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Review Artilce

# Cardiac Sarcoidosis

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## Abstract

Studies have revealed that clinically apparent cardiac disease occurs in approximately five per cent while myocardial involvement may be diagnosed in one fourth of the sarcoidosis patients at autopsy. The true prevalance of cardiac sarcoidosis is unknown. Approximately one fourth of the sarcoidosis patients have clinically silent cardiac disease. The essential manifestations of cardiac involvement are conduction abnormalities, ventricular arrhythmias and heart failure. Ventricular remodelling may lead to ventricular dysfunction that may cause sudden cardiac death as a common feature of cardiac sarcoidosis. Prognostic outcome for cardiac sarcoidosis is usually poor with a less than two years median survival time following the clinical manifestations of myocardial disease. Cardiac involvement may account for one fourth of deaths from sarcoidosis. There are no specific clinical, laboratory or imaging findings to identify cardiac involvement in sarcoidosis patients. It is also uncertain to determine the patients that carry a high risk for a poor prognosctic outcome. Cardiac involvement in sarcoidosis is a diagnostic dilemma for the clinician. Early diagnosis, appropriate potential treatment and a meticulous follow-up appears to be the hallmark to improve patient survival.

***Keywords:*** *Sarcoidosis; Cardiac Sarcoidosis; Pulmonary Sarcoidosis*

## Introduction

Sarcoidosis is a granulomatous disease of unknown cause presenting with variable symptoms, different organ involvement and an unpredictable prognosis. The disease course may show spontaneous remission or becomes evident with execarbations. Natural history of sarcoidosis is extremely protean from a totally asymptomatic profile to a malignant clinical course with ongoing remissions and exacerbations in between [1,2]. The disease is a source of considerable dispute due to its uncertain etiology, distinct and variable presentations with diverse patterns of prognostic outcomes. Heterogeneity of sarcoidosis arises from the interaction of environmental, humoral, and genetic factors. The synergy of distinct factors lead to an unstable or inconsistent clinical sarcoidosis profile in regard to disease severity, organ involvement and prognosis. None of the organs is immune for sarcoidosis. While sarcoidosis commonly involves the lungs and less frequently the eyes or the skin, isolated organ sarcoidosis is observed in 2 to 5% of patients [3]. Studies suggest that clinically manifest cardiac sarcoidosis occurs in only 5% of patients with pulmonary or systemic disease. The clinical features of cardiac sarcoidosis are bound to the location, extent and activity of the disease [4-6]. Cardiac sarcoidosis has a poor prognosis with less than a 2 years median survival following the development of clinical symptoms of myocardial disease [5].

Identification of cardiac involvement is one of the most crucial aspects of sarcoidosis because it accounts for approximately 13 - 25% of deaths and is the second most common cause of mortality from sarcoidosis following lung disease [6]. In Japan, 85% of deaths are

reported to be from cardiac sarcoidosis which may suggest an environmental, humoral and genetic tendency [5]. Diagnosis of cardiac sarcoidosis, even in patients with a previously known sarcoidosis disease is a diagnostic dilemma for the clinician because there are no specific or pathognomonic symptoms, laboratory and imaging findings. In clinical practice, neither the symptoms nor the laboratory findings are exclusive or conclusive enough to warrant the cardiac involvement in sarcoidosis patients and thereby to reach the final diagnosis creates great difficulties requiring a detailed differential diagnostic algorithm. This review enlightens the epidemiologic and clinical findings including the current treatment options and the prognostic outcome for cardiac sarcoidosis.

## Epidemiology

Sarcoidosis is usually a benign disease that may show a variable course and an unstabile prognosis. The disease profile may manifest unpredictable remissions and exacerbations. An estimated 50% of the patients are asymptomatic and usually present with silent bilateral hilar adenopathy. The disease most frequently affects the lungs and intrathoracic lymph nodes in approximately 95% of the subjects while the pulmonary symptoms are present in only half of the sarcoidosis patients [2,7,8]. On the other hand, the true prevalence of cardiac sarcoidosis is unknown and is probably underestimated due to its silent and subclinical disease manifestations. The frequency of cardiac sarcoidosis shows great variability among different ethnic groups or regions of the world as the disease itself [9-11]. The frequency of heart involvement also depends upon the study type, diagnostic clinical tools performed and whether the autopsy was done or not. Studies reveal a cardiac sarcoidosis incidence of about 5% and 11% among the patients [12]. Another study based on noninvasive tests like ECG, Holter and echocardiogram showed that 40% of outpatients had cardiac sarcoidosis while half of these patients were asymptomatic [13]. Clinically apparent cardiac sarcoidosis is observed only in a minority of sarcoidosis patients while approximately in one fourth of patients with systemic sarcoidosis had myocardial involvement identified by autopsy [14]. Diagnosis of cardiac disease in sarcoidosis is extremely crucial because these patients usually have a poor prognosis with a less than 2 years of survival following signs and symptoms myocardial involvement [5]. Cardiac involvement accounts for approximately 25% of deaths from sarcoidosis and is the second leading cause of death from sarcoidosis. Among Japanese sarcoidosis patients up to 85% of deaths is reported be from cardiac sarcoidosis [5]. These findings suggest that cardiac involvement from sarcoidosis may vary according to the population studies probably due to the effect of genetic, ethnic, environmental and humoral factors.

