, may resolve spontaneously.[199,210] Spontaneous resolution of splenomegaly may be more common when the spleen tip is less than 4 cm below the left costal margin.[199] Treatment is indicated for (1) symptomatic abdominal pain from splenomegaly, (2) hypersplenism, (3) functional asplenia, or (4) splenic rupture.[62] The effectiveness of corticosteroids in decreasing splenic size is unpredictable,[211] and the corticosteroid dose is not standardized.[62] Corticosteroids have also been effective for hypersplenism with normalization of leukopenia, thrombocytopenia, anemia, and pancytopenia.[199,200] Splenectomy is rarely performed for splenic sarcoidosis.[212] Indications include gross enlargement or discomfort, infarction, rupture, and hypersplenism, with reduction in one or several blood cell lines.[211,212] A corticosteroid trial is warranted prior to consideration of splenectomy.

Miscellaneous

Sarcoidosis may cause peripheral lymphadenopathy.[213,214] Isolated granulomatous inflammation in a peripheral lymph node is not diagnostic of sarcoidosis because in ~8% of cases this may represent a "sarcoid-like reaction" from inflammatory disease or malignancy.[213]

Hematologic abnormalities are present in ~30% of sarcoidosis patients.[215] Patients with more active sarcoidosis often experience more problems with anemia and thrombocytopenia, whereas lymphopenia and leukopenia are more common in patients with chronic disease.[216] Four mechanisms exist by which sarcoidosis can affect the hematologic system: (1) direct involvement of the bone marrow by granulomas, (2) sequestration of cells into areas of inflammation, (3) splenic sequestration, and (4) immunologic destruction.[217]

Sarcoidosis muscle involvement is usually asymptomatic and resolves spontaneously.[190] Skeletal muscle weakness occasionally occurs.[218] Rarely, an acute myopathy resembling polymyositis, palpable intramuscular nodules, and progressive myopathy may occur.[219,220]

Sarcoidosis of the breast may occur, presenting as a palpable breast mass or a lesion seen on mammography.[221,222] It is important that a breast mass in a sarcoidosis patient not be assumed to be related to the disease because the patient may have concomitant breast carcinoma. This is particularly pertinent given that patients with breast carcinoma may have related sarcoid-like reactions in extramammary sites.[223]

Sarcoidosis may rarely involve the male and female reproductive tracts.[217] Cases of sarcoidosis of the male testis are particularly problematic because of the concern for possible testicular carcinoma. Elevated α-fetoprotein (AFP) and β-human chorionic gonadotrophic (β-HCG)

levels are elevated in approximately half of patients with nonseminomatous testicular carcinoma.[224] However, normal levels of these proteins do not exclude the diagnosis of malignancy. In an effort to avoid unnecessary orchiectomy, young males with known sarcoidosis or a clinical situation compatible with sarcoidosis and normal AFP and β-HCG levels could be considered for close observation and repeated ultrasound, a brief empirical trial of corticosteroids, or possibly an excisional biopsy.[217] Sarcoidosis may affect any portion of the female genitourinary tract, including the ovary,[225] fallopian tube,[226] uterus,[227] and vulva.[228]

Although 20% of patients with sarcoidosis may demonstrate granulomas in the kidneys, the clinical syndrome of granulomatous interstitial nephritis is rare.[173] Membranous glomerulonephritis, mesangioproliferative glomerulonephritis, immunoglobulin A (IgA) nephropathy, and crescentic glomerulonephritis have been reported sporadically.[173]

Peritoneal sarcoidosis is rare and can present with ascites.[229] The CA-125 serum level may be elevated; therefore, this entity may be confused with ovarian carcinoma.[230]

Rarely sarcoidosis can affect the thyroid gland, presenting as a nodule, mass, or thyroiditis.[231,232]

DIAGNOSIS

The diagnosis of sarcoidosis requires a compatible clinical picture, histological demonstration of noncaseating granulomata, and exclusion of other diseases capable of producing similar histological or clinical findings.[4] Table 2 displays the differential diagnosis of noncaseating granulomatous inflammation in extrapulmonary organs. All of these diagnoses need to be excluded for the diagnosis of sarcoidosis to be established. Cultures and stains of biopsy material should be routinely stained and cultured for mycobacteria and fungi to exclude these pathogens. Because sarcoidosis is a diagnosis of exclusion, the diagnosis can never been confirmed with 100% certainty.

The presence of noncaseating granulomata in a single organ does not establish the diagnosis of sarcoidosis because, by definition, sarcoidosis is a systemic disease that should involve multiple organs. There are idiopathic granulomatous diseases of individual organs that are distinguished from sarcoidosis. For example, idiopathic granulomatous hepatitis, where noncaseating granulomas of unknown cause are only found in the liver, is rarely found to be sarcoidosis (extrahepatic granulomas usually do not develop over time).[233] Another example is idiopathic panuveitis, a granulomatous uveitis without any other organ involvement, which is very common in the southeastern United States.[234]

One exception to the requirement of multiple organ involvement to establish the diagnosis of sarcoidosis is lung involvement. Most clinicians will accept the diagnosis of sarcoidosis if a lung biopsy shows noncaseating granulomatous inflammation of unknown cause and if the chest radiograph shows bilateral hilar

Table 2 Major Pathological Differential Diagnosis of Sarcoidosis at Biopsy and Surgical Pathology

