Case In Point: Sarcoidosis presenting as severe congestive heart failure

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The patient was a 40-year-old African American woman, with no significant past medical history, who presented to our medical center with a 4-week history of shortness of breath and lower extremity edema. The onset was progressive and initially occurred only with moderate exertion until about 2 weeks before presentation; at that time, her symptoms had worsened to the point where she experienced shortness of breath at rest. Orthopnea also developed at this time. The patient also reported intermittent palpitations, wheezing, and a dry cough of unknown duration.

THE CASE

The patient was a 40-year-old African American woman, with no significant past medical history, who presented to our medical center with a 4-week history of shortness of breath and lower extremity edema. The onset was progressive and initially occurred only with moderate exertion until about 2 weeks before presentation; at that time, her symptoms had worsened to the point where she experienced shortness of breath at rest. Orthopnea also developed at this time. The patient also reported intermittent palpitations, wheezing, and a dry cough of unknown duration.

On further questioning, the patient relayed that she had “not been feeling like herself lately” and described having flu-like symptoms and easy fatigability over the past 1 to 2 months and a previous 30-lb weight loss. She denied chest pain, diaphoresis, nausea or vomiting, fevers, chills, night sweats, and any recent illness. She was not taking any medications on a regular basis. There was no significant cardiac or pulmonary family history. She denied illicit drug and tobacco use and admitted to social alcohol use only.

The physical examination revealed that the patient was tachycardic, with a heart rate ranging between 110 and 170 beats per minute, and tachypneic, with a respiration rate of 42 breaths per minute. Her blood pressure was 120/70 mm Hg, and she was afebrile. Jugular venous distention was noted to the angle of the mandible with the patient lying at a 45-degree angle. She had an S3 gallop and a grade 2/6 systolic murmur. Her breath sounds were decreased at the bases with crackles noted posteriorly, excluding only the superior one fourth of the lung fields bilaterally. There was 3+ pitting edema noted in the lower extremities bilaterally. Findings from the rest of the physical examination were unremarkable. An ECG showed a supraventricular tachycardia. An echocardiogram showed global left ventricular (LV) dysfunction with an ejection fraction of 15%, LV enlargement, depressed right ventricular (RV) function with enlargement, mild mitral regurgitation, and moderate tricuspid regurgitation. Moderate pulmonary hypertension was also noted. A CT scan of the thorax showed a large right pleural effusion with compressive atelectasis, a small left pleural effusion, mild interstitial edema, and venous congestion (Figure 1).

The diagnosis of NYHA class IV CHF secondary to idiopathic cardiomyopathy was made. The patient was admitted to the critical care unit and was given intravenous loop diuretics. A repeated CT scan of the thorax showed ground-glass opacities consistent with pulmonary edema, a persistent large right pleural effusion, and prominent soft tissue in the anterior mediastinum consistent with lymphadenopathy (Figure 2).

The patient underwent a right-sided thoracentesis to improve her shortness of breath. After aggressive diuresis and 2 thoracenteses, the patient did not improve and underwent heart catheterization, which showed a cardiac index of 2.11 L/min/m². Over the next week, the Swan-Ganz catheter was left in place; the cardiac index worsened to a nadir of 1.34 L/min/m². The patient was given isotropic therapy with milrinone. She underwent electrophysiologic testing for persistent supraventricular tachycardia, but no foci were seen in the right atrium for ablation.

The patient underwent mediastinoscopy for collection of a biopsy specimen of the mediastinal lymph node that was noted on CT scan. The pathology revealed nonnecrotizing granulomas (Figure 3). Special stains of the specimen yielded negative results.

The diagnosis of sarcoidosis was made based on the noncaseating granulomatous adenopathy with
cardiac findings that could not be contributed to another process. The patient was given corticosteroids, a β-blocker, and an angiotensin-converting enzyme inhibitor. However, she still required inotropic support with milrinone.

The patient had a prolonged hospitalization with continuous milrinone therapy, so the decision was made to include her on the list for cardiac transplantation. She continued to receive the same medication regimen while classified as status IB on the transplant list. Her pleural effusions improved, and her compressive atelectasis resolved.

