Chapter

Cardiac Sarcoidosis

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Abstract

Sarcoidosis is a systemic disease of unknown origin characterized by the infiltration of non-necrotizing granulomas that can affect any organ. The presentation of cardiac involvement can range from slight infiltration to complete atrioventricular block, ventricular arrhythmia, or cardiac failure. The diagnosis requires a high index of suspicion; approach to treatment depends upon the presence, or absence, of extracardiac sarcoidosis; sometimes a biopsy of the myocardial tissue is the only way to obtain an accurate diagnosis. Nuclear magnetic resonance imaging is the imaging technique which can provide information useful in diagnosis of this condition. If there is active inflammation, the fundamental form of treatment is immunosuppression therapy. Other concomitant treatments can be required such as the implantation of devices or modulation of arrhythmias. The prognosis is conditioned depending upon the extent of the disease and response to the therapy.

Keywords: sarcoidosis, nuclear magnetic resonance imaging, cardiac block, cardiac failure, arrhythmias, immunosuppression

1. Introduction

Sarcoidosis is a systemic disease of unknown origin characterized by infiltration of non-necrotizing granulomas. This disease can affect any organ, including the heart. The heart can be involved to a variable extent depending on the area studied [1]. The ACCES study reported about 95% of findings compatible with cardiac involvement [2]. Others report mainly pulmonary involvement. Studies in Japan report cardiac infiltration up to 25% in contrast with the European studies in which the prevalence ranges from 2 to 7% [3].

2. Epidemiology

Sarcoidosis has a worldwide prevalence of 4.7–64 per 100,000 individuals; the highest rates are found in Northern Europe and among Afro-Americans, predominantly in females [4]. The real prevalence of cardiac sarcoidosis is unknown. In some cases, it can be isolated without extracardiac involvement and in others can have no symptoms; the average age for this disease is 50 [5]. When the clinical behaviors of isolated cardiac sarcoidosis among the group of patients who also register extracardiac compromise are compared, it is found that patients who have the disease confined to the heart exhibit a higher prevalence of complete block of the right branch, delayed myocardial enhancement, and less elevation of the angiotensin-converting enzyme in serum, as they are clinically very similar in their presentation.

3. Pathogenesis

This is a multisystem condition, of unknown etiology, which affects the lungs in most patients (90%) and usually involves the nodes and mediastinum. Cardiac involvement varies according to the population studied and can reach up to 25% [3]. The typical histological feature is the presence of non-necrotizing granuloma (see **Figure 1**) [6] with a central area rich in macrophages, epithelial cells, giant multinucleated cells, and T CD4-positive lymphocytes. In the periphery, there is an abundant population of T CD8 and CD4 lymphocytes, mast cells, and fibroblasts [7]. The origin of this condition is unknown, but one of the theories proposed is antigenic stimulation due to occupational and environmental exposure and infectious agents such as mycobacteria [8].

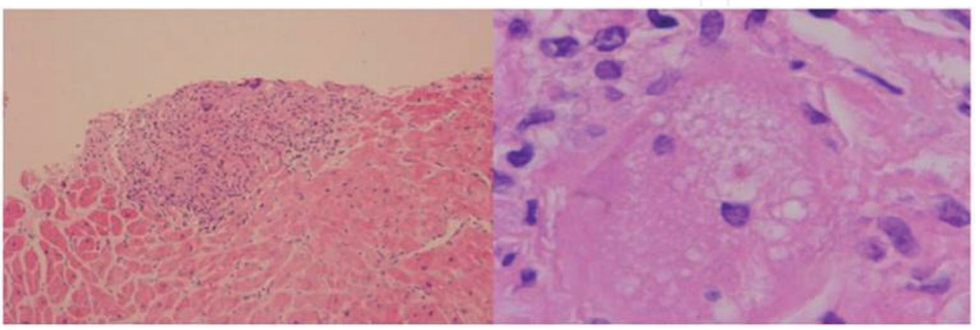

Figure 1.
Cardiac tissue biopsy. Fragments of myocardium can be observed with compromise due to multiple epithelial, non-necrotizing, focal, and coalesced granules, which involve about 30% of the tissue analyzed. The granules contain numerous multinucleated giant cells and, in the confluent areas, are associated with interstitial fibrosis. Stains were negative for mycobacteria and fungi.

