Review paper

Cardiac sarcoidosis: a comprehensive review

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Abstract

Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by noncaseating granulomas in involved organs. Organs involved with sarcoidosis include lymph nodes, skin, lung, central nervous system, and eye. Only 40-50% of patients with cardiac sarcoidosis diagnosed at autopsy have the diagnosis made during their lifetime. Cardiac sarcoidosis can manifest itself as complete heart block, ventricular arrhythmias, congestive heart failure, pericardial effusion, pulmonary hypertension, and ventricular aneurysms. Diagnostic tests such as the electrocardiogram, two-dimensional echocardiography, cardiac magnetic resonance imaging, positron emission tomography scan, radionuclide scan, and endomyocardial biopsy can be helpful in the early detection of cardiac sarcoidosis. Considering the increased risk of sudden death, cardiac sarcoidosis is an indication for early treatment with corticosteroids or other immunosuppressive agents. Other treatments include placement of a pacemaker or implantable defibrillator to prevent sudden death. In refractory cases, cardiac transplantation should be considered.

Key words: sarcoidosis, noncaseating granulomas, cardiac sarcoidosis.

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by the presence of noncaseating granulomas in the involved organs. The prevalence is 10-40/100,000 persons in the United States and Europe with an increased prevalence of sarcoidosis in African-Americans compared to Caucasians with a ratio ranging from 10-17 : 1 [1]. The Scandinavian population has a higher prevalence of sarcoidosis than other whites [2].

Sarcoidosis is more prevalent in women than in men. Virtually any body tissue may be involved. Organs commonly involved with sarcoidosis include lymph nodes, skin, lung, central nervous system, and eye. Although many patients may not manifest symptoms at the time of diagnosis, some patients present with systemic symptoms such as fatigue, anorexia, weight loss, and fever. Many patients report dyspnea on exertion, retrosternal chest pain, and cough. In 20% to 50% of patients with more acute presentations, the constellation of erythema nodosum, bilateral hilar lymphadenopathy, and polyarthralgia (Lofgren's syndrome) is seen. In the United States, more than half of patients present with chronic respiratory symptoms and few constitutional symptoms [2].

Cardiac involvement in sarcoidosis occurs in 20-30% of patients in pathology series [3]. Cardiac involvement in patients with sarcoidosis is being increasingly recognized and is associated with a poor prognosis. Silverman *et al.* reviewed 84 autopsy cases of pulmonary sarcoidosis and found myocardial granulomas in 27% of patients [4]. Cardiac involvement may be high as 58% in Japanese patients with sarcoidosis [5, 6] and may be responsible for as many as 85% of deaths of Japanese patients with sarcoidosis [6, 7]. Despite these findings, only 5% of patients with sarcoidosis have clinical manifestations of cardiac disease, and only 40-50% of patients with cardiac sarcoidosis at autopsy have the correct diagnosis made during their lifetime.

The etiology of cardiac sarcoidosis remains unknown. Environmental, occupational, and infectious causes have been hypothesized. These agents may act as immunologic triggers in genetically predisposed individuals. A multicenter case controlled study did not discover a single predominant cause of sarcoidosis, but identified several exposures that were linked to sarcoidosis risk including agricultural employment and exposure to insecticides or microbial bioaerosols [8]. A number of infectious organisms, including *Mycobacteria*, *Propionibacteria*, *Borrelia*, *Rickettsia*, and *Herpes virus* have been implicated as possible etiologies of sarcoidosis [9]. A provocative pilot study reported the empiric use of anti-fungal agents with corticosteroids for 3-6 months in 18 patients resulted in improvement of clinical symptoms, chest X-ray infiltration, and pulmonary function [10]. The role of infectious organisms in the etiology of sarcoidosis remains to be clarified. Myocardial sarcoidosis affects young and middle-aged patients without sex predilection. Myocardial involvement may occur in 25% of patients with sarcoidosis in the United States, and may account for as many as 13-25% of deaths from sarcoidosis.

