Cardiac Sarcoid: A Clinicopathologic Study of 84 Unselected Patients with Systemic Sarcoidosis

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SUMMARY Although sarcoid may involve the myocardium, there is little information on its incidence or significance. We studied 84 consecutive autopsied patients with sarcoidosis. The patients ranged in age from 18-80 years (average 46 years) and 61% were women; 23 (27%) of them had myocardial granulomas. In eight (35%) these were clinically silent, and in 15 (65%) there was a history of heart failure and/or arrhythmias and conduction defects. Of the 23 patients, only four (17%) had grossly evident, widespread myocardial lesions: three of these four (75%) had documented arrhythmias. All four had sudden, unexpected death at an average age of 36 years; in only two had sarcoid been suspected during life. The other 19 patients (83%) had microscopically evident granulomatous involvement. Of these, eight (42%) had a rhythm or conduction disturbance and three (16%) sudden death, although none of those who suffered sudden death had a recognized rhythm or conduction disturbance. None (15%) of those without cardiac sarcoidosis had a rhythm or conduction disturbance and eight (13%) suffered a sudden death.

The results show that although myocardial involvement occurs in at least 25% of patients with sarcoid, it most often involves a small portion of myocardium and is clinically silent. Since some of the 61 patients in whom myocardial lesions were not identified may still have had small microscopic granulomas, the true incidence of myocardial sarcoidosis may be even greater than suggested here. Rhythm and conduction disturbances are more common in the cardiac sarcoid group, but the findings suggest that only the small subset of patients with severe, grossly evident myocardial sarcoid are at increased risk for sudden death.

SARCOIDOSIS HAS BEEN known for over 100 years, but that sarcoid was a systemic disease, and specifically one that could affect the heart, took 60 years to achieve recognition. As early as 1869 Jonathan Hutchinson first observed a patient with the cutaneous lesions of sarcoid.1 In 1889 Besnier described a patient with cutaneous lesions similar to those described by Hutchinson, but he thought the lesions were not identical and named the condition “Lupus Pernio.”2 In 1898 Hutchinson described two additional cases in “Cases of Mortimer’s Malady,” named after one of the patients.3 In “Multiple Benign Sarkoid of the Skin,” Boeck reported in 1889 a skin affliction with cutaneous lesions “. . . described as perivascular sarcomatoid tissue . . . .”.4 It was Schaumann in 1914 who finally demonstrated that Lupus Pernio and Boeck’s Sarcoid were one disease with systemic manifestations,5 and Kuznitsky and Rifforf in 1915 supported the belief that this disease was a systemic process.6

In 1929 Bernstein7 first described cardiac sarcoidosis at postmortem and six years later Salvesen8 reported a patient with sarcoidosis and an electrocardiogram with bundle branch block and suggested myocardial sarcoidosis as the etiology, although there was no histologic evidence. In 1939 Cotter9 reported an 18-year-old male with atrial fibrillation and complete heart block, with extensive infiltration of the myocardium and pericardium by sarcoid at autopsy. In 1952 Longcope and Freiman reported a combined series from The Johns Hopkins Hospital and Massachusetts General Hospital of 160 cases of sarcoidosis, including 30 combined autopsied cases.10 They also reviewed the distribution of sarcoid lesions in the 62 autopsied cases reported in the literature at that time. Combining their experience with the cases in the literature, they described myocardial involvement in 20% of the 92 autopsied cases of sarcoid.

Since then sporadic case reports and reviews have appeared, but the incidence and spectrum of cardiac involvement in an unselected series of patients with sarcoidosis is unknown. Studies limited to patients with extensive cardiac sarcoidosis cannot provide this information. The spectrum of cardiac sarcoidosis extends from the secondary effect on the heart of pulmonary sarcoidosis to primary myocardial involvement. The former does not usually pose serious diagnostic problems, but myocardial sarcoidosis is difficult to recognize. This is due in part to its clinical presentation, which may include conduction disturbances and arrhythmias, congestive heart failure, mitral insufficiency, myocardial infarction, recurring pericardial effusion and sudden death. These presentations may raise the suspicion of cardiac involvement; but this can be substantiated only by histologic confirmation, which most often comes at postmortem examination. We reviewed the 84 consecutive autopsied cases of sarcoidosis autopsied at The Johns Hopkins Hospital since 1889 to examine the incidence as well
as the clinical and morphologic spectrum of cardiac sarcoidosis.