## Clinical findings and diagnosis

The presentation in cardiac sarcoidosis is extremely variable from an asymptomatic clinical profile to a severe disease course. Cardiac involvement presents with a wide spectrum of manifestations that alternate between a coincidentally detected disease and more severe conditions like heart failure or sudden death. Only 5% of cardiac sarcoidosis patients express clinical findings that point out to cardiac involvement [4-6]. The three cardinal features of cardiac sarcoidosis are conduction defects, ventricular arrhythmia and the heart failure. The symptoms are usually subtle and are associated with more common heart diseases thereby requiring an elaborate differential diagnosis. Due to disease involvement from scattered to diffuse cardiac sarcoidosis, the disease may present with a wide spectrum of clinical manifestations. Dyspnea and fatigue are the most frequent complaints. Palpitations and syncope may indicate involvement of the myocardium while chest pain may suggest myocardial or pericardial disease. Chest pain occurs secondary to microvascular contraction. Conduction system abnormalities including first, second degree or complete heart block are not uncommon. Sudden cardiac death, heart failure, ventricular aneurysm, cor pulmonale, pericardial effusion, ventricular or atrial arrythmias may occur rarely [6,16,17]. The symptoms or the findings of cardiac sarcoidosis are not specific and sensitive enough to warrant a clinical diagnosis which is a diagnostic dilemma for the clinician. In addition to cardiac manifestations, systemic symptoms including fatigue, malaise, fever and weight loss may develop. Cardiac manifestations may precede, follow or occur with lung disease. In patients without lung symptoms, cardiac sarcoidosis is unusual. Isolated cardiac sarcoidosis is rare but the absence of pulmonary disease does not exclude the diagnosis. A conduction abnormality, a

sustained reentrant ventricular tachycardia, restrictive cardiomyopathy of unknown etiplogy, AV block and dyspnea out of proportion to pulmonary disease should raise the query of cardiac sarcoidosis.

Heart failure is encountered in 23% of patients with cardiac sarcoidosis that leads to a significant mortality including both restrictive and dilated cardiomyopathy [14,15]. The endpoint is ventricular dysfunction eventuating in heart failure. Approximately half of the patients acquire diastolic dysfunction while cor pulmonale may develop as a sequela of secondary pulmonary hypertension [18,19]. Conduction abnormalities including third-degree or complete heart block is one of the most common disorders of cardiac sarcoidosis that occur as a result of granulomas or fibrotic scar tissues involving the conduction system. Ventricular tachycardia due to reentry mechanism is seen in 23% while atrial fibrillation is observed in 19% of the patients with cardiac sarcoidosis [5,18,20]. Pericardial disease present as pericardial effusion or pericarditis. Pericardial involvement has been identified by echocardiography in 19% of the patients. The incidence of asymptomatic pericardial effusion is high [20,21].

Even in patients with previously known sarcoidosis cardiac involvement is a diagnostic challenge for the clinician because there are neither specific symptoms, laboratory or radiologic findings associated with cardiac sarcoidosis. The American Thoracic Society (ATS) and World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) has defined the diagnostic criteria of cardiac sarcoidosis. These criteria include cardiac dysfunction, ECG abnormalities and thallium-201 scan defects with or without endomyocardial biopsy. Other useful criteria for diagnosis is the presence of treatment responsive cardiomyopathy, ECG with conduction defects and positive gallium scans. Cardiac sarcoidosis is also identified on the basis of histologic diagnosis of extracardiac sarcoidosis and the presence of associated ECG abnormalities including left axis deviation, AV block, VT, premature ventricular beats, abnormal Q or ST changes and with the addition of any one of the following criteria such as abnormal wall motion, regional wall thickening, ventricle dilatation, perfusion defect on thallium-201 scintigraphy, decreased ejection fraction, fibrosis and cellular infiltration on endomyocardial biopsy [15,22,23].

Histopathologic verification of myocardial disease is the sine qua non of the diagnosis for cardiac sarcoidosis. Lack of biopsy verification, absent or inadequate histologic findings on samples do not exclude the diagnosis of cardiac sarcoidosis. Sensitivity of endomyocardial biopsy is variable ranging from 25% to 75% while the specificity is 100% and the low sensitivity is relevant to sampling errors secondary to the patchy distribution of granulomatous inflammation [24-25]. Cardiovascular system is the third most frequent organ system in the autopsy studies following the lymphoid and the respiratory system. The granulomas of cardiac sarcoidosis appear as yellow, white, grey or light brown, amorphous and nonuniform grainy conglomerations. The most frequent location of the granulomas is the free wall of the left ventricular myocardium followed by the septum, right ventricle, and atria [26,27]. The conduction system is commonly involved while the the pericardium and endocardium may also display granulomatous inflammation usually as extensions of the myocardial disease [17,28]. There are no pathognomonic histopathologic findings of sarcoidosis. However, the presence of tight, non-necrotizing epithelioid granulomas support the diagnosis of sarcoidosis. The macrophages of the sarcoid granulomas become epitheloid and form multinucleated giant cells which later contain cytoplasmic inclusions like Schaumann or asteroid bodies. Tight non-necrotizing epithelioid granulomas, Langhans giant cells, patchy fibrosis with or without Schaumann or asteroid bodies may support the diagnosis [29]. However, clinicians should bear in mind that none of pathologic findings is adequate for final the diagnosis and they all must be contemplated as a segment of the entire clinical profile, including other histologic criteria. A thorough histopathologic differential diagnosis is required for the histopathologic verification of cardiac sarcoidosis. The patchy distribution of the lesions is another factor that decreases the sensitivity of endomyocardial biopsy for the definite diagnosis. As the disease progresses the granulomatous inflammation leads to fibrous scarring which is the hallmark of cardiac complications.