Pathology

The etiology of sarcoidosis is unknown, but the principal inciting event leads to granuloma formation, which can then either resolve or progress to fibrosis. Sarcoidosis requires at least 3 major events: exposure to antigen; acquired cellular immunity directed against the antigen mediated through antigen presenting cells and antigen specific T lymphocytes; and the appearance of immune effector cells that promote a more nonspecific inflammatory response.

The characteristic lesion of sarcoidosis is a discrete, compact, noncaseating epitheloid cell granuloma. The granuloma consists of highly differentiated mononuclear phagocytes and lymphocytes. Infectious and environmental agents have been implicated as potential antigens. These antigens are thought to trigger primarily the helper inducer T cells leading to formation of granuloma lesions. Early in the disease, sarcoid infiltrate mainly consist of mononuclear phagocytes and CD4 positive T cells with a T helper Type 1 response, secreting interleukin-2 and interferon-γ. At a later stage of lesion evolution, there is a shift of cytokine profile to that of T helper type 2 response which has been demonstrated during the fibroblastic phase of the granuloma and is believed to exert anti-inflammatory effects and result in tissue scarring (Figure 1). Furthermore, high concentrations of interleukin-6 are found in the circulation at the onset of disease and before the initiation of immunosuppressive therapy, but not thereafter. Interleukin-6 is thought to be involved in the maintenance of inflammation by inducing the proliferation of T cells [11].

Clinical manifestations of sarcoidosis are dependent on both the profusion and location of granulomas. Cardiac sarcoidosis is associated with noncaseating granulomas which may involve the left ventricular free wall, basal ventricular septum, right ventricle, papillary muscles, right atrium, and left atrium [12]. The pathologic features include 3 successive histological stages: edema, granulomatous infiltration, and fibrosis leading to post-inflammatory scarring. Pathologic samples of

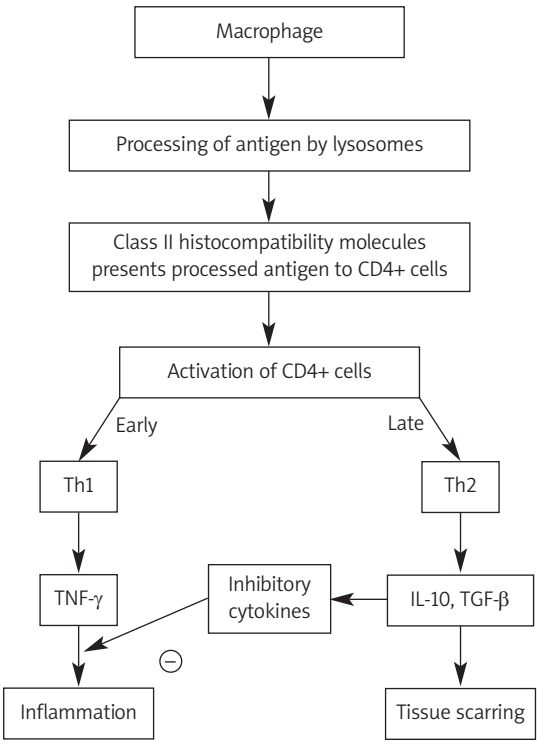

Figure 1. This figure illustrates the pathogenesis of cardiac sarcoidosis

Table I. Prevalence of cardiac findings in cardiac sarcoidosis

Complete heart block	23-30%
Bundle branch block	12-32%
Ventricular tachycardia	23%
Congestive heart failure	25-75%
Sudden death	25-65%

myocardium involved with sarcoidosis reveal the presence of numerous lymphocytes located at the border zones around the granulomas. A dense band of fibroblasts, collagen fibers, and proteoglycans usually encase this aggregate of inflammatory cells [12].