A follow-up CT scan showed pulmonary nodules consistent with sarcoidosis (Figure 4). This was particularly interesting because previous CT scans of the thorax failed to demonstrate nodules. It is believed that pulmonary nodules may have been initially masked by the patient's compressive atelectasis that was caused by the large effusions.

The patient's cardiac index slowly improved, and she was gradually tapered off milrinone. She was also tapered off prednisone because follow-up echocardiograms showed minimal improvement in her global myocardial dysfunction. She received an implantable cardiac defibrillator (ICD) before discharge, and her final echocardiogram demonstrated an ejection fraction of 25%. She has been out of the hospital for 6 months, and her CHF is currently NYHA functional class II. The patient is actively being monitored by advanced heart failure specialists.

**DISCUSSION**

Sarcoidosis is a chronic granulomatous disease of unknown etiology that affects many organs and tissues, most commonly the lungs. The incidence of sarcoidosis is 10 to 40 per 100,000 persons. The rate is slightly higher in African Americans, with an annual incidence of 35.5 per 100,000, than in whites, with an annual incidence of 10.9 per 100,000.\(^1\) There is a female predominance. The incidence is highest in Sweden, with a rate of 63 per 100,000. The incidence of sarcoidosis is also high in Japan, where there is a very high prevalence of cardiac involvement.\(^1\)

Cardiac sarcoidosis is an often underdiagnosed manifestation of this systemic disease, and it is a potential source of mortality.\(^1\) Classic reports have stated that 5% of patients with sarcoidosis have clinical evidence of myocardial involvement,\(^2\) although autopsy reports have shown that there are areas of granulomatous inflammation in 27%.\(^3\) In one Japanese report, more than 50% of patients with sarcoidosis at autopsy had evidence of myocardial involvement.\(^4\)

Underdiagnosis of cardiac sarcoidosis can have serious implications. Sarcoidosis is usually not lethal, but cardiac involvement significantly increases mortality. Sudden death from ventricular tachyarrhythmias or conduction block can account for up to 65% of deaths caused by cardiac sarcoidosis.\(^5\) More important, with improved diagnostic techniques, patients who receive the correct diagnosis and are subsequently treated with corticosteroids have 5-year survival rates greater than 75%, and sudden cardiac death is rare.\(^6\)

The high incidence of cardiac involvement in patients with sarcoidosis in Japan prompted the development of diagnostic guidelines by the Japanese Ministry of Health and Welfare.\(^7\) Although lacking prospective data proving statistical significance, these guidelines, nevertheless, are used by clinicians throughout the world to diagnose cardiac sarcoidosis.**Presentation and diagnosis**

The presentation of cardiac sarcoidosis can be similar to that of many other conditions affecting the heart, and this lack of specificity makes it a difficult diagnosis to establish. Symptoms include wheezing, dyspnea, palpitations, chest pain (which is atypical compared with chest pain related to pulmonary sarcoidosis), lower extremity edema, and syncope.\(^2\) Patients can present with a myriad of symptoms prompting a diagnosis of CHF. Patients with CHF may have clinical features of restrictive or dilated cardiomyopathy.

In patients with extensive fibrotic pulmonary sarcoidosis, secondary pulmonary hypertension may develop and lead to RV hypertrophy and eventually to RV insufficiency.\(^8\) Rare cases of cardiac sarcoidosis mimicking RV dysplasia or hypertrophic cardiomyopathy have been described in the literature.\(^8\) The most common areas of involvement are the LV free wall and the interventricular septum.\(^5\)

