

Diagnosis and Management of Cardiac Sarcoidosis

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Abstract

Cardiac sarcoidosis is an underdiagnosed disease that may be present in as many as 25% of patients with systemic sarcoidosis. Although most commonly recognized in patients with other manifestations of sarcoidosis, it may occur in isolation and its presence is often not appreciated. Cardiac sarcoidosis may present as asymptomatic left ventricular dysfunction, congestive heart failure, atrioventricular block, atrial or ventricular arrhythmia and sudden death. Although untested in clinical trials, early use of high-dose steroid therapy may halt or reverse cardiac damage. This article reviews the clinical manifestations, diagnosis and treatment of sarcoidosis, with an emphasis on new imaging techniques and therapies. (Prog Cardiovasc Dis 2010;52:336-346)

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Sarcoidosis is a multisystem disease characterized histologically by the formation of granulomas in many tissues. Most patients present with pulmonary involvement of whom approximately half have asymptomatic pulmonary involvement, characterized by hilar lymphadenopathy on chest x-ray.¹ The remainder have parenchymal disease and present most commonly with cough or dyspnea on exertion. In addition to the lungs, virtually any other organ system may be involved by sarcoidosis. Skin involvement, characterized by erythema nodosum or granulomas in scars and tattoos, seems to be the second commonest manifestation.^{2,3} After this, in decreasing order of frequency, are hepatic and gastrointestinal involvement, ocular involvement, and neurological sarcoidosis.² A recent review of sarcoidosis placed cardiac involvement at 2%, one of the least common manifestations.² However, cardiac sarcoidosis may be an asymptomatic accompaniment to pulmonary disease or may be the presenting feature of sarcoidosis. Among patients dying with sarcoidosis in whom an autopsy

is performed, the figure has been estimated to be between 20% and 25%,⁴⁻⁷ and sophisticated imaging studies show that a significantly higher proportion of patients have cardiac abnormalities than suspected from symptoms and examination alone.¹ Thus, it is likely that cardiac sarcoidosis is commoner than clinically recognized, although it remains a relatively uncommon disease.

In the United States, sarcoidosis is commonest in the African-American population. In a population-based study drawn from patients enrolled in a Health Maintenance Organization in Detroit, the age-adjusted incidence of sarcoidosis for the age group 20 to 69 years was 39.1 per 100,000 African-American females, 29.8 for African-American males, 12.1 for white females, and 9.6 in white males.⁸ African-American females in the age group of 30 to 39 years had the highest annual incidence at 107 per 100,000, representing an approximately 3-fold higher age-adjusted annual incidence compared with whites. Outside the United States, there are several populations that have a high incidence of sarcoidosis, particularly in Scandinavia and Ireland. Sarcoidosis also seems to be relatively common in Japan, and a large body of literature on the diagnosis and management of cardiac sarcoidosis comes from this country. Although considerable data exist on the

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Abbreviations and Acronyms**ACE** = angiotensin-converting enzyme**AV** = atrioventricular**CT** = computed tomography**FDG** = fluoro-2-deoxy-D-glucose**MRI** = magnetic resonance imaging**PET** = positron emission tomography

epidemiology and clinical manifestations of sarcoidosis, controlled trials of therapy are few for pulmonary sarcoidosis and are nonexistent in cardiac sarcoidosis.

Etiology

The etiology of sarcoidosis remains unknown, although infectious agents

and environmental exposures (eg, insecticides and agricultural employment) have been proposed.^{2,9,10} Reports of community outbreaks and clustering of cases among working colleagues, including nurses, firefighters, US Navy personnel, and neighbors are described, and a high prevalence of sarcoidosis, or sarcoid-like pulmonary disease, has been described in firefighters who were at the scene of the 2001 World Trade Center terrorist attack.¹¹ The likelihood is that there is a genetic predisposition as evidenced by such clustering and that an as yet unknown stimulus triggers an exaggerated immune response. Sarcoidosis occurs more commonly in monozygotic than dizygotic twins, and familial clusters of the disease have been described.^{12–14}

Pathology

The granulomas that characterize sarcoidosis are noncaseating and consist of aggregates of epithelioid histiocytes with minimal inflammation and large multinucleated giant cells (Fig 1).^{15–18} A similar histologic

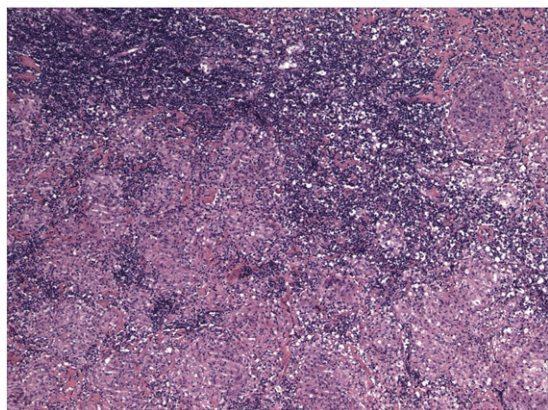


Fig 1. Lymph node from a patient with sarcoidosis showing numerous nonnecrotizing granulomas typical of sarcoidosis. Hematoxylin and eosin stain. Original magnification, $\times 40$. Courtesy of Dr Robert Padera, Brigham and Women's Hospital, Boston, Mass.

appearance can be seen in tuberculosis (in which caseation is usually present) and in a variety of other conditions including lymphoproliferative disorders and foreign bodies. Thus, it is important to interpret the histologic findings in conjunction with the clinical picture. The severity of the disease is not proportional to the number of granulomas, because advanced cases develop a fibrotic reaction that may cause permanent tissue damage. Whether fibrosis is a reaction to the granuloma itself or is a nonspecific reaction is unclear.