Materials and Methods

The records of all patients with sarcoidosis in the autopsy files of The Johns Hopkins Hospital were studied. In all patients the clinical and autopsy records and histologic sections were reviewed. At least five histologic sections from each heart were studied. Only those cases with characteristic non-caseating epithelial-cell granulomas involving lymph nodes and at least one organ were considered to be sarcoid (criteria modeled after Mitchell et al.\textsuperscript{11}). Myocardial fibrosis alone without evidence of granulomatous lesions was not considered to represent cardiac sarcoid whether or not the coronary arteries were narrowed. A total of 84 cases are reviewed, including the 12 cases from The Johns Hopkins Hospital reported by Longcope and Freiman in 1952. The conducting systems in 20 of the cases were examined histologically by a method described previously.\textsuperscript{12}

Morphologic Observations

Of the 84 cases, 23 (27\%) had myocardial sarcoidosis. Grossly visible involvement with widespread granulomatous myocarditis, however, was present in only four (17\%) of those 23 cases. The remaining 19 had myocardial involvement that was evident only histologically. The involvement was purely epicardial in five of the 19, and entirely myocardial in the remaining 14 cases. The extent of cardiac sarcoidosis in the 19 cases ranged from an isolated granuloma to more widespread active granulomatous myocarditis (fig. 1). There was no cardiac involvement in the remaining 61 cases. Morphologic findings in the patients with severe (group 1), mild (group 2), and no cardiac sarcoid (group 3) are summarized in table 1. Among the three groups there were no significant differences with regard to heart weight. The extent of extracardiac sarcoidosis also did not differ among the groups. The conducting system was examined in 20 cases, and a single case in the group with only histologically evident sarcoid showed involvement by sarcoid (fig. 2).

In the four patients with severe sarcoid involvement of the heart, gross inspection revealed diffuse yellow-white-gray irregular infiltration of the myocardium, described as “tumor like” in one of the autopsy protocols. The left ventricle was involved in each case, while the septum and right ventricle were involved in two cases and the papillary muscles were involved in three. In the case with the most extensive involvement, there was infiltration of both atria as well as the walls of the aorta, pulmonary artery and the superior and inferior vena cava. No aneurysms were observed and all valves were spared. Widespread fibrosis was evident in all four cases. The hearts ranged in weight from 525–330 g, with two greater than 400 g.

Clinical Observations (tables 2, 3 and 4)

Patients Without Myocardial Sarcoid

The 61 patients in group 3 ranged in age from 17–78 years (average 46 years), and 39 (64\%) were women. Seventeen (28\%) patients suffered left-sided congestive heart failure and 20 (33\%) had a history of hypertension. Of the 17 with congestive heart failure, 11 (65\%) were hypertensive, four (24\%) had coronary artery disease and three (18\%) had valvular heart disease. Nine (15\%) patients had a rhythm or conduction disturbance on a resting 12-lead electrocardiogram which included: three (5\%) with ventricular arrhythmias; three (5\%) with an intraventricular conduction defect (two with right bundle branch block and one with an alternating right and left bundle branch block); and three (5\%) with first degree heart block. There were no cases of complete heart block. Five (8\%) patients experienced supraventricular arrhythmias; two, atrial fibrillation; one, a wandering atrial pacemaker; one, a nodal tachycardia; and one, premature nodal contractions. Twenty-two (36\%) patients had cardiac symptoms as evidenced by either congestive heart failure or a rhythm or conduction disturbance, but in 19 (98\%) these symptoms could be accounted for by factors other than myocardial sarcoid. Fourteen (23\%) patients suffered from cor pulmonale. A clinical diagnosis of sarcoidosis was made in 30 (49\%) of the cases. Eight (13\%) of the patients experienced a sudden and unexpected death. One of these eight had a history of a rhythm and conduction disturbance: first degree heart block and occasional premature ventricular contractions (PVCs). The sudden deaths could be accounted for by factors other than myocardial sarcoid in seven (88\%).

