

Cardiac Sarcoidosis, the Great Chameleon of Mycardiopathies

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Sarcoidosis is a chronic multisystemic disease of unknown etiology, histologically determined by the formation of non-caseating granulomas in various organs of the body, which can also affect heart tissues, resulting in cardiac sarcoidosis (CS).¹

This disease continues to be enigmatic in such a way that, since its first description (1929), and over the years, the exact mechanism of its pathogenesis has still not been clarified, with the possibility of the existence of an important component of genetic predisposition added to types of environmental exposure.²

In addition to the “mysterious” pathogenesis, its highly varied clinical manifestations give this pathology the nickname of the *chameleon of cardiomyopathies*, as it can appear in practically any differential diagnosis in this area. No area of the heart is completely free of involvement, although the granulomatous inflammatory lesion mostly affects the myocardium in a multifocal and irregular manner. Therefore, the clinical spectrum of CS is widely varied and depends on the focus and extension of the disease, mainly occurring in the subclinical form. Most cases appear with blood flow abnormalities, ventricular arrhythmias, and heart failure, but sudden cardiac death (SCD) can also be the initial presentation.¹

CS generally appears in association with extracardiac involvement, especially the lungs and intrathoracic lymph nodes, but it can also be the first or even an isolated sign of sarcoidosis.¹ In addition to the undetermined pathogenesis, the multiplicity of phenotypes of cardiac involvement, and the simultaneous involvement or not of other organs, we must also deal with unspecific diagnostic criteria.¹

CS is still considered to be a rare disease, based on evidence from population studies, calculating its incidence in approximately 1 to 30 cases per 100,000 people, with a major prevalence found within the female, Afro-American population from the northern hemisphere. It has been observed clinically in 5% of all patients with sarcoidosis, while autopsy studies have shown cardiac involvement in 25% of the Caucasian and Afro-American patients, and in up to 80% of Japanese patients with sarcoidosis.³⁻⁵

The natural course of CS is often unpredictable and can be aggressive if it is not diagnosed and treated. It tends to

involve the progression of focal inflammation, leading to the formation of a scar on the free wall of the left ventricle and papillary muscles, which can result in the development of severe cardiomyopathies, malignant arrhythmias, and even SCD. Hence the importance of early diagnosis: patients with a strong likelihood or confirmed diagnosis of CS should be treated immediately to reduce the risk of severe or even fatal outcomes.⁶

Once the diffuse and irregular distribution of this inflammatory condition becomes rooted in a broad array of cardiological signs and symptoms, which are common to many heart conditions, there are no specific “red-flags” for the disease, which causes poorly trained clinicians in the area of cardiomyopathies to take longer to or even fail to recognize the disease. The possible manifestation of phenotypes are: (1) Silent CS leading to SCD – one Finnish study showed CS diagnosed through autopsy in up to 11% of the cases in which SCD was the first and only manifestation;⁷ (2) patients with extracardiac sarcoidosis who develop signs and/or symptoms of cardiomyopathy or are asymptomatic from the cardiovascular point of view and find cardiac alterations in routine exams, such as the electrocardiogram – it is estimated that approximately 5-9% of the patients with systemic sarcoidosis have symptomatic CS. Moreover, few series of autopsies and cardiac magnetic resonance (CMR) have reported a prevalence of subclinical CS of about 25-30% in these patients (in whom, to a great extent, the myocardial involvement includes a small portion and is clinically silent);^{8,9} (3) patients with predominant cardiac symptoms due to CS with or without clinical evidence of sarcoid involvement in other organs – the majority end up being infected by the disease in multiple organs, whereas isolated CS is a more rare and severe manifestation.^{2,10} Two large cohorts described that, when present, the more prevalent symptoms of CS are dyspnea (50-70%), palpitations (40-60%), and fatigue (30-45%), while the more common signs include advanced atrioventricular block (46%), heart failure with a reduced ejection fraction (18%), and sustained ventricular tachycardia (17%).^{7,11}