Among 84 patients with sarcoidosis who had an autopsy performed at Johns Hopkins Hospital during an 88-year period, 23 had myocardial sarcoidosis based on the histologic findings of myocardial granulomas, but only 4 had grossly visible myocardial abnormalities.⁶ All chambers were involved, although the ventricles were favored. In a more recent publication, autopsy findings in 25 patients dying of cardiac sarcoidosis were compared with 16 patients with sarcoidosis in whom sudden death was attributed to other causes.⁷ Sarcoidosis had been diagnosed premortem in only 16 of 46 patients. A dilated left ventricle was present in 25% of both those dying of cardiac sarcoidosis in those with other causes of sudden death. Gross involvement of the myocardium and pericardium with sarcoid was more frequent in sarcoid-related death than in incidental death. Sudden death attributed to sarcoidosis was associated with visible myocardial scarring, and no cases of death attributable to cardiac sarcoidosis occurred in patients in whom autopsy examination of the heart showed only microscopic features of the disease. Of note, 10 of 25 deaths attributed to sarcoid heart disease had no evidence of extracardiac disease. Both of these autopsy series, although suggesting that sarcoidosis clinically isolated to the heart is common, suffer from selection bias because a patient with unexpected death is more likely to be subject to an autopsy. Nevertheless, the findings underscore the fact that isolated cardiac sarcoidosis does occur and that its initial manifestation may be sudden death.

Clinical presentation of cardiac sarcoidosis

As noted above, asymptomatic heart involvement in patients with pulmonary sarcoidosis may be relatively frequent. Cardiac involvement may be present in the absence of any abnormality on standard cardiac testing, may manifest as an abnormal electrocardiogram alone, or may be recognized as an asymptomatic abnormality on echocardiography or cardiac magnetic resonance imaging (MRI). In a patient with established extracardiac sarcoidosis, the presence of congestive heart failure or the finding of impaired systolic function on echocardiography strongly raises the suspicion of cardiac involvement, unless another obvious cause, such as coronary artery disease,



Fig 2. Gross specimen of a heart from a patient with cardiac sarcoidosis explanted at the time of cardiac transplantation. The ventricles are dilated, and there are scattered white areas in the myocardium in a seemingly random distribution, which represent scar tissue typical of cardiac sarcoidosis. Courtesy of Dr Robert Padera, Brigham and Women's Hospital, Boston, Mass.

exists. In any patient with documented noncardiac sarcoidosis, electrocardiographic abnormalities should prompt the ordering of an echocardiogram to evaluate cardiac function, and disproportionate dyspnea in pulmonary sarcoidosis should always raise the possibility of concomitant cardiac involvement. It should, however, be recognized that the sensitivity and specificity of the echocardiogram for determining the presence of minor degrees of cardiac sarcoidosis have not been established.

The clinical presentation of sarcoidosis of the heart reflects both the predilection of the granulomas for the conduction system and the myocardial changes caused by granulomatous deposition and subsequent fibrosis. Complete heart block in a young patient suggests sarcoidosis, particularly if ventricular arrhythmias with congestive heart failure are also present. Isolated complete heart block may occur in the presence of normal left ventricular function. Other causes of heart block that present in a relatively young person with normal ventricular function, such as Lyme disease, need to be excluded because these may be reversible with therapy and may not need permanent pacing. Congestive heart failure with features of a dilated cardiomyopathy (Fig 2) is also a common presenting feature, and mitral regurgitation may be a significant contributory factor, due to papillary muscle involvement. As noted, sudden cardiac death may be an early or presenting feature of the disease.⁷ Although pericardial involvement at autopsy is relatively frequent, clinical pericarditis is uncommon. A rare presentation is acute sarcoid myocarditis, which is characterized by high-degree atrioventricular (AV) block, malignant ventricular arrhythmias, and congestive heart failure.^{19–21} This may be difficult to distinguish from giant cell myocarditis, as discussed below. Frequent asymptomatic ventricular

arrhythmias noted on Holter monitoring are quite common in cardiac sarcoidosis and might suggest a propensity to sudden death. Persistent atrial arrhythmias are also relatively frequent and, although usually associated with generalized cardiac involvement, have very rarely been associated with sarcoidosis limited to the atria. Patients with severe pulmonary sarcoidosis may have cor pulmonale, producing signs and symptoms of right-sided congestive heart failure. The prognosis with cardiac involvement is much worse than other manifestations of the disease, and it is estimated that, in Japan, nearly 80% of patients who die of sarcoidosis do so from cardiac involvement, either from sudden death or heart failure.¹⁹

Laboratory investigations

Blood test abnormalities in sarcoidosis are nonspecific and nondiagnostic. Anemia and leucopenia and/or a raised sedimentation rate may be present.¹⁶ Hypercalcaemia may occur due to an activation of vitamin D by macrophages in sarcoid granulomas,^{20,21} and there may be nonspecific increase in serum immunoglobulins. Serum angiotensin-converting enzyme (ACE) level is often elevated in patients with sarcoidosis and has been used to monitor progress in response to therapy.²² However, in the healthy population, the range of ACE is quite large, and normal levels have been found in patients with newly diagnosed sarcoidosis. Polymorphism in the ACE gene has been shown to be responsible for a considerable proportion of the variation in levels in the healthy population, and it has been suggested that genotype-corrected reference values should be used when following ACE levels.²³ This may not be available in all laboratories, and although an elevated ACE level in a patient with suspected sarcoidosis

Table 1

Summary of the 2006 revised guidelines for diagnosing cardiac sarcoidosis of the Japanese Society of Sarcoidosis and Other Granulomatous Disorders

1. Histological diagnosis

Cardiac sarcoidosis is confirmed when cardiac biopsy specimens demonstrate noncaseating epithelioid cell granuloma with histologic or clinical diagnosis of extracardiac sarcoidosis.