Genetic factors

A Case Controlled Etiologic Sarcoidosis Study (ACCESS) concluded that first-degree relatives of patients with sarcoidosis had a relative risk of sarcoidosis that was five times that of control subjects [13]. Genetic factors appear to play a role in defining the risk of the disease. On exposure to antigens, some individuals trigger an exaggerated cellular immune response and the formation of granulomas which may be due to genetic predisposition. The genetic factors also determine the pattern of disease, its severity, and prognosis. Monozygotic twins are more commonly affected than dizygotic twins. Familial clusters occur with a rate of at least 19% in affected black families and 5% in white families. Multiple serologic studies have identified primary associations with class 1 HLA-A1 and B8 and class II HLA-DR3 in whites [2]. The occurrence of cardiac sarcoidosis in Japanese female patients is associated with the presence of HLA-DQB1*0601 and the allele TNFA2 [14, 15].

Clinical manifestations

Sarcoidosis can be widespread, or limited to involvement of only a single system at a time. Many asymptomatic cases may be discovered by chest radiography which may or may not progress to clinically symptomatic disease. However, a proportion of patients may present with systemic symptoms which include fever, fatigue, malaise, and weight loss. Intrathoracic involvement occurs in more than 90% of patients. About one-third of patients have palpable peripheral lymph nodes. Abnormalities of liver function tests are common. Cutaneous involvement may occur in 25% of patients and may present as erythema nodosum, granulomatous nodule, or papules. Other organ systems may be involved including eye, nervous system, gastrointestinal tract, hematological, parotid, endocrine, reproductive organs, and kidneys.

Cardiac involvement occurs in 20-27% of sarcoid patients in the United States and may be as high as 58% in Japan [6]. If cardiac manifestations occur in a patient with multi-systemic sarcoidosis, the diagnosis, although circumstantial, is strongly suspected. However, when cardiac dysfunction is the only manifestation of sarcoidosis, the diagnosis is frequently not entertained [16]. The patients who come with only the symptoms in Table I and are suspected to have cardiac sarcoidosis should undergo a detailed investigation including myocardial biopsy if needed. Even when the diagnosis is considered, it is not often confirmed because of unavailability of specific diagnostic tests.

Early diagnosis and treatment is essential since treatment improves prognosis. The failure to diagnose cardiac sarcoidosis is partly attributable to the relative rarity of clinically apparent forms of the disease. Only 40-50% of patients with cardiac sarcoidosis at necropsy have clinical evidence of myocardial involvement during lifetime [4]. Serious cardiac dysfunction is detected in 5% to 10% of cases. In a significant proportion of patients with cardiac sarcoidosis, the initial presentation is sudden death. In 37% of patients with cardiac involvement, there were no clinical signs or symptoms of the disease [4].

Complete heart block

Complete heart block is one of the most common finding in patients with clinically evident cardiac sarcoidosis and occurs at a younger age in patients with sarcoidosis than in patients with complete heart block of other causes [17]. Complete heart block (Figure 2) and bundle branch block have been reported in 23-30% and 12-32%, respectively of patients with myocardial sarcoidosis. They are caused by involvement of the basal septum by scar tissue, granulomas, or involvement of the nodal artery causing ischemia in the conduction system [6]. Sudden death may be a direct result of complete heart block. For Japanese patients, notably women over 50 years of age, complete heart block is frequent and leads to the diagnosis of cardiac sarcoidosis in 11% of cases [18]. Patients with sarcoidosis who present with syncope or presyncope should be evaluated for complete heart block with electrocardiographic and Holter monitoring. Sarcoidosis should be included in the evaluation of patients with syncope, especially when it occurs in a younger patient.