4. Clinical manifestations

The manifestations of sarcoidosis vary and depend on the presence or absence of extracardiac compromise, extension, localization, and activity. The majority of heart signs and symptoms are subsequent to arrhythmia, anomalies in atrioventricular conduction, and ventricular arrhythmia (including sudden death) as well as cardiac failure [4]. A less frequent clinical presentation is vasculitis of the coronary arteries. The clinical presentation ranges from palpitations, dyspnea, chest pain, to cardiorespiratory arrest.

Anomalies in atrioventricular conduction are the most frequent manifestation of cardiovascular compromise. They can have a variable clinical presentation that ranges from fixed prolongation of the PR interval (atrioventricular block degree 1) to the presence of branch blocks and in more advanced cases complete atrioventricular block. A prospective study identified that up to 34% of patients with atrioventricular block who were younger than 60 years old, without an apparently clear cause, were eventually diagnosed with sarcoidosis [9], the reason this entity should always be suspected in young patients who present with these alterations without an evident etiology.

The second form of presentation is ventricular arrhythmias which include the presence of premature ventricular complexes and ventricular tachycardia (sustained and non-sustained), mostly subsequent to an increase in cardiac automatism or a reentrant mechanism around the scar caused by granulomas in the myocardium. This type of compromise takes place in ~30% of patients [5]; even these arrhythmias can be the first manifestation of sarcoidosis [6].

Another form of presentation of arrhythmia is supraventricular tachycardia. In a retrospective study of 100 cases, the global prevalence of these arrhythmias was 32%, with auricular fibrillation being the most frequently detected arrhythmia; the methods used for detection were continuous electrocardiogram, Holter monitoring devices, and electrophysiological studies. The majority of patients were asymptomatic (96%), and after atrial fibrillation, in order of frequency, they had atrial tachycardia and atrial flutter. The presence of diastolic dysfunction, increase in the size of the left atrium, and arterial hypertension were the most important factors in the multivariate analysis [10].

Sudden death is a more unusual situation in cardiac sarcoidosis, but when it takes place, it is usually subsequent to severe malfunction in atrioventricular conduction or ventricular arrhythmia. It seems that the presence of delayed enhancement with gadolinium in nuclear magnetic resonance imaging correlated with this outcome; however, these findings are yet to be confirmed.

In some people, cardiac failure can be the main manifestation, followed by dyspnea, orthopnea, and lower limb edema [11]. The right or left ventricular function may be compromised; there may be disorders of segmental or global contractility, as well as valvular compromise, and pulmonary hypertension [12]. There should be a high degree of suspicion regarding this condition, principally when there is a manifest extrapulmonary clinical picture or antecedents of such condition are not present.

The involvement of the epicardial coronary arteries is rare; however, there are reports of cases of vasculitis presenting as acute coronary syndrome and even spontaneous dissection of the coronary arteries, cardiac tamponade, and death in patients without any known antecedents of cardiac sarcoidosis [13, 14].

5. Diagnosis

The diagnosis of this condition in particular starts with a high index of suspicion; other possible causes must not be overlooked, taking into consideration the wide clinical spectrum of this pathology. The treatment of this condition requires a significant medical effort with clinical imaging and, in many cases, histological correlation.

Cardiac compromise due to sarcoidosis should be suspected when the following conditions take place in which the most frequent causes are excluded [15]:

- Advanced atrioventricular block in patients younger than 60 years old
- Cardiac failure
- Ventricular arrhythmia

In addition, clinical suspicion should be higher in all patients with antecedents of extracardiac sarcoidosis that occurred with a cardiovascular symptom such as syncope, arrhythmias, or cardiac insufficiency.

Thus, the diagnosis of this pathology starts with clinical suspicion generated after a detailed medical record and an exhaustive physical exam of those conditions that might explain the current clinical picture is ruled out and identification of extracardiac compromise is found to be due to sarcoidosis.