2. Clinical diagnosis group

Cardiac sarcoidosis is diagnosed in the absence of an endomyocardial biopsy specimen or in the absence of typical granulomas on cardiac biopsy when extracardiac sarcoidosis has been proven and a combination of major or minor diagnostic criteria has been satisfied as follows.

1. More than 2 of 4 major criteria are satisfied, OR
2. 1 of the 4 major criteria and 2 or more of the minor criteria are satisfied.

Major criteria

- (a) Advanced AV block
- (b) Basal thinning of the ventricular septum
- (c) Positive cardiac gallium uptake
- (d) Left ventricular ejection fraction less than 50%

Minor criteria

- (a) Abnormal electrocardiogram findings including ventricular tachycardia, multifocal frequent premature ventricular contractions, complete right bundle branch block pathologic Q waves, or abnormal axis deviation
- (b) Abnormal echocardiogram demonstrating regional wall motion abnormalities, ventricular aneurysm, or unexplained increase in wall thickness
- (c) Perfusion defects detected by myocardial scintigraphy
- (d) Delayed gadolinium enhancement of the myocardium on cardiac MRI scanning
- (e) Interstitial fibrosis or monocyte infiltration greater than moderate grade by endomyocardial biopsy

may increase suspicion, a normal level should not rule out the diagnosis. A role for ACE measurement remains in providing some indication of the extent and severity of the disease progression and response to therapy, but imaging studies are probably more accurate for this. The definitive diagnostic test is the finding of noncaseating granuloma in a biopsy from an involved organ, although as discussed below, the yield of cardiac biopsy is low.

In 2006, the Japanese Society of Sarcoidosis and Other Granulomatous Disorders published revised guidelines for the diagnosis of cardiac sarcoidosis²⁴ and which are shown in Table 1. These guidelines are useful, particularly in a patient with proven noncardiac sarcoidosis in whom a suspicion of cardiac involvement exists.

Myocardial biopsy

The finding of noncaseating granulomas on endomyocardial biopsy performed in a patient with a dilated cardiomyopathy is virtually pathognomonic for the diagnosis of cardiac sarcoidosis (Fig 3). However, it is recognized that endomyocardial biopsy may frequently be negative in cardiac sarcoidosis.²⁵ This has been attributed

to the patchy distribution of the granulomas, but it also may be related to the observation that disease progression is associated with extensive myocardial fibrosis so that an area previously containing granulomas loses them as fibrosis supervenes.²⁶ In a 15-year period, 1235 patients underwent endomyocardial biopsy for unexplained cardiomyopathy at Johns Hopkins Hospital.²⁵ Twenty-eight patients had a clinical diagnosis of systemic sarcoidosis with documented extracardiac involvement, and a concomitant cardiomyopathy believed to be due to the disease. Only 7 of these patients had a biopsy documenting noncaseating granulomas, most likely reflecting the insensitivity of endomyocardial biopsy for the diagnosis rather than suggesting a nonsarcoid cause of the cardiomyopathy. Of the approximately 1200 remaining patients, the cause of the cardiomyopathy was unknown before endomyocardial biopsy, and only 3 had biopsy features suggestive of sarcoidosis. The median survival of the 10 patients with a positive biopsy was 8 months after the procedure, compared with a median survival of 28 months in those with systemic sarcoidosis, cardiomyopathy, and a negative biopsy. The authors raised the question as to whether the negative biopsy in patients with cardiomyopathy and systemic sarcoidosis was due to the patchy nature of the granulomas and/or their location in an area of the heart not usually biopsied or due to the possibility that systemic sarcoidosis causes left ventricular dysfunction by cytokines or by an unknown toxic mechanism.

It would thus seem that endomyocardial biopsy adds little to the diagnosis of cardiac sarcoidosis in a patient with a positive noncardiac biopsy for sarcoid and coexistent unexplained cardiomyopathy. If performed in someone with a clinical suspicion of sarcoidosis in other organs and found to be negative, a search for a positive noncardiac biopsy (eg, of enlarged mediastinal lymph

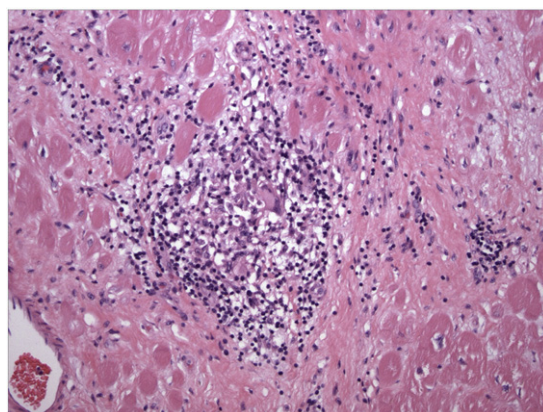


Fig 3. Example of a myocardial granuloma, diagnostic of cardiac sarcoidosis. There is associated fibrosis. Hematoxylin and eosin stain. Original magnification, $\times 100$. Courtesy of Dr Robert Padera, Brigham and Women's Hospital, Boston, Mass.

nodes) should be pursued. Most patients will have bilateral hilar lymphadenopathy, often with right paratracheal adenopathy, and mediastinoscopy can be performed to biopsy paratracheal lymph nodes.¹ Up to 75% of patients will have asymptomatic liver granulomas, providing an additional biopsy site. Approximately 1 in 4 will have ocular involvement in the form of an anterior uveitis, which can be diagnosed on slit lamp examination.