Ventricular arrhythmias

Sudden death caused by ventricular tachyarrhythmias or complete heart block may account for 25-65% of deaths caused by cardiac sarcoidosis,

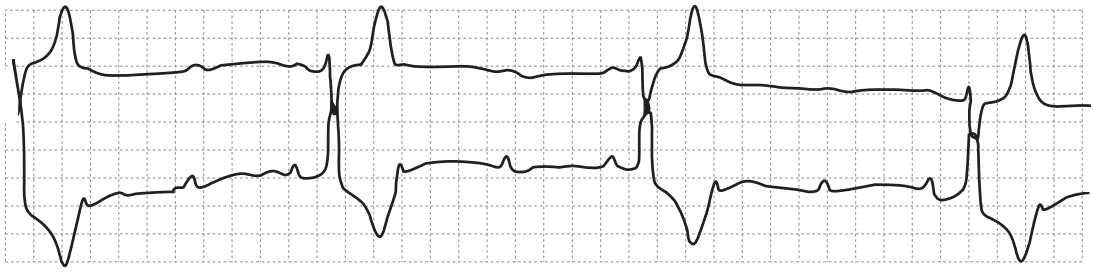

Figure 2. This figure illustrates complete heart block with an atrial rate of 76 beats per minute and an idioventricular pacemaker with a ventricular rate of 26 beats per minute

and this may be the initial presentation in 40% of patients with cardiac sarcoidosis [19]. Ventricular tachycardia is also one of the most frequent arrhythmia noted in cardiac sarcoidosis, and one study demonstrated a 23% incidence of ventricular tachycardia (Table I) [20]. Sarcoid granulomas may serve as foci for abnormal automaticity or to disperse both ventricular activation and recovery processes that can cause reentrant tachycardias. The reentrant pathway can result from active granulomatous inflammation but also can be found in association with the healing of cardiac granulomas in the inactive phase of the disease. Atrial arrhythmias are less common than ventricular arrhythmias, occurring in 15-17% of cases. They are often the result of atrial dilatation or pulmonary involvement rather than the result of atrial granulomas [12].

Congestive heart failure

Progressive heart failure accounts for 25% to 75% of cardiac deaths in patients with cardiac sarcoidosis [21]. Heart failure may be secondary to left- sided cardiac involvement with either systolic or diastolic dysfunction and can occur when there is extensive infiltration of the myocardium by non-caseating granulomas. Differentiating cardiac sarcoidosis from idiopathic dilated cardiomyopathy (IDC) can be difficult. Yazaki *et al.* retrospectively compared 15 patients having cardiac sarcoidosis and left ventricular systolic dysfunction to 30 patients with IDC [22]. The sarcoidosis group had a significantly higher frequency of complete heart block (67% vs. 0%), right bundle branch block (57% vs. 17%), and abnormal left ventricular wall thickness (73% vs. 17%).

Pericardial effusion/valvular involvement/ventricular aneurysm

Pericardial involvement is uncommon even in the presence of extensive myocardial infiltration. It is observed in fewer than 10% of patients with cardiac sarcoidosis, and these patients usually remain asymptomatic. Small pericardial effusions detected by echocardiography were found in 19% of patients with sarcoidosis [23, 24]. Direct valvular involvement occurs in fewer than 3% of patients, but valvular incompetence secondary to papillary muscle dysfunction can be seen in approximately 68% of patients [25]. Mitral regurgitation may result from papillary muscle dysfunction or dilatation of the left ventricle secondary to diffuse disease.

Ventricular aneurysms occur in 10% of the patients with sarcoidosis. The anterior and septal wall segments are more commonly affected, and it is unusual that wall motion of only the apical segment is reduced. Extension of ventricular lesions may lead to aneurysm formation. Long-term corticosteroid therapy can heal sarcoid granulomas, replacing myocardium with fibrous tissue, but steroid therapy has been associated with ventricular aneurysms [26, 27]. Nonetheless, corticosteroids should be used if clinically indicated since ventricular aneurysm is common in untreated patients with myocardial sarcoidosis. Myocardial aneurysms may be associated with frequent and complex ventricular arrhythmias. These arrhythmias may resolve after resection of the aneurysm. Impaired arterial perfusion in the vicinity of granulomas may impair the local delivery of anti-arrhythmic drugs. Therapy is also complicated by the presence of certain acidic acute phase reactants that bind to drugs with high pK, thus interfering with serum levels.