In general, the complementary exams represent good allies in corroborating the clinical diagnosis of CS, although its specificity and its sensitivity are limited.¹² As the confirmation of the presence of myocardial granulomas is difficult, due to the heterogeneous distribution of the sarcoid lesions, due to the limitation of the endomyocardial biopsy, or due to the fact that it refers to a method that is far from being widely available in cardiology services, different groups of criteria are used for the clinical diagnosis of CS, although none of them has been validated or adopted universally.² The diagnosis becomes especially arduous when the only manifestation is that of cardiac dysfunction (isolated CS) – a case in which the endomyocardial biopsy itself has a low sensitivity and often requires a series of histopathological studies for confirmation.¹³ Nonetheless,

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this diagnosis should be strongly suspected in patients with multisystemic sarcoidosis.⁶

In addition, since the pathogenesis of CS is rare and unknown, proper therapy has not been well established and there are no controlled trial data.² Although the immunosuppression is recommended, there are limited data about the beginning, duration, therapeutic scheme, and ideal doses. All of the recommendations are based on small observational studies.⁶ Thus, anti-arrhythmias can be used in those patients who are against immunosuppression therapy, and ablation by catheter can be considered when the immunosuppression and anti-arrhythmic therapy fail, as can the possibility of an implantable cardioverter-defibrillator (ICD).¹³

The clinical presentation of patients with CS differs a bit from other patients with heart failure. The point to be highlighted here is related to the classification of sarcoidosis, which in many text books or review articles is defined as an infiltrate, or even restrictive, cardiomyopathy. However, when we further analyze the histopathological and image findings, what appears is an inflammatory cardiomyopathy with peculiar characteristics. Based on this principle, we can view this disease from a different perspective, from the cardiovascular point of view, mainly in relation to its complementary exams and its diagnosis, treatment, and prognosis.

The ECG can be completely normal or present unspecific findings in patients with CS, but, in cases in which the ECG is altered, highly varied blood flow abnormalities, arrhythmias, and ventricular extrasystoles are quite common.^{14,15} In this sense, other cardiomyopathies are implied with these findings and should be researched within an appropriate clinical context: ischemic cardiopathy, right ventricle arrhythmogenic cardiomyopathy, tachycardia-induced cardiomyopathies, Chagas disease, and even cardiac amyloidosis.

The echocardiogram (ECHO) is one of the most commonly used tools in the evaluation of a patient suspected of CS. It is commonly the first imaging exam applied in the investigation of the majority of patients. It also presents a low sensitivity; therefore, a normal ECHO result does not exclude the disease and is rarely recommended for screening. One of the more suggestive alterations of this pathology is the tapering of the interventricular septum, mainly in the basal region, which can lead to a septal aneurysm.¹ Other manifestations include an alteration in the segmental contractility, generally with non-coronary distribution; ventricular dilation; worsening of the systolic and/or diastolic function of the right and left ventricle, which is an important prognostic and less common indicator; myocardial thickness simulating other pathologies that can lead to left ventricular hypertrophy (infiltrate diseases, for example), or the hypertrophic cardiomyopathy itself.¹⁶ More recently, it was demonstrated that the echocardiographic evaluation with a longitudinal global strain can improve the capacity to provide an earlier detection of myocardial involvement.¹⁷

Myocardial perfusion scintigraphy (MPS) at rest or with effort detects areas of myocardial injury at rest, as well as areas in which the myocardial perfusion reserve during effort or at rest is decreased. The lesions associated with CS appears in the nuclear image as segmented reductions the tracer uptake in the myocardium. These perfusion defects

differ from the coronary arterial disease, as they do not respect the territory of the coronary arteries. Moreover, the microvascular vasoconstriction associated with the granulomas of sarcoidosis results in the phenomenon of “reverse distribution”, in which the myocardial perfusion defects increase at rest, as compared to during effort.¹ The Gallium-67 citrate scintigraphy (67Ga) is another method of detection for CS, as this marker connects to an acute phase agent (lactoferrin) near the active focus of the inflammation, and can identify cardiac and extracardiac sites. The combination of 67Ga with CPM increases the sensitivity and the diagnostic accuracy of CS, corroborating its inflammatory etiology.¹⁸