The histologic differential diagnosis of sarcoid granulomas includes giant cell myocarditis. Occasionally, cardiac sarcoidosis may present acutely with fulminant congestive heart failure, ventricular arrhythmias, and AV block, and it may be difficult to distinguish this from giant cell myocarditis or myocarditis of another origin. In a comparison of 42 patients with cardiac sarcoidosis to 73 patients with idiopathic giant cell myocarditis, 31% of patients with sarcoidosis were of African origin compared with only 4% with giant cell myocarditis.¹⁷ Syncope and AV block were much commoner in sarcoidosis, whereas there was a slight increase in the prevalence of left-sided heart failure in the giant cell myocarditis group. In a multivariate analysis, patients with giant cell myocarditis more commonly presented with heart failure of short duration, whereas more than 9 weeks of symptoms and presentation with heart block was more commonly seen in cardiac sarcoidosis. Histologically, myocyte damage, eosinophils, and foci of lymphocytic myocarditis favored giant cell myocarditis, whereas granulomas and fibrosis were more frequent in cardiac sarcoidosis. Intriguingly, only one third of the patients ultimately diagnosed as cardiac sarcoidosis had evidence of extracardiac disease.

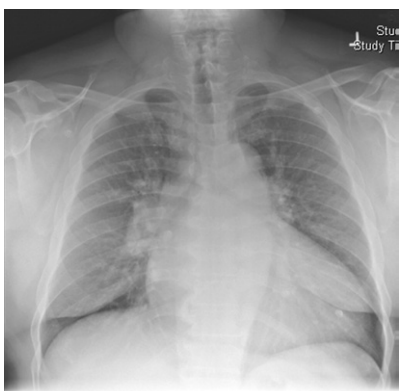


Fig 4. Chest x-ray from a 49-year-old man who presented with congestive heart failure and global left ventricular hypokinesis, an estimated ejection fraction of 25% to 35%, and mild to moderate mitral regurgitation. Coronary angiography was normal, and endomyocardial biopsy showed nonspecific changes only. He was readmitted with worsening heart failure, and after diuresis, the x-ray above was obtained. It shows marked cardiomegaly with bilateral hilar fullness. The hilar fullness, originally attributed to heart failure, had not resolved with diuresis, and a chest CT scan showed widespread hilar adenopathy. Mediastinoscopic lymph node biopsy showed noncaseating granulomas in all biopsied lymph nodes, and his heart failure improved after high-dose steroid therapy.

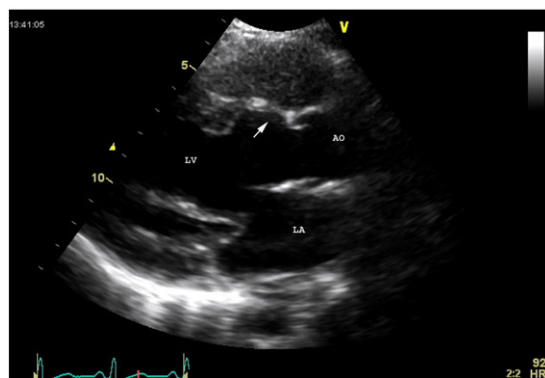


Fig 5. Parasternal long-axis view of the echocardiogram from a 38-year-old woman with peripartum heart failure, originally attributed to peripartum cardiomyopathy. Her left ventricular systolic function was mildly impaired but did not improve postpartum. The basal septum (arrow) shows marked thinning and increased echogenicity, highly suggestive of sarcoidosis. She had a history of pulmonary sarcoidosis and was found to have marked hilar adenopathy and evidence of active disease. Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle.

Although this may represent selection bias (patients without organ involvement elsewhere are probably more likely to have a cardiac biopsy), cardiac involvement as the presenting feature of sarcoidosis has been described frequently in other series.

Imaging and cardiac sarcoidosis

Different imaging techniques have been used both for the diagnosis and follow-up of patients with suspected cardiac sarcoidosis. These include echocardiography, myocardial perfusion with thallium or Tc-99 nuclear scintigraphy, gallium-67 scintigraphy, positron emission tomography (PET) with fluoro-2-deoxy-D-glucose (¹⁸FDG), and MRI and cardiac computed tomography. With increasing sophistication of these techniques, it is becoming possible to diagnose cardiac sarcoidosis noninvasively.

Chest x-ray

There is nothing specific about the cardiac contour in cardiac sarcoidosis on the chest x-ray. Nonspecific cardiomegaly is often present, reflecting the dilated ventricle. If cardiac sarcoidosis coexists with pulmonary sarcoid, hilar lymphadenopathy and/or pulmonary parenchymal changes may give a clue as to the diagnosis (Fig 4). However, hilar fullness on a chest x-ray may be a feature of congestive heart failure or may represent pulmonary artery dilation secondary to the cardiac disease. If hilar adenopathy is suspected on a chest x-ray, computed tomography (CT) imaging of the chest should be performed to look for hilar adenopathy and pulmonary parenchymal disease. High-resolution CT is particularly sensitive for detection of pulmonary involvement,^{19,20} whereas standard contrast-

enhanced CT may be better for delineation of mediastinal and hilar lymphadenopathy.