Pulmonary hypertension and cor pulmonale

Pulmonary hypertension (PH) is a predictor of poor outcome in sarcoidosis. Shorr *et al.* reported that the frequency of PH was as high as 73.8% in 363 advanced sarcoidosis patients listed for lung transplant [28]. In a study by Tomhiro *et al.*, the frequency of PH in Japanese sarcoidosis patients who were followed in an outpatient clinic was 5.7% [29]. There are multiple mechanisms for PH in sarcoidosis. Pulmonary hypertension can be a consequence of impaired forward flow and result from poor left ventricular function. Pulmonary hypertension may occur in patients with pulmonary sarcoidosis, especially those with hypoxic vasoconstriction, resulting in cor pulmonale. Alveolar hypoxia, irrespective of the cause, not only

causes vasoconstriction but can result in pulmonary vascular remodeling. At times elevated pulmonary arterial pressures are associated with normal or near normal lung function and arterial blood gases. This may suggest the presence of an intrinsic sarcoid vasculopathy. Encroachment of the pulmonary vasculature by intimal and medial infiltration by noncaseating granuloma and extrinsic compression of pulmonary arteries by enlarged mediastinal lymph nodes can also cause PH [30]. Pulmonary hypertension has been associated with more severe pulmonary involvement as reflected by chest X ray and pulmonary function tests. There may be multiple causes of sarcoid-associated PH, and therefore these patients should undergo a complete and careful diagnostic work-up.

Diagnosis

Only after a thorough clinical evaluation documenting a syndrome consistent with sarcoidosis and biopsy documentation of the presence of non-caseating granulomas can a diagnosis of sarcoidosis be made. All other causes of non-caseating granulomas must be reasonably excluded. The presence of signs, symptoms, or findings suggestive of cardiac involvement warrant additional assessment to confirm presence of cardiac sarcoidosis [2].

Endomyocardial biopsy

A definite diagnosis of cardiac sarcoidosis can be made by endomyocardial biopsy. The sensitivity of endomyocardial biopsy for non-caseating granulomas is low, usually less than 20% [31]. It is believed that this low sensitivity is a consequence of patchy myocardial involvement which frequently involves the intraventricular septum and the left ventricle. Despite its low sensitivity, early myocardial biopsy can be considered when the diagnosis of cardiac sarcoidosis is entertained. Endomyocardial biopsy can help to rule out other causes of cardiac myopathy and may confirm the diagnosis of cardiac sarcoidosis [2]. In the absence of granulomas, it might be difficult to distinguish between cardiac sarcoidosis and idiopathic giant cell myocarditis [32] as both of these diseases have giant cells and are associated with ventricular tachycardia and heart block. The differential diagnosis will include connective tissue diseases like Lyme disease, rheumatoid arthritis, dermatomyositis, cardiac amyloidosis and alcohol related cardiomyopathy, but these can be distinguished based on clinical findings.

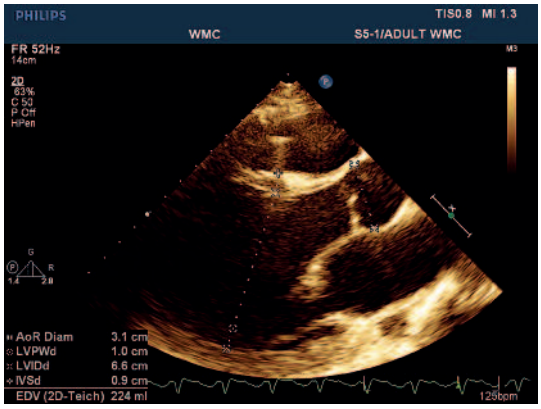

Figure 3. This figure is a 2-dimensional echocardiogram showing a dilated cardiomyopathy. The left ventricular internal dimension at the end of diastole is 6.6 cm