Currently, CMR is considered to be one of the major diagnostic modalities in ischemic and non-ischemic cardiomyopathies, due to its capacity to characterize the myocardium with high-resolution imagery. In suspected CS, the CMR images enable one to see not only the anatomy and function, but also the myocardial edema, necrosis, and presence of fibrotic scars.¹⁹ Much like with ECHO, it allows one to observe segmental alterations of non-coronary patterns, septal tapering, thickening, and ventricular aneurysm. In a more acute stage, it detects the presence of myocardial edema observed in the increase of the sign in the modality of the T2 map and the presence of inflammation with a myocardial enhancement after 3 to 5 min of the administration of gadolinium.²⁰ At a later stage, the imaging modality that stands out the most, and is the key point in the diagnosis, is the late gadolinium enhancement (LGE), representing areas of tissue necrosis with substitution by fibrotic tissue. Typically, the LGE involves basal segments of the left ventricle (LV) and the septal region of the right ventricle (RV), but any region of the heart can be affected. It is often distributed in an irregular manner with a non-ischemic pattern, and is limited or preserves, to a great extent, the subendocardial and mid-mesocardial regions. However, transmural patterns or even involvement of the free wall of the RV are possible,¹ and can even mimic other cardiomyopathies (ischemic, chagasic, for instance). The “hook or hug sign” with the presence of continuous LGE of the septum and the entire free wall of the RV is an important marker of the image in CS, but the identical pattern can be seen in the myocarditis of gigantic cells.² Other uses of CMR include the capacity to increase the sensitivity of the endomyocardial biopsy, identifying the areas of greater probability of involved tissues and their prognostic value, with the LGE representing an important risk factor for fatal events, as well as a follow-up of the treatment response.²¹

Among the imaging exams with a greater sensitivity and specificity for CS, what stands out is the 18F-Fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT). Its rationale is based on the inflammatory activity of the cells in the granulomas of sarcoidosis, which appear with a high craving for glucose and its analogues, leading to an increase in the sign in that region,² which, combined with the PET of the entire body, enables one to identify the activity of the extracardiac disease and evaluate the cardiac perfusion through its respective tracers. Depending on the stage of the disease, the findings can vary from only pure inflammation with an

uptake of 18F-FDG or only a perfusion defect in the case of terminal scar or treated CS.²² The critical point of the exam that suggests an active area of CS is the overlapping of a “hot point” of one or more areas of uptake of 18F-FDG with the presence of the perfusion defect, considered a characteristic funding of CS (mismatch pattern). The perfusion defects result in the healing of the ventricle or in the reversible involvement of the microcirculation. The hibernating myocardium, other forms of myocarditis, rheumatological diseases with cardiac involvement, and some genetic cardiomyopathies can also cause an abnormal absorption of 18F-FDG. The absence of extracardiac uptake diminishes the specificity of the PET for CS.²³ New studies show that the simultaneous analysis of the CMR and the FDG/PET increase the sensitivity in the diagnosis of CS and lead to a lower rate of false positives, having a synergetic effect, enabling the detection of patients in early pre-clinical stages and guiding treatment, in which the implementation of immunosuppression can be more beneficial.²⁴ It is important to remember that in patients who already use immunosuppressants or who are in a spontaneous remission stage of CS, a PET negative for inflammation does not exclude its diagnosis.

The endomyocardial biopsy is considered to be the gold standard for the diagnosis of cardiac sarcoidosis, whose histological marks are non-necrotic (caseating) granulomas and gigantic (epitheloid) cells isolated with or without surrounding lymphocytic/granulocytic infiltration combined with myocardial fibrosis, and without extensive eosinophilia or myocyte necrosis.^{25,26} However, as the cardiac involvement is generally focal and irregular, it has a low sensitivity, and tends to be positive in only 20% of the cases.^{13,27,28} Although there are reports of higher sensitivity when the biopsies are conducted under the guidance of another imaging exam, many centers prefer to perform the extracardiac biopsy (when possible), arguing that the sensitivity and security are better.² It is important to highlight that the finding of non-caseating granuloma, as well as the lymphocytic infiltration and accumulation of macrophages also found in CS, can also be found in infectious, occupational, toxic, and neoplastic diseases, and vasculitis, as well as in the myocarditis of gigantic cells or dilated cardiomyopathy.^{29,30}