Systolic or diastolic dysfunction can occur, as can aneurysmal dilatation of the myocardial wall.\(^5\) The aneurysmal dilatation has been considered to be a result of corticosteroid therapy, which can alter the active granuloma to a nidus of scar tissue easily dilated in a high-pressure environment, such as the ventricle. In rare instances, sudden cardiac death can be the presenting sign, but with the increasing use of corticosteroids, the most common cause of death now is CHF. An ECG can show a range of abnormalities from ectopic beats to complete heart block.\(^9\) The ECG findings in 68% of patients\(^10\) include varying degrees of atroventricular (AV) block; intraventricular block; supraventricular and ventricular tachyarrhythmias\(^10,11\); atrial flutter and fibrillation; a pseudoinfarction pattern; and signs secondary to lung fibrosis and cor pulmonale, such as right heart strain, RV hypertrophy, right bundle-branch block, and right atrial enlargement.\(^9,10,12\) The most
frequent symptomatic manifestation of cardiac sarcoidosis is heart block, which is more common and occurs at a younger age in patients who have sarcoidosis than in the general population.\(^2\)

The results of a study by Yoshida and associates\(^1\) provide a good argument for general screening of patients with high-degree AV block, especially young women. This study examined 89 patients with high-degree AV block and detected 10 cases of cardiac sarcoidosis. Eight of the 10 patients were women who were aged 40 to 69 years.

Ventricular tachyarrhythmias, the second most common ECG finding, occur as a result of granulomatous inflammation and scar formation in the myocardium. These areas can be foci of abnormal automaticity, or they can cause problems with activation and recovery of the electrical circuit of the myocardium in some patients.

This involvement in activation and recovery, called inhomogeneity, has been investigated. Uyarel and associates\(^1\) evaluated QT dispersion, which is the maximal interlead difference in QT interval on a 12-lead ECG, in patients both with and without cardiac sarcoidosis. It may be inferred that a high QT dispersion is related to an inhomogeneity of ventricular recovery. An increase in QT dispersion has been associated with an increase in the incidence of sudden death in patients with heart failure\(^4\) and an increase in ventricular tachyarrhythmias.\(^1\)

Uyarel and associates\(^1\) found a statistically significant increase in the QT dispersion and increase in premature ventricular contractions in patients with cardiac sarcoidosis compared with patients who had sarcoidosis without cardiac involvement and with control patients. The study is limited by the unavailability of end points and the fact that QT dispersion by nature has low reliability and is not standardized in its recognition on an ECG. However, it is a promising noninvasive method of evaluating patients who could be at significantly increased risk for sudden cardiac death. Further research could prove it to be an independent predictor of sudden death from sarcoidosis.

Echocardiography can show various abnormalities in patients with cardiac sarcoidosis. Global or segmental wall motion abnormalities can be seen. Regional wall motion abnormalities are frequently seen, and the anterior and apical walls are preferentially affected in patients with cardiac sarcoidosis.\(^1\)

Thickening or thinning of the ventricular septum can be seen as well. Thickening of the ventricular septum, probably caused by granulomatous infiltration or interstitial edema, is one of the most important clues suggesting cardiac sarcoidosis.\(^1\) Valvular dysfunction can be seen with improper mitral valve closure, papillary muscle involvement and, less frequently, aortic valve regurgitation.\(^9\)

Thallium scans are part of the diagnostic evaluation of cardiac sarcoidosis. A decreased uptake in a segmental distribution corresponds to granulomatous involvement. Interestingly, these decrements may disappear with stress testing. This can distinguish the resting lesions from those of coronary artery disease. This phenomenon, called reverse distribution,\(^2\) has been noted in multiple reports.

Thallium scintigraphy has been reported to be beneficial in the diagnosis of cardiac sarcoidosis and in monitoring the response to therapy.\(^1\) However, it is not diagnostic and does not predict prognosis.\(^1\) Kinney and Caldwell\(^1\) reported that data from 52 patients with sarcoidosis indicated that findings from thallium scintigraphy appeared to be too nonspecific to be used for diagnosis or screening for cardiac sarcoidosis. They also noted that myocardial scan abnormalities were not associated with survival.\(^1\)

The reduced uptake of thallium in the cardiac lesion affected by sarcoidosis has been attributed to the presence of granulomatous lesions. However, reduced uptake also has been observed in cases of ischemic heart disease or cardiomyopathy. Technetium scintigraphy, like thallium imaging, does not provide a highly specific means of diagnosing or following the progression of cardiac sarcoidosis.