Electrocardiographic and Holter monitoring

The electrocardiogram (ECG) should be part of the routine evaluation of the patient with a diagnosis of sarcoidosis. The electrocardiogram changes are found in as many as 50% of patients with systemic sarcoidosis. This may occur without clinical evidence of cardiac involvement [33-35]. Although the ECG is an important part of patient evaluation, it is often nondiagnostic or non-specific. In a study by Suzuki *et al.* 24-h Holter monitoring detected cardiac sarcoidosis with a sensitivity of 67% and a specificity of 62% when ventricular ectopic beats numbered more than 100/day [36]. An electrical abnormality even as insignificant as sinus tachycardia should be investigated as it may indicate myocardial infiltration. QT dispersion (QTd), the maximal interlead difference in QT interval on the surface 12 lead ECG, may be a predictor of sudden cardiac death. A preliminary study of 35 patients with systemic sarcoidosis, the subgroup with cardiac sarcoidosis had a significantly greater QTd than the noncardiac sarcoidosis group and a control group. The incidence of premature ventricular complexes on ECG in a limited follow-up group was greater in the cardiac sarcoidosis group than in the noncardiac sarcoidosis group [37]. Carvedilol has been reported to significantly reduce QTd [38].

Doppler echocardiography

Echocardiography is an important tool in the diagnosis and surveillance of patients with cardiac sarcoidosis. In a recent study of 41 patients, Doppler echocardiography was abnormal in 67% of patients with dilated cardiomyopathy in 32% of patients (Figure 3), with abnormal left ventricular relaxation in 29% of patients, and with diffuse or localized dyskinesia or hypokinesia in 26% of patients [39]. Two-dimensional echocardiographic abnormalities for cardiac sarcoidosis include abnormal septal thickening or thinning, dilatation of the left ventricle (Figure 3), and systolic dysfunction of the left ventricle [25]. Doppler echocardiography may also identify left ventricular diastolic dysfunction which

can be an early sign of granulomatous involvement of the myocardium [40]. Echocardiography may not detect mild localized myocardial abnormalities which occur in the early stage of cardiac disease. The cycle dependent variation of myocardial integrated backscatter (CV-IB) is another new technique. It can be decreased in the basal septum in patients with cardiac sarcoidosis even in the absence of 2-dimensional echocardiographic abnormalities [41]. Mechanisms may include decreased regional myocardial contraction function, altered myocardial acoustic properties influenced by myocytolysis, and cell infiltration in the myocardium. This may be a useful method to detect early myocardial involvement in patients with sarcoidosis.

Radionuclide studies

Nuclear medicine imaging is another important tool in the diagnosis of cardiac sarcoidosis. The fibrogranulomatous lesions in the myocardium display segmental areas of decreased uptake in nuclear imaging. Most useful studies are performed with thallium 201 and technetium 99m sestamibi [42]. Improvement or complete resolution with dipyridamole differentiates cardiac sarcoidosis from coronary artery disease in which defects at rest worsen or fail to improve with exercise, dipyridamole, or adenosine. Myocardial perfusion abnormalities in sarcoidosis are reversible after pharmacological dilation which may be due to possible microvascular vasoconstriction in myocardial sarcoidosis. This phenomenon is referred to as "reverse distribution" [43, 44].

Thus, in order to assess cardiac sarcoidosis, a baseline resting myocardial scan should be performed in addition to a scan after dipyridamole infusion. Sestamibi single-photon emission computer tomography (SPECT) is more sensitive than thallium in the diagnosis of myocardial sarcoidosis. However this modality is not specific for cardiac sarcoidosis. Gallium is highly sensitive for cardiac sarcoidosis since it accumulates in the inflamed areas and is useful in judging the response of the disease to steroid therapy. Unfortunately, myocardial gallium SPECT images are not sufficiently clear in distinguishing gallium uptake in the myocardium from that in the lung or mediastinum. Therefore, the clinical usefulness of gallium SPECT scanning has not been adequately established [45].