The use of complementary studies should follow a logical sequence that supports or rules out the suspicion generated in the clinic. The following complementary tests must be performed:

5.1 Chest image

Chest image continues to be the initial study; it is used to identify the typical anomalies of cardiac sarcoidosis; chest images are reported as abnormal in up to 95% of the cases [16] reserving high-resolution tomography for those cases in which the thorax image is normal or presents atypical findings. Image analysis should always take into consideration the multiple differential diagnoses, infections, or conditions that might compromise the lung in a similar way [17].

5.2 Electrocardiogram and Holter

The electrocardiogram is abnormal in the majority of patients with symptomatic cardiac sarcoidosis, compared with patients that have a silent compromise in which the abnormality does not go above 9% [4, 18].

In the screening of asymptomatic patients with extracardiac sarcoidosis confirmed via biopsy [19], the most suggestive findings are:

- Right or left branch block
- One or more signals of a signal-averaged ECG
- One or more premature ventricular complexes
- Presence of Q wave in two or more adjacent leads in the absence of myocardial infarction
- Fragmented QRS in two or more adjacent leads in the absence of myocardial infarction
- Atrial arrhythmia (atrial tachycardia or atrial fibrillation)

Table 1 summarizes the ECG manifestations with variable prevalence according to the course of the cardiac sarcoidosis [19].

As noted before, up to 34% of cases show malfunction in atrioventricular conduction (57% of patients being reversible in some series after immunosuppression therapy) [19]. Other alterations identified are changes in the ST T wave and rarely epsilon waves [4].

Ambulatory electrocardiographic monitoring which continues for 24–48 h (Holter) is useful for identification of arrhythmias, as well as their response to treatment [20].

5.3 Echocardiogram

The echocardiographic findings are diverse with low sensitivity and specificity; however, they are useful for follow-up of patients to monitor progression of the disease [3]. The alterations that stand out include anomalies of the segmental and global contractility (usually following a non-coronary epicardial pattern), thickening or thinning of the interventricular septum (especially toward the base), diastolic dysfunction, and ventricular hypertrophy which can simulate a hypertrophic cardiomyopathy and aneurysms [4]. In recent studies, interest has grown in utility of longitudinal deformity of the left ventricle via Speckle-tracking analysis to identify patients with cardiac sarcoidosis; this can be a useful tool in the early diagnosis and the follow-up of the disease [21].

Presentation	Prevalence (%)
Atrioventricular block	26–67
Bundle block	12–61
Atrial arrhythmias	23–25
Ventricular arrhythmias	11–73

Table 1.
Prevalence of ECG abnormalities.

5.4 Advanced cardiovascular imaging

5.4.1 Nuclear magnetic resonance imaging

Nuclear magnetic resonance imaging is one of the most useful imaging techniques for the assessment of cardiac sarcoidosis. There is no pattern that can be defined as typical; however, the delayed enhancement of the gadolinium is patched (and does not follow a vascular pattern); it compromises the myocardium and the subepicardium, unlike acute myocardial infraction that compromises the subendocardium; it usually affects the basal segments of the septum and the inferolateral wall. Left ventricle involvement is more common. Transmural and right ventricle compromise is infrequent; however, these findings do not rule out the presence of the cardiac sarcoidosis. Some series report a negative predictive value up to 100% with epidemiological limitations with respect to the gold pattern. For this reason, although a negative cardiac resonance image is not common, cardiac compromise due to this pathology cannot be disregarded, especially if the probability and clinical suspicion are high [22, 23]. The superiority of the cardiac nuclear magnetic resonance imaging in the diagnosis of sarcoidosis was proven by Ichinose et al. [24]; he found sensitivity from 75 to 100% and specificity from 39 to 78%. He showed that the NMRI is superior to SPECT with thallium and gallium [25]. The increase in the T2 signal correlated in some subjects with inflammation and major adverse events; NMRI continues to be studied [20, 22]. The limitations of NMRI include patients with implanted cardiac devices (relative), chronic renal disease (stage 4/5), and claustrophobia.

5.4.2 Fluorodeoxyglucose positron 18 emission tomography

This imaging technique is useful in cardiac sarcoidosis for the identification of possible areas with active inflammatory processes; an algorithm has been proposed as a response test to treatment [3]. As a diagnostic guide, a meta-analysis concluded 89% sensibility and 78% specificity; however, these results should be viewed with caution and with the diagnostic criteria used as a pattern [26].