Echocardiography

Generally, echocardiography is nondiagnostic in terms of etiology in a patient in whom a new cardiomyopathy has been found, but it may be very helpful in suggesting cardiac sarcoidosis if abnormal in a patient with biopsy-proven systemic sarcoidosis at another site. The usual echocardiographic appearance of cardiac sarcoidosis is that of a dilated cardiomyopathy. The ventricle may be globally hypokinetic or the patchy nature of sarcoid infiltration of the heart may result in regional wall motion abnormalities. Mild wall thickening may be present related to edema or infiltration. More commonly, areas of wall thinning are seen, most commonly in the ventricular septum and probably associated with scarring. A typical but uncommon finding is the thinning of the basal anterior septum, the appearance of which in a young patient with a dilated cardiomyopathy is highly suggestive of sarcoidosis²⁷ (Fig 5). On rare occasions, an appearance similar to hypertrophic cardiomyopathy has been described.^{28,29} Diastolic dysfunction is a common but nonspecific finding.³⁰

Radionuclide scintigraphy

²⁰¹Thallium scintigraphy myocardial perfusion studies have been used for a number of years in evaluating patients with suspected cardiac sarcoidosis. If sarcoidosis is present in the heart, there are typically segmental areas of decreased uptake in the ventricular myocardium that disappear or decrease in size during stress or after intravenous administration of dipyridamole.^{31,32} However, this reverse distribution is not specific for cardiac sarcoidosis because it may also occur in other cardiomyopathies. Gallium-67 scintigraphy has also been used to demonstrate both cardiac and extracardiac disease,¹ and the detection of clinically silent extrathoracic uptake may provide sites for biopsy. It has also been used for follow-up of active disease (both cardiac and extracardiac) with treatment. Studies in which both ²⁰¹thallium and gallium-67 scintigraphy were performed in patients with suspected sarcoidosis showed that areas of reduced uptake were more common using ²⁰¹thallium than with gallium-67.³³ In patients in which both scans were positive, there was more severe cardiac involvement, as indicated by a reduced ejection fraction. ^{99m}Tc sestamibi has been described in combination with gallium-67 scintigraphy as increasing the sensitivity for the diagnosis of cardiac sarcoidosis.³⁴

Cardiac MRI

With more widespread availability of cardiac MRI and increasing availability of cardiac PET scanning, thallium (or

sestamibi) and gallium imaging has become less frequently used, because MRI and PET seem to be more sensitive and specific for the diagnosis of both pulmonary and extrapulmonary sarcoidosis. Due to its high spatial and soft tissue resolution, MRI is now increasingly being shown to be a technique of choice for evaluation and diagnosis of cardiac sarcoidosis.³⁵ Cardiac MRI can demonstrate both scar and myocardial edema. Acute myocardial inflammation presents as focal areas of thickening and increased signal intensity on T2-weighted images and early gadolinium-enhanced images. Myocardial edema, which is present in the active stage of cardiac sarcoidosis, can rapidly resolve with steroid treatment, resulting in rapid decrease in thickened areas and resolution of increased T2 hyperintensity.³⁶ In cardiac sarcoidosis, delayed gadolinium enhancement is found predominantly in the midmyocardium and epicardial areas but rarely in the endocardium.³⁷ A predilection for abnormalities in basal and lateral segments of the left ventricle has been described,^{38,39} and the papillary muscles are frequently involved.³⁷ In addition to the delayed gadolinium enhancement, cardiac MRI can precisely determine regional wall motion abnormalities and areas of wall thickening but may represent myocardial edema or infiltration. Abnormalities of delayed gadolinium enhancement or T2 imaging for edema have been used to target endomyocardial biopsy in an attempt to increase the sensitivity of this technique.

Cardiac MRI is useful not only in patients with a cardiomyopathy of unexplained origin but also in determining the presence or absence of cardiac sarcoidosis in patients with documented pulmonary disease. In a series of 58 patients with histologically proven pulmonary sarcoidosis who underwent both thallium myocardial scintigraphy and cardiac MRI, late gadolinium enhancement was found in 19 patients, most commonly in the basal and lateral left ventricular segments.³⁸ Ten patients were found to have a reduction in left ventricular ejection fraction, for a total of 22 patients with abnormalities. Only 12 patients had an abnormality on thallium scintigraphy. In a similar series of patients with documented pulmonary sarcoidosis and no previously diagnosed cardiac sarcoidosis, one third of patients had abnormalities on cardiac MRI and 80% had metabolic abnormalities on PET scanning.⁴⁰ All of these patients had 1 or more cardiac abnormalities on the electrocardiogram or on a Holter monitoring, and thus, the relatively high percentage potential disease represents a relatively selected population. All these studies indicate that cardiac abnormalities are relatively common in patients with noncardiac sarcoidosis, a finding that is concordant with the prevalence of cardiac sarcoid involvement at autopsy.