A study by Kasawa *et al.*, showed that the use of dual SPECT scanning with gallium and technetium could be a useful diagnostic imaging technique and improved the diagnostic specificity of gallium SPECT for the diagnosis of cardiac sarcoidosis [46]. Studies have shown that myocardial uptake of gallium may predict responsiveness to steroid therapy [45].

Magnetic resonance imaging

Sarcoid infiltrates are visible by magnetic resonance imaging (MRI) as a zone of increased intramyocardial signal intensity. These are more pronounced on T2 weighted images because of the edema associated with inflammation and granulomatous lesions. These images can be enhanced on gadolinium diethylene pentaacetic acid enhanced MRI. Focal myocardial thickening is often seen as a result of the edema [47-50].

Increased signal intensity on T2 weighted sequences without myocardial thickening and without gadolinium uptake can also be observed. This feature may be noticed in patients already receiving corticosteroids or on the follow-up MRI after treatment. Delayed enhanced MRI is considered a useful method for the early identification of cardiac sarcoidosis. Delayed hyperenhancement is frequently associated with a reduction of regional wall motion and thallium-201 perfusion defects. The area with delayed enhancement represents myocardium that has been replaced by the fibrogranulomatous tissue of sarcoidosis, resulting in decreased wall motion [51].

Positron emission tomography

Positron emission tomography (PET) can also identify sarcoid cardiac involvement and assess severity. The PET scan may be useful in patients with a pacemaker or cardioverter-defibrillators implanted who are unable to undergo MRI because of the safety concerns related to potential adverse effects on the device arising from the strong magnetic and radiofrequency forces generated by MRI. These include the possibility of erratic and inappropriate device functioning during or after the scan, over-sensing that can cause high rate pacing or thermal damage to the device, and induced voltages on leads that can cause over- and under-sensing. Moreover, combined effects can cause component failures, mechanical vibration, and device damage [52].

Yamigishi *et al.* studied 17 patients with cardiac sarcoidosis using PET [53]. Positron emission tomography imaging was positive in 14 (82%) of these patients [53]. Only 6 of 17 patients (35%) showed 201 thallium defects, and only 3 of 17 patients (18%) revealed abnormal 67 gallium accumulation. In addition, the patients who were treated with steroids showed a decrease in uptake and hence improvement on PET. Positron emission tomography has the potential to be an important tool in the diagnosis and monitoring of patients with cardiac sarcoidosis.

Other studies

Cardiac catheterization is indicated in patients with sarcoidosis to rule out coronary artery disease

in patients with chest pain, congestive heart failure, or abnormal imaging. In the presence of normal coronary arteries, the perfusion defects on thallium scanning in a patient with sarcoidosis strongly point toward the existence of cardiac sarcoidosis. However, sarcoid patients with cardiac dysfunction, ECG abnormalities, or thallium-201 imaging defects should be presumed to have cardiac sarcoidosis even when endomyocardial biopsy shows no granulomas.

Cardio-pulmonary exercise studies, including measurement of peak oxygen consumption, can be very helpful in the evaluation for heart failure [54].

Treatment and prognosis

Immunosuppressive therapy

Cardiac sarcoidosis is an indication for treatment because of increased risk of sudden death. Treatment is given to reduce inflammation. Corticosteroids, the most common initial therapy, should be started in patients with a definite or strong probability of cardiac sarcoidosis on different imaging studies, even with a negative myocardial biopsy. Chiu *et al.* showed that long- term steroid use in patients with a left ventricular ejection fraction (LVEF) > 55% may prevent LV remodeling and altered cardiac function. Steroids most benefited those patients with a LVEF < 54% who showed significant reduction in LV volumes and LVEF improvement [55]. In patients with a LVEF < 30%, steroid therapy did not improve the LV volume or function. These investigators concluded that in early or middle stage disease, steroid therapy may be protective or therapeutic but may not be as effective in the late stages.