Patients with Mild Myocardial Sarcoid

The 19 patients in group 2 ranged in age from 23–80 years (average 49 years), and nine (47\%) were women. Seven (37\%) were hypertensive. Six (32\%) had a history of left-sided congestive heart failure; three (50\%) of these were hypertensive, two (33\%) had coronary artery disease and one had valvular heart disease. Eight (42\%) had rhythm or conduction disturbances on ECG, including two (11\%) with ventricular arrhythmias, six (32\%) with intraventricular conduction disturbances, three (16\%) with first degree heart block, and three (16\%) with supraventricular arrhythmias. Supraventricular arrhythmias included atrial fibrillation in one patient, paroxysmal atrial tachycardia in one, and premature atrial contractions in one. A patient with paroxysmal atrial tachycardia, left bundle branch block (LBBB) and occasional PVCs required a permanent pacemaker. Twelve (63\%) of the group 2 patients had cardiac symptoms manifested by either congestive heart failure or a rhythm or conduction disturbance; in eight (67\%) these symptoms could be attributed to factors other than myocardial sarcoid. Sarcoidosis was diagnosed clinically in eight (42\%) of
the 19. Three patients (16%) had cor pulmonale. Three (16%) patients sustained a sudden and unexplained death. None of these three had a history of rhythm or conduction disturbance, and in all three the sudden death could be attributed to a factor other than myocardial sarcoid. The one patient with complete heart block known for at least eight years committed suicide at age 42. The group 2 patients had three times the incidence of arrhythmias than those in group 3.

To determine whether this could be due to random distribution of coronary, valvular or other diseases rather than the presence of small myocardial granulomas, we excluded from both groups 2 and 3 patients in whom diseases other than myocardial sarcoid could be responsible. Only two of 61 (3%) patients in group 3 had truly unexplainable electrocardiographic disorders, whereas in four of 19 (21%) in group 2 were they unexplainable, suggesting that
the myocardial sarcoid made the difference in this latter group.

Patients with Severe Myocardial Sarcoid

The four patients with extensive sarcoidosis ranged in age from 24–43 years (average 36 years), and three (75%) were women. There was a clinical history of cardiac abnormality in three (75%); one suffered left-sided congestive heart failure, and three had abnormal electrocardiograms. Ventricular arrhythmias were present in two of the four patients and one had atrial flutter. None experienced cor pulmonale. A clinical diagnosis of sarcoidosis was made in two patients and sudden and unexplained death occurred in all four. None of the cardiac symptoms or sudden death could be accounted for by a factor other than myocardial sarcoid. Clinical details of these four patients, who represent a unique and relatively small (5%) subgroup of the entire series of 84 patients, are summarized below.

Case 1

A 24-year-old black female had a several-month history of palpitations and dyspnea on exertion. One month before her first admission she had a syncopal episode. Upon regaining consciousness she noted that her heart was beating extremely rapidly. She had a similar episode the day before admission. Her physical exam was remarkable for cervical adenopathy and a tachycardia of 230. Her paroxysmal tachycardia, believed to be atrial flutter, was unresponsive to usual maneuvers but was resolved with quinidine. She did well until four months later, when, while playing cards, she noted sudden severe shortness of breath, palpitations and weakness, and collapsed. She was dead on arrival at The Johns Hopkins Hospital emergency room.

Case 2

A 40-year-old black male was reportedly in good health. He had been seen at The Johns Hopkins Hospital one time before his death — in the ENT clinic in 1932 (five years before death) with the impression of left middle ear deafness; no other problems
were noted. No electrocardiogram is available. While sitting on his doorstep he suddenly fell unconscious and was dead on arrival at The Johns Hopkins Hospital.

Case 3

A 37-year-old black female had a diagnosis of sarcoidosis when she presented with dimming of vision and was found to have corneal changes compatible with sarcoidosis. Further evaluation revealed bilateral hilar adenopathy on chest x-ray and a positive Kveim test. One year later she was admitted to the hospital with a cough and shortness of breath, frequent multifocal PVCs and runs of ventricular tachycardia, and mild left-sided congestive heart failure. Steroids were instituted because of the suspicion of cardiac sarcoidosis but the day after admission she developed ventricular fibrillation and died.

Case 4

A 41-year-old woman with a diagnosis of sarcoidosis made on the basis of uveitis, a maculopapular rash, ninth, tenth and peripheral seventh nerve palsies and dyspnea on exertion. Her chest x-ray revealed hilar adenopathy, a skin biopsy demonstrated non-casating granuloma, and a Kveim test was positive. She was treated with prednisone 40 mg daily for five months, but because of acute psychosis it was discontinued and chloroquin was instituted. At that time premature atrial and ventricular contractions with coupling were noted and she was treated with quinidine. A thallium-201 myocardial perfusion scan demonstrated areas of decreased thallium uptake in the left ventricle. Four weeks after her last sarcoid clinic appointment she was found dead at home.