Advanced cardiovascular imaging is advised in the following clinical contexts [27]:
Patients with extracardiac compromise

- Presence of more than one of the following symptoms: 2 weeks + of palpitations, pre-syncope, or syncope

- One or more of the following anomalies in the electrocardiogram: complete block of right or left branch, presence of unexplained pathologic Q waves in two or more leads, atrioventricular block at any degree of severity, and sustained or non-sustained ventricular tachycardia

- One or more of the following echocardiographic anomalies: anomalies in the regional movement of a wall, ventricular aneurysm, thinning of the interventricular septum (basal segment), and ejection fraction of the left ventricle below 50%

Patients without extracardiac compromise

- Atrioventricular block second-degree Mobitz II or third degree in adults younger than 60 years old without an evident cause
- Monomorphic ventricular tachycardia without a clear cause

5.5 Biomarkers

The angiotensin-converting enzyme has been found to be high in 75% of the patients with non-treated sarcoidosis, it does not have much diagnostic value due to its low sensitivity and specificity, and multiple conditions such as diabetes mellitus, tuberculosis, hyperthyroidism, and lung cancer, among other entities, can alter its levels [28]. The measurement of the soluble receptor of interleukin 2 has been proposed as an inflammatory marker in patients with extrapulmonary disease [28]; more studies are needed to assess its use in the clinical setting.

5.6 Endomyocardial biopsy

Being an invasive procedure and considering that sarcoidosis is usually a disease with multisystem compromise, it is preferred to identify a possible extracardiac site for biopsy and histological studies (lymph nodes or lungs). In cases in which the histological tests are not conclusive or there is only cardiac compromise, the endomyocardial biopsy becomes important in the diagnosis of this condition. The diagnostic performance of a blind biopsy is 25% [29] increasing to 50% when guided by images or electroanatomic mapping; this is logical when taking into consideration the multifocal nature of the infiltration [30, 31].

6. Diagnostic criteria

There is no global consensus accepted for the diagnosis of cardiac sarcoidosis. In 2014 The European Heart Rate Society (HRS) published a consensus for the histological and clinical diagnosis of sarcoidosis with cardiac compromise which is shown in **Table 2** [27].

7. Differential diagnostic

The differential diagnosis of this condition is difficult considering all the pathologies that can manifest in a similar form. The complete medical record and the physical exam are the most important ways to make a diagnostic approach.

8. Management

The medical and interventional management in sarcoidosis requires interaction of a multidisciplinary team that includes a cardiologist, electrophysiologist, rheumatologist, pneumologist, and other specialists.

Histological diagnosis of myocardial tissue
Presence of granuloma not classified in the histological exam of the myocardial tissue without an alternative identified cause (including staining for microorganisms)
Clinical diagnosis (invasive studies and noninvasive): recognized as probable
a. Histological diagnosis of extracardiac sarcoidosis
b. One or more of the following:
I. Cardiac block or cardiomyopathy with response to immunosuppression therapy with steroids
II. Ejection fraction of the left ventricle reduced in an unexplainable form (<40%)
III. Sustained ventricular tachycardia with no clear cause (spontaneous or induced)
IV. Atrioventricular block second-degree Mobitz II or cardiac block third degree
V. Irregular captation in a positron emission heart tomography (a consistent pattern with cardiac sarcoidosis)
VI. Delayed enhancement with gadolinium in a cardiac nuclear magnetic resonance (in a pattern consistent with cardiac sarcoidosis)
VII. Positive gallium captation (in a pattern consistent with cardiac sarcoidosis)
c. Other causes of the cardiac manifestations have been reasonably excluded

Table 2.
Diagnostic criteria for sarcoidosis (HRS) 2014.

Left ventricular dysfunction and evidence of myocardial inflammation
Cardiac block Mobitz II and degree III and evidence of myocardial inflammation
Sustained ventricular arrhythmia and evidence of myocardial inflammation
Non-sustained ventricular arrhythmia and frequent ventricular ectopy and evidence of myocardial inflammation

Table 3.
Indication of immunosuppression therapy.

All patients with cardiac sarcoidosis should have a proper control of cardiovascular risk factors, management of cardiac failure in case it occurs, treatment of ventricular arrhythmias and atrioventricular conduction malfunction, as well as immunosuppression therapy.