The severity of congestive heart failure is the most powerful prognostic predictor of survival in steroid treated patients with cardiac sarcoidosis. Yazaki *et al.* reported that the 5-year survival was about 90% in steroid treated patients with preserved systolic function [21, 22]. There was no significant difference in survival curves for patients treated with a high initial dose vs. a low dose of steroids. It is reasonable to start a steroid dose with prednisone 60-80 mg a day and taper the dose over 6 months to a dose of 10-mg a day. If the disease appears to be improved and dormant, then the steroids can be slowly tapered further. At any sign of recurrence, steroids should be started at the dose of 60 mg/day or higher. Long-term corticosteroid therapy is often required.

Smedema *et al.* concluded that once symptomatic cardiac sarcoidosis develops in pulmonary sarcoidosis patients, the prognosis becomes very poor. In contrast with asymptomatic cardiac sarcoidosis, the prognosis of asymptomatic cardiac involvement in patients with pulmonary sarcoidosis is better. Therefore, it is appropriate to screen pulmonary sarcoidosis patients with an electrocardiogram and clinical evalution and reserve more specialized cardiac evalution for those with abnormalities [56].

Treatment with methotrexate, azathioprine, or cyclophosphamide can be used as steroid sparing agents and in those whose disease is refractory to high-dose steroids [57, 58]. Tumor necrosis factor is critical in the genesis and maintenance of granulomatous inflammation. Case reports have described cardiac conduction abnormalities which improved after use of infliximab, a tumor necrosis factor alpha inhibitor [59]. There is no consensus on the duration of therapy, and recurrence can occur after cessation of therapy. There are no reported randomized controlled trials describing the superiority of one treatment over another. A commonly used approach would be to start treatment with corticosteroids with addition of immunosuppressive agents in refractory cases. In cases where steroids are contraindicated, use of immunosuppressive agents would be given as initial therapy.

Other therapies

Ventricular tachycardia is a common complication, and steroids have usually failed to prevent ventricular tachycardia. Antiarrhythmic drug therapy for ventricular tachycardia in patients with cardiac sarcoidosis is associated with a high rate of recurrence or sudden death. Amiodarone use in this group of patients may be limited by the occurrence of pneumonitis and/or pulmonary fibrosis. These drug-induced pulmonary changes are indistinguishable radiographically from pulmonary sarcoidosis and may compromise the patients' respiratory status. β-Blockers have been shown to increase the incidence of heart block in patients with cardiac sarcoidosis. Given these limitations, implantation of an implantable cardioverter defibrillator should be considered as primary therapy in such patients. The indications for permanent pacing are similar to those in patients without cardiac sarcoidosis. Permanent pacing is effective in the prevention of sudden cardiac death and in advanced atrioventricular block and other bradyarrhythmias.

Cardiac transplantion

Cardiac transplantation is reserved for end-stage disease unresponsive to medical therapy [60]. Major indications for cardiac transplantation are resistant ventricular tachyarrhythmias and severe intractable heart failure, especially in younger patients. Cardiac sarcoidosis results in progressive fibrosis and scarring leading to ventricular dysfunction. Patients

with stage D heart failure who are refractory to treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers and diuretics should be considered for cardiac transplantation [61]. Cardiac transplantation can be avoided if corticosteroid treatment is started before the occurrence of severe systolic dysfunction. Sarcoidosis can recur in the transplanted heart and has been documented to recur 24 weeks to 19 months after transplantation. Transmission of sarcoidosis from an allograft donor, who was not known to have sarcoidosis, to its recipient has been reported [62]. An increased dosage of steroids may be required to achieve complete resolution in all recurrences after transplantation.

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