The diagnosis of CS requires a combination of clinical, histological, and imaging modalities. To date, the two most commonly used diagnostic criteria for CS were published by the Japanese Society of Sarcoidosis and other granulomatous diseases (adapted in 2019 - Table 1) and the Heart Rhythm Society (HRS – published in 2014).^{10,25,26} Nevertheless, these guidelines were based mainly on a consensus among specialists and lack the proper validation from other prospective studies.³¹ The most recent Brazilian recommendation on the theme, published in 2022, follows up on the last recommendation from the Japanese society (2019) for the diagnosis of CS, whether it is followed by an extracardiac sarcoid lesion or not.³²

Although they agree on the concept that the endocardial biopsy is the most accurate diagnostic method, other secondary diagnostic tools can aid in the diagnosis and enable either a non-invasive or minimally invasive evaluation for the diagnosis of cardiac sarcoidosis.¹ In this sense, the findings from the myocardial scintigraphy, CMR, and PET-CT with 18F-FDG take on special relevance. In fact, the simultaneous

application of CMR with PET-CT is currently being studied, with good diagnostic accuracy.²⁴

Even if the progress in imaging methods has enabled a new way to establish the diagnosis of CS – often discarding the endocardial biopsy (gold standard), a more accurate clinical suspicion is still necessary, since the diagnostic rationale moves from this to the diagnostic confirmation using complementary exams. In this sense, recognition programs and screening protocols are essential to achieve the desired early diagnosis, thus enabling an opportune treatment of this medical condition before it becomes fatal (mainly due to sudden arrhythmic death). It is easier and should be remembered that the diagnostic suspicion should always emerge in patients with the extracardiac disease, which presents cardiac signs and symptoms. Likewise, it is prudent to consider the finding of unexplainable 2nd and 3rd degree atrioventricular block (AVB), sustained ventricular arrhythmias, or the presence of heart failure with ventricular dysfunction, discarding ischemic or chagasic cardiopathy, as being indicative for research.

In the opinion of the authors, there is no way to reach a diagnosis of CS without a multimodal approach. Possibly, with the adoption of “red-flags”, as proposed in the presente article (Table 2), associated with an imaging exam that is suggestive and provides evidence of active myocardial inflammation, more diagnoses can be performed without the need for endomyocardial histopathological analyses, which are seldom available in our field.

It is well-known that chameleons are easier to be found at night, when they lose their capacity for camouflage. This may well be the reason why we have been unable to find this chameleon cardiomyopathy: the fact that we are in the dark, needing to shed light on our diagnostic criteria and push away the differential diagnoses that it mimics.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for important intellectual content: Coutinho DS, Montenegro CEL; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Coutinho DS, Fraga FJO, Montenegro CEL.

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This article does not contain any studies with human participants or animals performed by any of the authors.

Table 1 – Japanese Society of Sarcoidosis (2017). SJC recommendation for the diagnosis of cardiac sarcoidosis 247. Criteria for cardiac involvement The cardiac findings should be evaluated based on the greater and lesser criteria

Clinical findings that satisfy the following 1) or 2) strongly suggest the presence of cardiac involvement.

- 1) Two or more of the five principles (a) to (e) are met.
- 2) One of the five criteria (a) to (e) plus two or more lesser criteria (f) to (h) are met.

Major criteria

- a) High-degree atrioventricular block (including full atrioventricular block) or fatal ventricular arrhythmia (for example, sustained ventricular tachycardia and ventricular fibrillation)
- b) Basal tapering of the ventricular septum or abnormal anatomy of the ventricular wall (ventricular aneurysm, tapering of the upper or mid-ventricular septum, thickness of the regional ventricular wall)
- c) left ventricular contractile dysfunction (left ventricle ejection fraction less than 50% or alteration of segmental contractility)
- d) The 67Ga citrate or PET 18F-FDG scintigraphy reveals an abnormally high accumulation of markers in the heart
- e) the MR with gadolinium shows a delay in the myocardial contrast

Minor criteria

- f. Normal ECG findings: ventricular arrhythmias (unsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), deviation of axis or abnormal Q waves
- g. Perfusion defects in the myocardial perfusion scintigraphy
- h. Endomyocardial biopsy: monocyte infiltration and moderate or severe myocardial interstitial fibrosis.