Lymph Node	Skin	Liver	Bone Marrow	Other Biopsy Sites
Tuberculosis	Tuberculosis	Tuberculosis	Tuberculosis	Tuberculosis
Atypical mycobacteriosis	Atypical mycobacteriosis	Brucellosis	Histoplasmosis	Brucellosis
Brucellosis	Fungal infection	Schistosomiasis	Infectious mononucleosis	Other infections
Toxoplasmosis	Reaction to foreign bodies: beryllium, zirconium, tattooing, paraffin, etc.	Primary biliary cirrhosis	Cytomegalovirus	Crohn's disease
Granulomatous histiocytic necrotizing lymphadenitis (Kikuchi's disease)	Rheumatoid nodules	Crohn's disease	Hodgkin's disease	Giant cell myocarditis
Cat-scratch disease		Hodgkin's disease	Non-Hodgkin's lymphomas	GLUS syndrome
Sacroid reaction in regional lymph nodes to carcinoma		Non-Hodgkin's lymphomas	Drugs	
Hodgkin's disease		GLUS syndrome	GLUS syndrome	
Non-Hodgkin's lymphomas				
Granulomatous lesions of unknown significance (the GLUS syndrome)				

Adapted from Reference 4.

adenopathy or a gallium 67 scan shows positive hilar lymph nodes. Without thoracic adenopathy, the diagnosis of sarcoidosis must be made cautiously. A diligent search for an occupational exposure, bioaerosol exposure causing a hypersensitivity pneumonitis, and other causes of granulomatous lung disease, such as a vasculitis, should be made before the diagnosis of sarcoidosis is accepted. In these cases, it is prudent to bear a healthy degree of skepticism for the diagnosis and follow the patient closely for additional clues supporting an alternate diagnosis.

The requirement of two organs being involved with sarcoidosis to establish the diagnosis does not require that two organs be biopsied. A consensus of sarcoidosis experts has developed clinical criteria for when a second organ can be considered involved with sarcoidosis without biopsy (this presumes that noncaseating granulomas have been detected in the "first" organ) (Table 1).[128]

SCREENING FOR ORGAN INVOLVEMENT

Table 3 lists the recommended initial evaluation of patients diagnosed with sarcoidosis.[4] All sarcoidosis patients should have a physical examination to detect extrapulmonary organ involvement. Careful attention should be paid to the skin, neurological examination, cardiac auscultation, and abdominal organs. Patients should undergo an eye examination (slit lamp and funduscopic), an electrocardiogram, and the laboratory tests listed in Table 3 to detect extrapulmonary manifestations of the disease.

TREATMENT

The treatment of extrapulmonary sarcoidosis has already been discussed as it pertains to specific organs. In general, corticosteroids are the drug of choice at an initial dose of 20 to 40 mg/day of prednisone equivalent.[4] Higher doses are often required for cardiac and neurological involvement. The corticosteroid dose should be tapered to the lowest effective dose. If corticosteroids cannot be tapered to less than 10 mg/day of prednisone equivalent within 3 to 6 months, consideration should be given to alternative agents. These agents are often steroid sparing, although it is problematic to completely wean off corticosteroids. Table 4 lists drugs for which there are some data to support effectiveness for the various forms of extrapulmonary sarcoidosis.

Table 3 Recommended Initial Evaluation of Patients with Sarcoidosis

1. History (occupational and environmental exposure, symptoms)
2. Physical examination
3. Posteroanterior chest x-ray
4. Pulmonary function tests: spirometry, DL_{CO} and K_{CO}
5. Peripheral blood counts: white blood cells, red blood cells, platelets
6. Serum chemistries: calcium, liver enzymes (alanine aminotransferase, asparate aminotransferase, alkaline phosphatase); creatinine, blood urea nitrogen
7. Urine analysis
8. Electrocardiogram
9. Routine ophthalmologic examination
10. Tuberculin skin test

Adapted from Reference 4.
DL_{CO}, diffusing capacity for carbon monoxide.

Table 4 Indications for Treatment by Organ

	No Treatment	Treatment[a,b]
Skin		
Localized		Topical (creams/injections)
Generalized		X
Eye		
Anterior uveitis		Topical (eyedrops)
Other manifestations		X
Liver		
Asymptomatic, elevated alkaline phosphate	X	
Synthetic dysfunction (INR ↑, ALB ↓)		X
Cholestatic symptoms		X
Neurological		
Other than facial (seventh) Nerve (Bell's palsy)		X
Cardiac		
Symptomatic		X
Hypercalcemia/nephrolithiasis		
Serum calcium < 11 mg/dL		Low calcium diet, hydration
Serum calcium ≥ 11 mg/dL, elevated serum creatinine		X
Sarcoidosis of the upper respiratory tract		
Localized		injection
Generalized		X
Bone/Joint		
Arthritis		NSAIDs
Joint destruction		X
Spleen		
Hypersplenism		X

[a]Systemic corticosteroids are the drug of choice.
[b]Asymptomatic patients generally not treated except for eye, neurological, and possibly cardiac.
ALB, serum albumin; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.

SUMMARY

Sarcoidosis is not a pulmonary disease but a systemic disease that can affect any organ in the body. The most common extrapulmonary organs affected are the eye and skin. Other than the lungs, mortality from sarcoidosis is related to neurological and cardiac involvement. Treatment may vary depending on the organ that is involved, although corticosteroids are usually the drug of choice when treatment is required.

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