Discussion

Numerous case reports and reviews of cardiac sarcoidosis have provided information as to how sarcoid may affect the heart, but these reports do not explain the incidence and significance of such findings. In this study we examined 84 consecutive, unselected autopsy patients with sarcoidosis to determine the incidence and the clinical and morphologic manifestations of cardiac sarcoidosis. We found sarcoid in the heart in 27% of these patients, which is close but somewhat higher than the commonly quoted figure of 20%, based on Longcope's and Freiman's combined experience and review of the literature in 1952, and much higher than the 13% incidence they found in their own autopsy series of 30 patients. Since the gross
TABLE 4. Cardiac Symptoms in Patients with Systemic Sarcoidosis: Etiologic Factors

<table>
<thead>
<tr>
<th>Cardiac involvement</th>
<th>Severe</th>
<th>Mild</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>4</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
<td>24–43 (36)</td>
<td>50–59 (55)</td>
<td>39–78 (60)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>2 (67%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cor Pulmonale</td>
<td>0</td>
<td>1 (33%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Other contributing disease</td>
<td>0</td>
<td>0</td>
<td>1 (13%)*</td>
</tr>
<tr>
<td>Symptoms accounted for by factors other than myocardial sarcoid</td>
<td>0</td>
<td>3 (100%)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Number of patients</td>
<td>38</td>
<td>38–68 (52)</td>
<td>32–71 (47)</td>
</tr>
<tr>
<td>Age</td>
<td>0</td>
<td>1 (17%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>2 (33%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>1 (17%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Hypertension with LVH at autopsy</td>
<td>0</td>
<td>3 (50%)</td>
<td>11 (65%)</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>0</td>
<td>0</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Other contributing disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms accounted for by factors other than myocardial sarcoid</td>
<td>0</td>
<td>5 (83%)</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>Arrhythmias or conduction disturbances</td>
<td>3</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Number of patients</td>
<td>24–43 (35)</td>
<td>23–68 (49)</td>
<td>20–78 (50)</td>
</tr>
<tr>
<td>Age</td>
<td>0</td>
<td>1 (13%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>1 (13%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>1 (13%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Hypertension with LVH at autopsy</td>
<td>0</td>
<td>1 (13%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>0</td>
<td>3 (38%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>0</td>
<td>1 (13%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Other contributing disease</td>
<td>0</td>
<td>2 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms accounted for by factors other than myocardial sarcoid</td>
<td>0</td>
<td>4 (50%)</td>
<td>7 (78%)</td>
</tr>
</tbody>
</table>

*This patient had a poorly characterized neurologic disorder, thought possibly to be myasthenia gravis; his death was due to sudden respiratory distress.
†One patient had squamous cell carcinoma of the lung metastatic to the myocardium. The other patient was a chronic alcoholic with frequent episodes of severe electrolyte abnormalities and hypomagnesemia.

Specimens were not available for us to review in all cases, it is possible that the true incidence of cardiac involvement by sarcoid in patients with this systemic disease is, if anything, greater than 27%.

Cardiac symptoms are common in patients with systemic sarcoidosis, but our findings suggest that in less than half the cases do these symptoms reflect myocardial infiltration with sarcoid. Although 44% of our patients had cardiac symptoms, less than half had any demonstrable granulomas in their hearts, and about 10% had grossly evident disease. As shown in table 4, in those with no histologic evidence of myocardial sarcoid, nearly all arrhythmias, conduction disturbances, congestive heart failure or sudden death could be attributed to a systemic disease or a cardiac disorder other than myocardial sarcoid. Similarly, nearly all patients with sudden death or congestive heart failure in the group with histologically detectable sarcoid had an explanation other than granulomas in the heart. In this sarcoid group, however, only 50% of those with arrhythmias or conduction disturbances had another possible etiology, such as coronary or valvular heart disease for these disturbances, along with sarcoid.

That microscopic sarcoid did account for the increased incidence of arrhythmias and conduction disturbance is suggested by the greater incidence of unexplained arrhythmias in the group 2 patients (21%) compared with the group 3 patients (3%) who did not have myocardial sarcoid. In all patients with severe myocardial sarcoid, the myocardial sarcoid was the only evident cause for their severe cardiac symptoms.