Guidelines for the diagnosis of cardiac sarcoidosis

- 1) Histological diagnosis group (those with positive findings in the myocardial biopsy): cardiac sarcoidosis is histologically diagnosed when the endomyocardial biopsy or the surgical samples show non-cereating granulomas
- 2) Clinical diagnosis group (that with negative findings in the myocardial biopsy or those that were not submitted to the myocardial biopsy): the patient is diagnosed clinically as cardiac sarcoidosis (1) when non-cereating granulomas are found in other organs other than the heart, and clinical findings strongly suggest cardiac involvement mentioned above are present; or (2) when the patient shows in his/her clinical picture findings that strongly suggest pulmonary or ophthalmologic sarcoidosis (bilateral hilar lymphadenopathy, high ECA serum activity or high serum levels of lysozyme, high serum sIL-2R, significant accumulation of markers in the 67Ga citrate or PET 18F-FDG scintigraphy, high percentage of CD4/CD8 lymphocytes, ratio >3.5 in the LBA liquid). The imaging results strongly suggest the previously mentioned cardiac involvement.

Guidelines for the diagnosis of cardiac sarcoidosis

Pre-requisites

1. No clinical characteristics of sarcoidosis in other organs other than the heart are not observed (the patient should be examined in detail to evaluate respiratory, ophthalmologic, and cutaneous involvements of sarcoidosis.) When the patient is symptomatic, other etiologies that can affect the corresponding organs should be discarded.
2. The 67Ga citrate or PET 18F-FDG scintigraphy shows no abnormal accumulation of markers in any other organ other than the heart.
3. The chest computed tomography (CT) does not show signs of CS in the lungs or hilar and mediastinal lymphadenopathy (smaller axis >10 mm).

Histological diagnosis group

1. Isolated cardiac sarcoidosis is histologically diagnosed when the endocardial biopsy or surgical samples show non-cereating granulomas.

Clinical diagnosis group

1. Isolated cardiac sarcoidosis is clinically diagnosed when the criteria (d) and at least three other greater criteria (a) to (e) are satisfied. When the patient meets at least four criteria of cardiac involvement that do not include criteria (d) or when the patient meets criteria (b) and (d) plus one of the remaining criteria, the patient is suspected of having isolated cardiac sarcoidosis.

ACE: angiotensin conversion enzyme; ECG: electrocardiogram; BAL: bronchoalveolar lavage; PET 18F-FDG: 18F-Fluorodeoxyglucose positron emission tomography; MR: magnetic resonance. Adapted from Terasaki et al.²⁶