Gallium is highly specific to inflammatory disease and is a useful indicator of the activity of sarcoidosis. The increased uptake of gallium within the myocardium reflects the presence of activated macrophages and the accompanying epithelioid cell granuloma. It has also been used to evaluate therapeutic efficacy. In a small report, gallium scans were noted to demonstrate therapeutic efficacy after administration of corticosteroids.\(^1\)

However, myocardial gallium images are often not sufficiently clear, and distinguishing gallium uptake in the myocardium from that in the lung or mediastinum is frequently difficult. Therefore, the clinical usefulness of gallium scanning has not been established despite some previous reports confirming abnormal gallium uptake in the myocardium.\(^2\)

Nakazawa and colleagues\(^2\) studied the addition of technetium to improve the accuracy of gallium scintigraphy in 14 patients with cardiac sarcoidosis. The technetium portion could be used as an outline of myocardial involvement, which improved the diagnostic accuracy of gallium scintigraphy. This dual imaging modality also allowed the response to therapy to be evaluated more accurately. This provides significant support for the use of both modalities in the diagnosis of cardiac sarcoidosis.
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and in assessing the therapeutic response.\textsuperscript{20} \textsuperscript{18}F-Fluoro-2-deoxyglucose positron emission tomography (\textsuperscript{18}F-FDG PET) is a newer imaging technique used in patients with cardiac sarcoidosis that can identify lesions undetected by gallium or technetium \textsuperscript{99m}Tc sestamibi (\textsuperscript{99m}Tc-MIBI) scintigraphy. In a study by Ishimaru and associates,\textsuperscript{21} 32 patients with sarcoidosis and 30 controls were evaluated with standard diagnostic testing and PET scanning. The results were categorized as no involvement, diffuse, focal, and focal-on-diffuse. All of the controls were in either the no-involvement group or the diffuse group; none had any focal findings. In contrast, 10 of the patients with sarcoidosis had focal or focal-on-diffuse patterns. What is most important about this study’s findings is that none of the 10 patients with focal lesions on PET had abnormalities on gallium scintigraphy and only 4 had abnormalities on \textsuperscript{99m}Tc-MIBI scintigraphy. This modality, therefore, has the potential to identify abnormalities in patients with cardiac sarcoidosis that cannot be detected by conventional scintigraphy.\textsuperscript{7} After corticosteroid therapy, \textsuperscript{11}N-ammonia (\textsuperscript{13}N-NH\textsubscript{3}) defects exhibited no significant change, whereas \textsuperscript{18}F-FDG uptake was markedly diminished in size and intensity or disappeared completely.\textsuperscript{22} These findings suggest that cardiac \textsuperscript{11}N-NH\textsubscript{3}/\textsuperscript{18}F-FDG PET is the most useful method for identifying cardiac involvement in sarcoidosis, and decreased uptake on \textsuperscript{18}F-FDG PET may be useful for the assessment of disease activity.\textsuperscript{23} This assessment of disease activity may have promise in monitoring a patient’s response to corticosteroid therapy. \textsuperscript{18}F-FDG PET detects areas of inflammation, while \textsuperscript{99m}Tc-MIBI localizes only perfusion defects.\textsuperscript{18} F-FDG PET can detect macrophages and lymphocytic infiltrate in the early inflammatory stage of sarcoidosis.\textsuperscript{24} This occurs before the formation of noncaseating granulomas and associated fibrosis, which are associated with more advanced disease.

This was examined in a study of 11 patients who had cardiac sarcoidosis diagnosed on the basis of the Japanese Ministry of Health and Welfare’s criteria (with exception of criterion 2c).\textsuperscript{24} The diagnosis was made by endomyocardial biopsy in 3 patients, and a clinical diagnosis was made in 8. All patients with cardiac sarcoidosis underwent imaging with gallium, \textsuperscript{99m}Tc-MIBI, and \textsuperscript{18}F-FDG PET. The results showed that \textsuperscript{18}F-FDG PET was more capable of demonstrating defects in patients in the clinical diagnosis group than in those in the histologic diagnosis group. The abnormalities represented impaired myocardium in the advanced stage, evidenced by more defects noted in the histologic diagnosis group. Therefore, \textsuperscript{18}F-FDG PET may be a valuable predictor of early disease and may contribute significantly to the early initiation of treatment--before the formation of fibrotic scar.\textsuperscript{24} In another small series, scintigraphy using \textsuperscript{99m}Tc-labeled depreotide (a somatostatin analog) correctly identified all sites of major, clinically significant cardiac involvement in sarcoidosis.\textsuperscript{25} Although this was a small study, it holds promise for future large trials.