Thus, the major clinical difference between those with cardiac sarcoid (severe and mild) and those without was a greater incidence of a rhythm or conduction disturbance in the former group (fig. 3). Congestive heart failure had no value in distinguishing the three groups. Sudden, unexplained death appeared to be a manifestation of sarcoid myocardial disease, but only in its severest form.

It is not clear why electrocardiographic abnormalities are increased in the patients with microscopic cardiac sarcoidosis. Although cardiac involvement was often minimal, a lesion involving the conducting system would potentially be more significant. Only one of nine conducting systems studied histologically in this group was involved, although four of the cases had a rhythm or conduction disturbance. The one patient with sarcoids and fibrosis in the conducting system was a 42-year-old black male with complete.
heart block for at least eight years as well as prolongation of the QRS interval from 0.10–0.13 seconds. He had syncopal episodes, but his death was due to suicide.

Sudden unexplained death was the clinical manifestation common to all four cases with severe myocardial sarcoid, and in three of the four arrhythmias were noted during life. Although our study group is small, in a recent review limited to cases of severe myocardial sarcoid, sudden death was described as "the most common cardiac manifestation of clinically significant cardiac sarcoidosis." In our four patients, two with severe lesions were recognized clinically after presenting with noncardiac symptoms, and all four had involvement of multiple organ systems at autopsy. The frequency of a clinical diagnosis of sarcoid was similar in those with severe, mild and no cardiac sarcoidosis. Thus, with these limited numbers, we have not found, as has been suggested, that patients with cardiac sarcoidosis have minimal sarcoidosis of other organs or that symptomatic involvement of extracardiac systems generally indicates that severe cardiac sarcoid is not likely to occur.

What seems clear from our study and from those previously reported is that the patients at greatest risk for sudden death are those with extensive, grossly evident cardiac sarcoidosis. How can we identify these patients? One of the four patients had a thallium-201 myocardial perfusion imaging scan which revealed areas of decreased thallium concentrations. Thallium-201 may be a useful noninvasive technique for the recognition of cardiac sarcoidosis. Possibly, however, such scans may be "too sensitive," detecting those with only trivial granulomas. This makes it even more essential to know the clinical significance of "mild" cardiac sarcoid.

Arrhythmias appear to be the most predictive of cardiac sarcoid, extensive or mild. Three of the four patients with severe myocardial sarcoid had recognized arrhythmias. Although an arrhythmia or conduction disturbance is not predictive of sudden death, as demonstrated from the other two groups, selecting among those patients with arrhythmias for further study with myocardial perfusion imaging may permit identification of those patients at risk for sudden death. Particularly important is whether patients with mild myocardial sarcoid progress to severe involvement and at what rate, and whether any therapy, such as corticosteroids, can prevent this progression if started early. Our data show that the only effective way of identifying cases with mild cardiac sarcoidosis is by the presence of an electrocardiographic abnormality. Using this criteria, 15% of cases without cardiac sarcoidosis would have been candidates for steroid therapy, and 58% of cases in group 2 would have been excluded. The use of 24-hour continuous ambulatory electrocardiographic recordings or stress testing may improve the sensitivity of detecting the group 2 patients, as a resting 12-lead ECG is a relatively insensitive means of detecting rhythm disturbances. As noted above, however, whether treatment is warranted, or will alter progression in patients with what appears to be benign cardiac sarcoid, is not clear.

In our series of 84 patients with sarcoidosis, only 5% had grossly evident widespread involvement, and 23% had only microscopically detectable cardiac involvement. These two groups appear to differ significantly; the latter group is clinically more like those without cardiac involvement, with one exception. Patients with no cardiac involvement and those with only microscopically detectable cardiac sarcoidosis had
similar ages, cardiac symptoms, and sudden death frequency, but there was a greater incidence of rhythm or conduction disturbances in those with microscopic cardiac sarcoidosis. This increased incidence of electrocardiographic abnormalities may permit identification of these patients. Whether these patients are candidates for any therapy such as corticosteroids is not established, and these patients are not at greater risk for sudden death than those without cardiac sarcoidosis. The reason for treatment would be to prevent progression of microscopic cardiac sarcoidosis to grossly evident extensive cardiac sarcoidosis, which has a very high incidence of sudden death — 100% in our series. The patients with extensive, grossly evident cardiac sarcoidosis may be identified by the presence of a rhythm or conduction disturbance and a defect on thallium-201 myocardial perfusion imaging in the absence of a history of ischemic heart disease. It has not been determined whether any therapy is likely to be effective in reducing the incidence of sudden death in these patients.

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