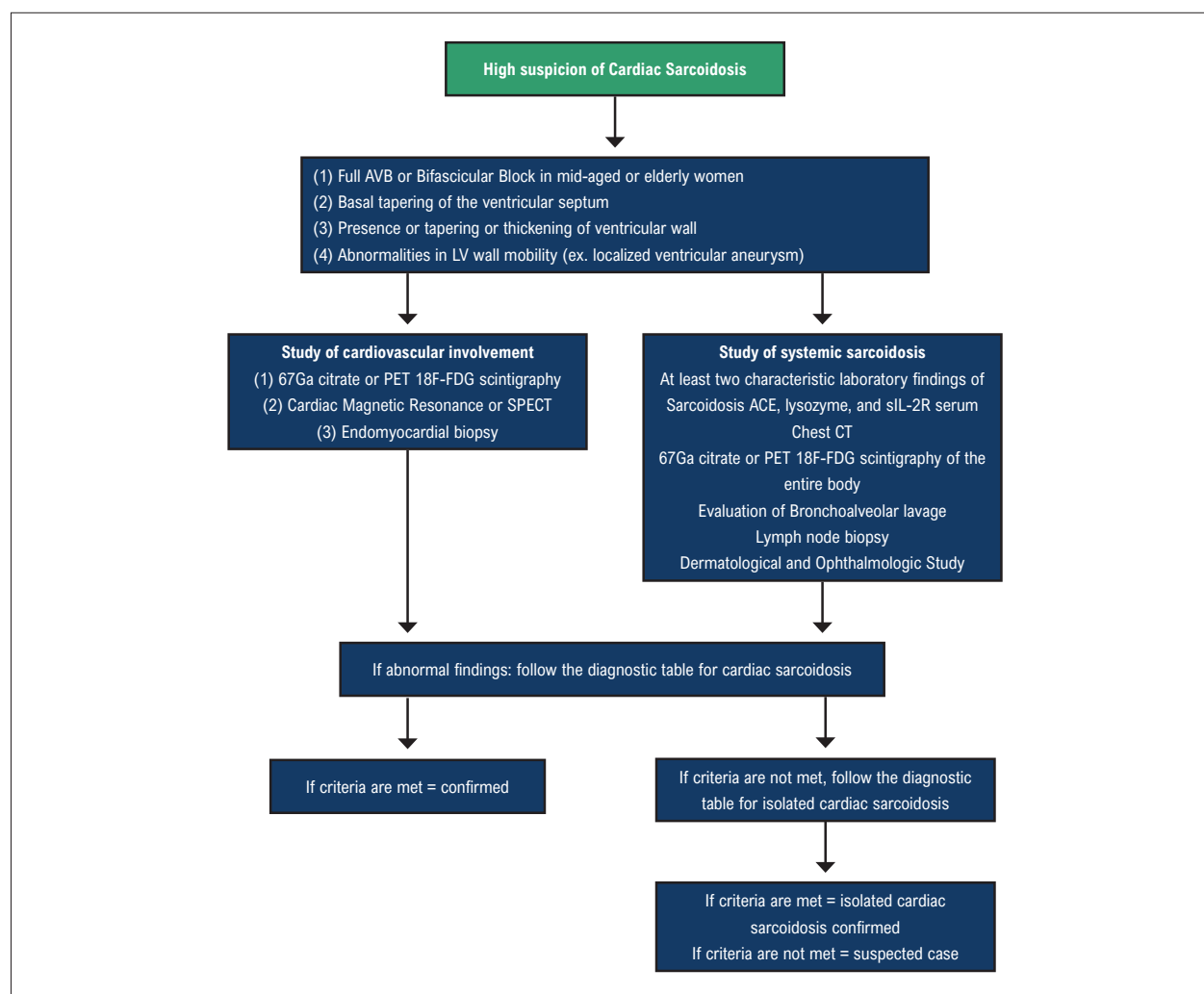


Figure 1 – Diagnostic flowchart of cardiac sarcoidosis; Brazilian Guideline for Myocarditis and Pericarditis; Montera et al.³² AVB: atrioventricular block; LV: left ventricle; CT: computed tomography; PET 18F-FDG: 18F-Fluorodeoxyglucose positron emission tomography.

Table 2 – “Red flags” of cardiac sarcoidosis

“Red flags” of cardiac sarcoidosis
Clinical manifestation Sudden cardiac death Manifestation suggestive of tachycardia-induced cardiomyopathy
ECG/ HOLTER 24H 2 nd and 3 rd degree AVB Q pathologies with no ischemic disease Frequent and/or polymorphic ventricular arrhythmias Alternation (Holter) of advanced AVB with frequent ventricular arrhythmias
Echocardiogram Tapering of basal region of the interventricular septum Septal Aneurysm Segmental contractile alteration of non-coronary pattern
CPM/67Ga Reverse distribution pattern (uptake at rest) Uptake with gallium of active areas

Cardiac magnetic resonance

Myocardial edema (T2 map) or late gadolinium enhancement in basal regions of the LV and septal regions of the RV, preserving the subendocardial region “Hug sign” in the RV (continuous enhancement in the free wall and septum of the RV)
Late transmural enhancement, excluding ischemic disease or chagasic cardiopathy

18F-FDG PET/CT

“Mismatch pattern” and associated extracardiac uptake

Extra-cardiac signs

Extracardiac granulomatous lesions

AVB: atrioventricular block; LV: left ventricle; RV: right ventricle; ECG: electrocardiogram.

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