¹⁸FDG PET scanning

¹⁸F-fluoro-2-deoxy-D-glucose PET scanning is widely used in evaluation of tumors, vasculitis, and inflammatory

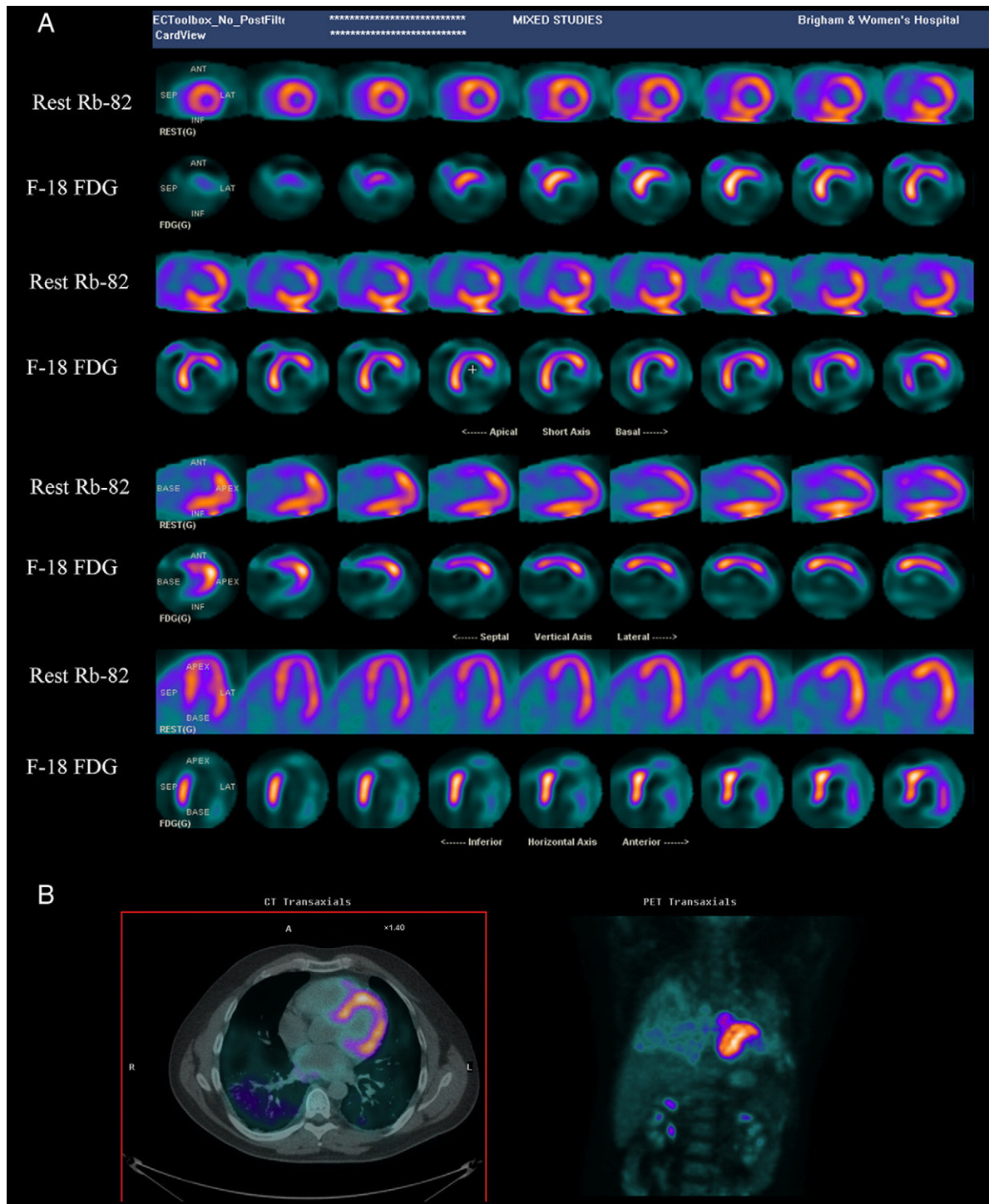


Fig 6. A, Combined resting PET scan using rubidium-82 and ¹⁸F-FDG scanning in a 53-year-old man with a history of pulmonary sarcoidosis who presented with palpitations and atrial flutter. From the top, each pair of images represents the rubidium-82 scan and, underneath it, the corresponding ¹⁸F-FDG image. The scans show a basal and midanteroseptal perfusion defect with intense FDG uptake in these regions suggestive of myocardial inflammation. Normal myocardium has no FDG uptake because it is using free fatty acids. B, CT images in the same patient demonstrating the intense cardiac uptake (left panel: combined PET-CT scan). Courtesy of Dr Sharmila Dorbala, Brigham and Women’s Hospital, Boston, Mass.

diseases . Organ involvement in sarcoidosis can be clearly demonstrated by this technique, and it can be used either alone or in combination with a CT scan for the diagnosis

and follow-up of cardiac sarcoidosis (Fig 6). In a series of 20 patients with biopsy-proven sarcoidosis, ¹⁸F-FDG PET successfully identified 28 of 36 biopsy-proven sites of the

disease.⁴¹ In a Japanese series of 21 patients with sarcoidosis and suspected cardiac involvement, cardiac MRI, ¹⁸F-FDG PET, and sestamibi scintigraphy were performed.⁴² Based on the Japanese guidelines for diagnosing cardiac sarcoidosis (Table 1; which includes an abnormal myocardial sestamibi scan as one of the features), 8 patients were considered to have cardiac sarcoidosis before the scans. Fifteen patients had abnormal PET scans, and 11 had abnormal cardiac MRI scans characterized by delayed gadolinium enhancement in 9 (1 of whom also had features of myocardial edema) and abnormal T2 images suggesting myocardial edema in 2. It is likely that abnormalities on PET scanning or MRI in these patients represent cardiac sarcoidosis even in the absence of clinical cardiac abnormalities. Interestingly, 7 patients exhibited abnormalities on PET scanning alone and only 1 on MRI alone. Although it is conceivable that this indicates that PET scanning is more sensitive than MRI, it may be that the PET abnormalities were nonspecific or that they represent active sarcoid inflammation without myocardial edema or scarring, which might not be apparent on cardiac MRI. Further work needs to be done on the significance of the discrepant findings to determine whether or not cardiac MRI and PET scans will be complementary to one another for the investigation and follow-up of cardiac sarcoidosis.