Cardiac MRI may also be beneficial in investigating myocardial sarcoidosis. Limited, nontransmural, or patchy myocardial scar tissue may remain undetected by ECG, ultrasonography, or scintigraphy, but it may be detected by cardiac MRI because of its high resolution. The additional value of gadolinium- enhanced MRI to standard assessment of cardiac sarcoidosis was demonstrated by Smedema and associates.\textsuperscript{26} Ventricular dilatation, functional impairment, and ventricular arrhythmias, all known markers of sudden death, were seen on cardiac MRI when late gadolinium enhancement was used.\textsuperscript{26}

Another important message can be taken from Smedema and colleagues’\textsuperscript{26} study of symptomatic and asymptomatic patients with cardiac sarcoidosis. Of the symptomatic patients, 84% received a diagnosis of cardiac sarcoidosis. Of the asymptomatic patients, 4% had granulomatous involvement of the myocardium after intense diagnostic evaluations, including electrocardiography; echocardiography; scintigraphy; and, in some patients, MRI, endomyocardial biopsy, and angiography. Therefore, it can be concluded that cardiac sarcoidosis is common in patients with symptoms but uncommon in those without symptoms.

The accurate localization of a granulomatous lesion can be used for endomyocardial biopsy.\textsuperscript{18} Furthermore, there is increasing evidence that cardiac MRI can be useful in monitoring the response to treatment with corticosteroids.\textsuperscript{18} The definitive diagnosis of cardiac sarcoidosis is established by endomyocardial biopsy, which reveals the classic noncaseating granuloma surrounded by lymphocytes (Table).\textsuperscript{27} However, difficulties with this procedure are often cited outside of specialized centers, and sensitivities are low. The difficulty seems to be 2-fold. First, the patchy nature of distribution of sarcoid granulomas in the heart can result in sampling error. Second, the areas of the heart that are most commonly affected by sarcoidosis are very difficult to reach to obtain a biopsy specimen. A multitude of evidence shows that a negative biopsy result should not preclude treatment, as exemplified by a study from Japan by Uemura and associates.\textsuperscript{23} In that study, 26 patients in whom
Cardiac sarcoidosis was strongly suspected, based on the Japanese Ministry of Health and Welfare’s guidelines, underwent endomyocardial biopsy. Only 19% of the biopsy specimens showed features of sarcoidosis. Interestingly, there was a higher success rate in patients who presented with dilated cardiomyopathy (36%) than in those who presented with conduction disturbances (6%). The research group recommended that the lack of confirmation by biopsy should not preclude the decision to treat a patient with symptoms of cardiac sarcoidosis and other positive diagnostic information.

A study from Johns Hopkins University examined more than 1000 patients who had undergone endomyocardial biopsy, including 28 with a diagnosis of sarcoidosis. Of those 28 patients, 10 had biopsy-proven sarcoidosis. Their mean survival was lower than that of the biopsy-negative patients, although only marginal statistical significance was reached. This illustrates that most patients who undergo endomyocardial biopsy do not have sarcoidosis and that biopsy specimens showing noncaseating granulomas may be a poor prognostic indicator. This may be attributable to more extensive involvement of the myocardium with granulomas.

**Treatment**

Corticosteroids have significantly improved the prognosis of cardiac sarcoidosis. Older studies had shown that two thirds of patients with cardiac sarcoidosis die suddenly. Ventricular tachycardia was one of the most frequently reported cardiac arrhythmias and, with complete heart block, was presumed to be the cause of sudden death in most patients with myocardial sarcoidosis. However, only 18% of those who died suddenly had been treated with corticosteroids. Follow-up of patients in subsequent trials has shown an improved survival rate. Fleming and Bailey showed a 5-year survival rate of 44%.