Abnormalities of ECG findings that are non-specific occur in approximately half of the patients with cardiac sarcoidosis. First, second or third degree blocks are the most commonly encountered conduction defects. Atrioventricular blocks may show resolution with steroid treatment. Echocardiography may be useful for indirect assessment of cardiac sarcoidosis revealing systolic, diastolic function and

regional wall motion abnormalities while other non-invasive imaging tools MRI, FDG/PET, thallium or gallium scintigraphy may identify areas of cardiac involvement.

Thallium-201, gallium scintigraphy and more recently FDG/PET scanning may identify myocardial areas of active granulomatous inflammation in patients with cardiac sarcoidosis. Thallium and gallium scans may detect myocardial areas of active inflammation approximately in one third of the patients whereas FDG/PET detected myocardial abnormalities in 82% of the patients [30-33]. These three nuclear medicine imaging modalities may provide crucial clues for heart involvement in sarcoidosis and detect the myocardial biopsy sites for pathologic confirmation. In addition to its diagnostic benefit, FDG/PET is useful to determine the treatment response by revealing suppressed inflammation. Cardiac magnetic resonance imaging (MRI) has revealed a sensitivity and specifity of 100% and 78% respectively for cardiac sarcoidosis [34]. The negative predictive value of cardiac [MRI] is 55% while the positive predictive value is 100% for cardiac involvement in sarcoidosis.

### Treatment and prognosis

Corticosteroids are the hallmark of treatment in sarcoidosis patients with a progressive clinical course. All symptoms of cardiac involvement like dyspnea, arrhythmia and cardiomyopathy are suppressed by steroid treatment. Chapelo-Abric revealed signs of clinical resolution in 83.7% of the patients [35]. Yazaki reported a 5-year survival rate of 75% in patients who received streoid treatment while the 5-year survival rate was 10% in those patients without treatment [35]. The recommendation to use high dose steroids at the initial treatment is weak. There was no significant difference between low dose or high dose treatment protocols. Higher doses of steroids may be used in patients with severe and progressive disease. Intravenous steroids may be initiated in patients with severe symptoms while the treatment is initiated to oral route as the symptoms are stabilized. Lifelong steroid treatment is used to prevent relapse. There is increased risk of sudden cardiac death in cases of abrupt discontinuation or rapid dose reduction of steroid treatment [4,5,8]. Mortality is usually due to fatal arrhytmias or conduction defects that cause sudden cardiac death. Progressive heart failure as a result of extensive myocardial inflammation and fibrosis may lead to fatal outcome in a smaller group of patients [5,35]. Treatment of cardiac sarcoidosis must be commenced without delay after diagnostic confirmation. Other immunosuppressive agents and TNF-α inhibitors may be started in patients unresponsive to steroids to prevent or to delay the serious prognostic outcome in these patients.

## Conclusions

Cardiac involvement is one of the most crucial aspects of sarcoidosis because of its high morbidity and mortality. The clinical manifestations of cardiac sarcoidosis usually depend on the location and the intensity of myocardial granulomatous inflammation that may result in fibrosis promoting contractile dysfunction. Identification of cardiac disease is a diagnostic challenge for the clinician because neither the symptoms nor the laboratory, the imaging or the pathologic findings are specific enough on their own to warrant a definitive diagnosis. Furthermore, the symptoms and the clinical findings of cardiac involvement may simulate any other cardiac disease. The survival in most patients is about two years after the occurrence of cardiac manifestations. Early diagnosis with effective treatment is therefore the hallmark of cardiac sarcoidosis to improve the prognostic outcome in these patients. The follow-up of patients is another important aspect of cardiac sarcoidosis for clinicians. Patients with cardiac sarcoidosis should be followed with extreme caution while the steroid treatment must be lifelong. The dose of steroid treatment is the most important factor to improve the prognosis because the mortality of cardiac sarcoidosis is high. Dose of steroid treatment should be individualized for every patient. The clinicians should avoid excessive dose adjustments because sudden death may occur due to abrupt discontinuation or rapid dose reduction of steroid treatment. In patients with an unresponsive treatment response, immunosuppressive agents or TNF-α inhibitors may be commenced. Cardiac sarcoidosis frequently shows a difficult clinical profile and a high index of suspicion is essential for definitive diagnosis. Early treatment may lead to a better prognostic outcome eliciting a longer survival in many patients.

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