Management of cardiac sarcoidosis

The management of cardiac sarcoidosis is similar to that of other forms of dilated cardiomyopathy, namely, diuretics, ACE inhibitors, or angiotensin-receptor blockers and β - blocking agents. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have antifibrotic properties and have the theoretical potential to modify the progressive fibrosis that accompanies many cases of cardiac sarcoidosis. Although there are no controlled randomized trials addressing the arrhythmia management in this disease, the apparently high incidence of sudden cardiac death has led many clinicians to adopt a relatively aggressive approach in terms of prophylactic defibrillators. In addition to the management of congestive heart failure and cardiac arrhythmias, attention in cardiac sarcoidosis should be direct toward therapies aimed at decreasing the inflammatory process. Corticosteroids are the mainstay of such therapy.⁴³ Arrhythmia therapy and the value of steroids and other anti-inflammatory therapies are addressed in the following sections.

Cardiac arrhythmia

The first manifestation of cardiac sarcoidosis may be high-degree AV block, sustained atrial arrhythmias, or malignant ventricular arrhythmia (including sudden

death). The substrate for arrhythmias may be active granuloma formation in the myocardium or myocardial fibrosis. The widespread involvement of the heart by the disease may result in the coexistence of these arrhythmias in a single individual, and the onset of an atrial arrhythmia may portend a ventricular arrhythmia. An intriguing presentation of cardiac sarcoidosis is as a mimic of arrhythmogenic right ventricular dysplasia. Twenty-three patients referred for suspected arrhythmogenic right ventricular dysplasia underwent endomyocardial biopsy and 3 were found to have noncaseating granulomas consistent with sarcoid.⁴⁴ Of note, a reduced left ventricular ejection fraction was present in all 3 of these patients but was only found in 2 of 17 patients with suspected arrhythmogenic right ventricular dysplasia.

Presentation with sustained ventricular tachycardia or ventricular fibrillation is a clear indication for implantation of a defibrillator. Catheter ablation of the site of origin of ventricular arrhythmias has been used to decrease the frequency of defibrillator shocks. However, the widespread scarring and progressive nature of cardiac sarcoidosis are generally considered unfavorable for such therapy. Koplman and coworkers²⁶ reported their experience with attempted ablation therapy for refractory ventricular tachycardia in 8 patients with sarcoidosis. Although small, this case series underscores some of the difficulties in the diagnosis and treatment of this disorder. Endomyocardial biopsy had been performed in 7 patients and was negative for sarcoid granulomas in 3. In 1 patient, who subsequently underwent cardiac transplantation, the explanted heart showed extensive fibrosis without granulomas, whereas an endomyocardial biopsy performed just 4 months before had shown granulomatous infiltration. Two of the patients had a previous diagnosis of arrhythmogenic right ventricular dysplasia and presented with ventricular arrhythmias before a diagnosis of sarcoidosis was made. Multiple monomorphic ventricular tachycardias were induced and ablation, although they abolished individual ventricular tachycardias, was rarely completely successful in an individual patient. Five patients subsequently underwent cardiac transplantation, the indication being intractable arrhythmia in 4 of them.

The decision in whom to implant a defibrillator in patients with cardiac sarcoidosis not presenting with ventricular arrhythmia is complex, and there are no controlled data to guide the clinician. Prystowsky has cogently argued that the progressive nature of the disease is such that a defibrillator (all of which also have pacing capabilities) is the appropriate choice in a patient with cardiac sarcoidosis presenting with high-degree AV block.⁴⁵ He also favors an aggressive approach in a patient with documented extracardiac sarcoidosis and evidence of cardiac involvement on an abnormal

electrocardiogram or imaging study, based on the unpredictable and relatively high risk of sudden death in such patients. In contrast, Soejima and Yada²⁴ have suggested an algorithmic approach to sarcoidosis and arrhythmia, with pacemaker implantation alone for patients presenting with AV block in the absence of severe left ventricular dysfunction or heart failure, defibrillator implantation alone for those with spontaneous ventricular tachycardia/fibrillation and a narrow QRS and, a defibrillator plus cardiac resynchronization therapy for spontaneous ventricular arrhythmias associated with impaired ventricular function and a wide QRS. This approach is similar to that generally taken in idiopathic dilated cardiomyopathy with a moderately or severely reduced ejection fraction, a condition in which the risk of sudden death is also elevated. It is possible that PET imaging may serve as a “tie-breaker” in deciding in which patients with cardiac sarcoidosis and normal or mildly reduced ejection fraction to implant a defibrillator. Significant myocardial PET uptake, if assumed to indicate active disease, may identify a group at higher risk of sudden death either because of the activity of the disease or greater likelihood that it will progress. On the other hand, a patient with a mildly reduced ejection fraction and systemic sarcoidosis in whom there is no cardiac PET abnormality could be considered to have quiescent disease and may have a lower risk of sudden death. At present, there are no data to support this approach, but in theory, it remains attractive.