Immunosuppression therapy is prescribed in all patients with cardiac sarcoidosis. The criteria shown in **Table 3** should be fulfilled [27]. Corticosteroids (prednisolone goes from 30 to 40 mg/day) [32] and the clinical response should be assessed 1–3 months after the starting treatment. The dosage should be reduced gradually, as low as 5–15 mg/day, until completing 9–12 months of sustained treatment. The patients should undergo clinical follow-up for up to 3 years after the therapy to identify relapse. Other therapies (second or third line) include methotrexate, infliximab, cyclophosphamide, and azathioprine, used in refractory cases or when steroids adverse effects are not tolerated. In immunosuppression treatment it is essential to identify the inflamed myocardium via histological study or imaging. It is here where fluorodeoxyglucose positron 18 emission tomography becomes important. It is worth noting this is proposed as a follow-up strategy to define which patients should continue with or discontinue therapy [26, 27].

Table 4 lists the recommendations by consensus for the management of arrhythmias related to cardiac sarcoidosis [4, 27].

Management of conduction malfunctions	
The implantation of a device can be useful in patients with cardiac sarcoidosis with stimulation indication, even if the atrioventricular block is reverted transiently	IIa
Immunosuppression can be useful in patients with cardiac sarcoidosis with atrioventricular block second degree (Mobitz II) or third degree	IIa
The implantation of a cardioverter can be useful in patients with cardiac sarcoidosis and an indication of permanent implantation of a pacemaker	IIa
Management of ventricular arrhythmias	
The assessment of myocardial inflammation via fluorodeoxyglucose positron 18 emission tomography can be useful in patients with cardiac sarcoidosis with ventricular arrhythmias	IIa
Immunosuppression can be useful in patients with cardiac sarcoidosis with ventricular arrhythmias and evidence of myocardial inflammation	IIa
Therapy via antiarrhythmic medications can be useful in patients with ventricular arrhythmias refractory to immunosuppression therapy	IIa
Ablation with catheter can be useful in patients with cardiac sarcoidosis and ventricular arrhythmias refractory to immunosuppression and antiarrhythmic therapy	IIa
Indications for implantable cardioverter	
Spontaneous sustained ventricular arrhythmias, including previous cardiac arrest	I
Ejection fraction of the left ventricle smaller or equal to 35% even with optimal medical management and a period of immunosuppression (if there was active inflammation)	I
Implantation of cardioverter can be considered in cardiac sarcoidosis independent from ventricular function in one or more of the following: • Indication of permanent pacemaker implantation • Unexplained syncope or pre-syncope, if it is of arrhythmic etiology • Inducible sustained ventricular arrhythmias	IIa
Cardioverter implantation can be considered in patients with ejection fraction from 36 to 49% and/or ejection fraction of the right ventricle below 40%, even with optimal medical management for cardiac failure and a period of immunosuppression (if there was active inflammation).	IIb
Stratification of sudden death risk	
An electrophysiological study for the stratification of sudden death can be considered in patients with ejection fraction of the left ventricle >35% even with optimal medical management for cardiac failure and a period of immunosuppression (if there was active inflammation).	IIb
Cardiac magnetic resonance imaging can be considered for the stratification of sudden death risk.	IIb

Table 4.
Management of conduction malfunctions.

9. Prognosis

In a relatively long series, Tokuda et al. [33] compared behavior and course of the cardiac sarcoidosis, after ablation with ventricular tachycardia catheter in patients with sarcoidosis and patients with other types of dilated nonischemic cardiopathies; 23% of the patients with sarcoidosis had previous arrhythmic storm, and 31% had a previous ablation and had been refactored for management with two antiarrhythmics. More than 50% had received amiodarone or beta-blockers. Although they all shared similar mechanisms of arrhythmogenesis with other types of cardiopathies, the group of patients with sarcoidosis had a higher rate of recurrence of ventricular tachycardia. After ablation, survival, or rehospitalization

related to the recurrence of ventricular arrhythmias, was greater in patients with cardiac sarcoidosis. This shows that sarcoidosis has the worst prognosis among all other forms of nonischemic cardiopathy.

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