More recently, a study in Japan showed a 5-year survival rate of greater than 75% in patients with signs of cardiac sarcoidosis and 90% in those with preserved systolic function. Sudden cardiac death was rare, and most patients died of severe CHF rather than ventricular tachycardia. Further, this study showed that NYHA functional class and the increase in LV dimension through remodeling were independent predictors of increased mortality.

Early initiation of corticosteroid therapy may be critical. Echocardiographic stratification shows that worsening LV systolic function is related to worse outcome and that corticosteroids may help prevent LV remodeling and preserve LV function in the early or middle stage of the disease. In one study, 43 patients with cardiac sarcoidosis underwent echocardiography before and after corticosteroid therapy to determine the effectiveness of corticosteroids in preventing LV remodeling and improving LV contractility. In patients with initial LV ejection fractions of 55% or higher, long-term corticosteroid therapy showed preventive effects for LV remodeling and LV function.

Patients with LV ejection fractions of less than 54% had significantly reduced LV volumes and improved LV ejection fractions with corticosteroid therapy. However, corticosteroid therapy resulted in neither LV volume reductions nor improved LV ejection fractions in patients with LV ejection fractions of less than 30%.

Antiarrhythmic therapy and pacemaker implantation for symptomatic patients with cardiac sarcoidosis has proved invaluable. Because of the progress in antiarrhythmic therapy and pacemaker implantation, the primary cause of death in those with cardiac sarcoidosis has changed from sudden death to CHF. There are no official recommendations for pacemaker implantation in patients with cardiac sarcoidosis, and the expert opinion is to follow the indications for pacemaker implantation in the general population.

ICDs effectively terminate life-threatening arrhythmias in high-risk patients, with significant survival outcomes after the first appropriate ICD therapy. In addition, programmed ventricular stimulation identifies patients with cardiac sarcoidosis who are at high risk for arrhythmic events.

Interestingly, the necessity of aggressive diagnosis and treatment for symptomatic patients was illustrated by Smedema and associates, who studied 101 patients with sarcoidosis. Of the patients with symptoms of cardiac involvement, 20% died and 47% required either a defibrillator or pacemaker, while the course for asymptomatic patients after almost 2 years of follow-up was completely uneventful. Because sudden cardiac death can be the initial presentation of cardiac sarcoidosis and ventricular arrhythmias may recur despite antiarrhythmic medications, certain authors believe that once the diagnosis of cardiac sarcoidosis is made, ICD implantation should be strongly considered as a primary prevention of sudden cardiac death.

For patients with cardiac sarcoidosis whose condition continues to deteriorate because of severe CHF, heart transplantation is a potential option. Intermediate-term survival has been similar to that of patients who undergo transplantation for other indications. Despite the possibility of recurrence of sarcoidosis in the graft or the appearance of progressive extracardiac disease, available evidence supports transplantation in patients with extensive cardiac involvement and advanced heart failure.
as long as there is minimal extracardiac involvement.\textsuperscript{33} One recurrence was observed during a routine surveillance cardiac biopsy 6 months post-transplantation in a patient not previously known to have sarcoidosis; the biopsy revealed noncaseating granulomas consistent with sarcoidosis.\textsuperscript{34} Follow-up biopsies have been reported up to 3.5 years after transplantation without recurrence of noncaseating granulomas.\textsuperscript{34}

**Conclusions**

Survival rates have significantly improved in patients with cardiac sarcoidosis because of an increased recognition of its symptoms; improved diagnostic tools; and increased use of therapies such as corticosteroids, pacemakers, and ICDs. The spectrum of advanced disease is also changing as a result of mechanical and pharmacologic therapy; the most common cause of death is now heart failure rather than sudden cardiac death. However, the diagnosis is still imprecise\textsuperscript{18} and there is a need for large multicenter trials to determine proper screening for cardiac involvement in patients with sarcoidosis to prevent the dreaded presentation of sudden cardiac death and to minimize the ventricular damage with early initiation of corticosteroid therapy.

**References:**


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