Immunosuppressive therapy

The treatment of pulmonary sarcoidosis (other than asymptomatic hilar adenopathy in which treatment is not required) and many forms of extrapulmonary sarcoidosis is with high-dose corticosteroids,⁴³ even though definitive data on efficacy are lacking.⁴⁶ Several uncontrolled series of patients with cardiac sarcoidosis have been published, which suggest that steroid use may be valuable in this condition. However, there are no randomized controlled data. Because many patients with cardiac sarcoidosis have significant congestive heart failure, the usual complications of high-dose steroid therapy such as weight gain, hyperglycemia, osteoporosis, and increased susceptibility to infection additionally include the possibility of exacerbation of congestive heart failure. Consequently, if steroids are to be considered, it is vital that the diagnosis is as certain as possible and that the patient is followed very carefully. Most series of the effects of steroids in cardiac sarcoidosis suggest effectiveness of this therapy, although the optimal dose and duration of therapy are unclear. In a retrospective series from Japan of 48 patients with cardiac sarcoidosis, high-dose steroid therapy seemed to be ineffective in patients with a pretreatment left ventricular ejection

fraction of less than 30%, whereas there was an improvement in ejection fraction and a decrease in left ventricular end-diastolic volume in patients whose pretreatment ejection fraction was between 30% and 55%.⁴⁷ The authors suggested that severe left ventricular dysfunction in cardiac sarcoidosis may represent end-stage fibrosis, which is refractory to corticosteroid therapy. Corticosteroid therapy was used in most of the 41 patients described in a retrospective study from France.⁴⁸ Improvement in abnormal echocardiographic parameters was described in 78%, and 9 of 17 patients presenting with congestive heart failure had complete resolution of symptoms.

The dose of corticosteroids that is effective in cardiac sarcoidosis is unclear. The French group recommended an initial dose of 1 mg per kilogram per day of prednisone, maintained for 6 to 8 weeks followed by tapering of the dose with careful assessment of cardiac function.⁴⁸ In a retrospective study of cardiac sarcoidosis in 30 Japanese patients who were prescribed 40 mg or more of prednisone daily (range, 40–60 mg) and in 45 who were prescribed less than 30 mg/d (range, 10–30 mg), there was no apparent survival benefit of high-dose prednisone over the lower dose.⁴⁹ Based on these observations, the authors recommended prescribing an initial dose of 60 mg of prednisone every other day tapering, over a few months, to 10 mg every other day. Whether a high or intermediate dose is used, it is clear that the eventual dose should be the lowest possible dose effective in suppressing disease activity. Steroid therapy may eventually be discontinued, but it should be recognized that cessation of steroid therapy has been associated with a relapse rates of approximately 25%.

Additional immunosuppressive therapy has been tried in sarcoidosis including cyclophosphamide, methotrexate, and cyclosporine, but there are no data as to their efficacy in cardiac sarcoidosis. Recently, infliximab, an agent used for the treatment of rheumatoid arthritis that acts by opposing tumor necrosis factor- α has been proposed as a treatment for sarcoidosis. In a small study of refractory pulmonary sarcoidosis, changes imaged by ¹⁸F-FDG PET scanning correlated with improvement in pulmonary function⁵⁰ and case reports have described improvement in cardiac sarcoidosis after infliximab treatment.^{51–53} Infliximab poses an infectious risk because there is already a cellular defect due to the sarcoidosis and is not without serious adverse effects, and a case of fatal disseminated cryptococcosis in a patient with sarcoidosis treated with infliximab has been described.⁵⁴

Heart transplantation for sarcoid heart disease

Sarcoidosis can result in severe congestive heart failure necessitating consideration of cardiac transplantation.

Partly because of the uncommon nature of the disease and partly because of coexisting disease in other organs, the number of patients undergoing cardiac transplantation in whom cardiac sarcoidosis was documented pretransplant is quite small. Review of the United Network for Organ Sharing database between 1987 and 2005 revealed that 65 patients with cardiac sarcoidosis underwent cardiac transplantation.⁵⁵ This represents less than 0.2% of all transplants. Surprisingly, the 1-year post transplant survival for sarcoidosis patients was significantly better than the other contemporaneous patients (87.7% versus 84.5%), and survival benefit persisted out to 5 years.

The difficulty in diagnosing cardiac sarcoidosis has led to several cases in which cardiac transplantation was performed without realizing the etiology of congestive heart failure. Three of four patients with cardiac sarcoidosis transplanted in a Danish center had the diagnosis made at the time all examination of the explanted heart.⁵⁶ There were 2 long-term survivors, 1 patient died of primary graft failure of the other from cytomegalovirus. Recurrence of the disease has been reported in a transplanted heart,⁵⁷ but this seems to be a rare phenomenon. Thus, it seems that, in carefully selected cases, the outcome from cardiac transplantation in cardiac sarcoidosis is good.

Summary

Cardiac sarcoidosis, although an uncommon disease, should be considered in all cases of unexplained cardiomyopathy, particularly in young patients. A negative endomyocardial biopsy should not be taken as evidence of the absence of cardiac sarcoidosis, particularly if suspicion is high. Advances in cardiac imaging seem to be improving the diagnosis and, when highly suggestive, should prompt a search for a positive tissue biopsy in a visualized abnormal area of the myocardium or from a noncardiac site. Steroid therapy, although untested in randomized clinical trial, seem to be beneficial particularly when used relatively early in the course of the disease. Attention should be given to the risk of arrhythmia in this disease, with a strong consideration for prophylactic implantation of a cardiac defibrillator, particularly in the presence of ventricular arrhythmias or a reduced ejection fraction. Careful follow-up is mandatory when using high-dose steroids, and in the patient with severe heart failure and minimal extracardiac sarcoid, consideration can be given cardiac transplantation.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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