

Cardiac Sarcoidosis: The Chameleon of Cardiology

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Abstract

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology, characterized by the formation of non-caseating granulomas in multiple organs. Cardiac involvement, an important cause of morbidity and mortality in these patients, has been generating interest in cardiology, because it is a cause of heart failure, atrioventricular blocks, and ventricular arrhythmias with unfavorable prognosis; however, there are specific treatments with the potential to change the natural history of this condition. The main challenge of cardiac sarcoidosis (CS) is diagnosis, given that the gold standard method of endomyocardial biopsy has limited sensitivity due to the focal nature of the pathology.

Accordingly, cardiovascular imaging methods play the role of guiding most diagnoses of CS. In this scenario, knowledge about these methods, their main findings, and their rational use are essential to the diagnosis of this disease with such diverse presentations.

Electrocardiogram and echocardiography are practical and widely available exams; however, they provide greater diagnostic capacity in patients with clinically manifest disease. On the other hand, to identify incipient forms, which are often silent, it is necessary to use advanced imaging methods, such as positron emission tomography with 18F-fluorodeoxyglucose and cardiac magnetic resonance, which primarily identify signs of active inflammatory activity and fibrosis, respectively. Despite the advances in these imaging methods, due to the lack of studies comparing them with the gold standard (endomyocardial biopsy), the diagnosis of CS currently remains a major challenge.

Introduction

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology, characterized by the accumulation of T

lymphocytes and mononuclear phagocytes with the formation of non-caseating granulomas in various organs. Its genesis is believed to be the consequence of an immune-mediated response from antigenic triggers, which are not yet well understood, in people who are genetically predisposed.¹

Its prevalence varies worldwide, with particularities related to regions, ethnic groups, and sex, and descriptions range from 10 to 60 cases per 100,000 individuals.²

Systemic sarcoidosis generally manifests with lung and intrathoracic lymph node involvement, in more than 90% of cases; however, the disease can affect virtually any organ, such as the skin, eyes, heart, nervous system, musculoskeletal system, renal system, and endocrine system.¹

The importance of myocardial involvement in cardiac sarcoidosis (CS) is mainly due to its prognostic implications, associated with the fact that there are targeted treatments that are potentially capable of preventing severe complications.

CS is a known cause of ventricular dysfunction, conduction disturbances, and ventricular arrhythmias, which eventually present in the form of sudden death.³

In several samples, CS appears as one of the main causes of death in individuals with sarcoidosis, accounting for approximately 50% of deaths in a North American sample and up to 85% in an Asian population.^{3,4}

Despite the severity, the identification of these patients still poses a challenge, since the majority of them have subclinical cardiac involvement. Thus, the prevalence of myocardial involvement described in the literature varies from 5% (considering patients with clinically evident cardiac involvement) to approximately 54%, when advanced imaging methods are used, identifying asymptomatic patients, who are known as subclinical.⁵

The gold standard for diagnosis is the presentation of a suggestive clinical picture associated with histological evaluation of myocardial tissue showing evidence of a non-caseating granulomatous process, after excluding other potential causes of granuloma formation (especially infectious and neoplastic causes). However, due to the focal nature of the disease (involvement beginning with the formation of granulomas), endomyocardial biopsy has low sensitivity, revealing the presence of non-caseating granulomas in less than 25% of patients who undergo the procedure.⁶

Therefore, the main guidelines have established an alternative route that is not dependent on myocardial histopathology to diagnose CS. In the case of patients with a histopathological diagnosis of extracardiac sarcoidosis, with myocardial structural changes compatible with the disease that cannot be explained by other etiologies, myocardial involvement due to sarcoidosis is inferred.^{7,8}

Keywords

Sarcoidosis; Electrocardiography; Echocardiography; Positron Emission Tomography Computed Tomography; X-Ray Computed Tomography.

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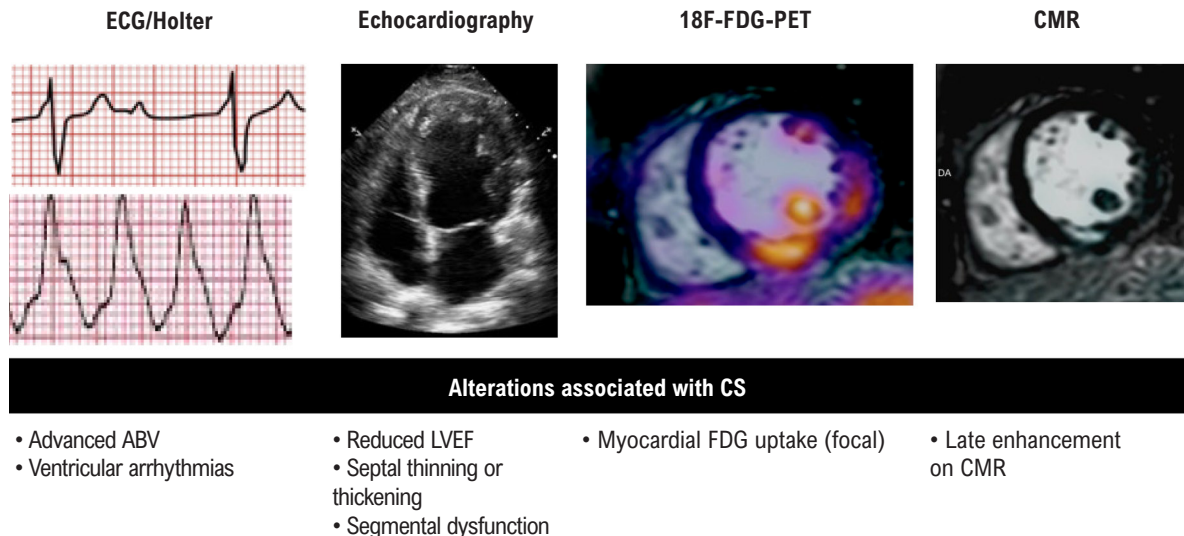
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Central Illustration: Cardiac Sarcoidosis: The Chameleon of Cardiology



Imaging methods in diagnosis of CS



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18F-FDG-PET: positron emission tomography with 18F-fluorodeoxyglucose; ABV: atrioventricular block; CMR: cardiac magnetic resonance imaging; ECG: electrocardiography; LVEF: left ventricular ejection fraction; CS: cardiac sarcoidosis.

Accordingly, the diagnosis of CS, except for cases in which endomyocardial biopsy presents compatible histopathology, depends on the presence of specific cardiac changes observed in complementary exams such as electrocardiogram (ECG), echocardiogram, cardiac magnetic resonance (CMR), and nuclear medicine exams, with emphasis on positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (18FDG) combined with computed tomography (CT) (Central Illustration).

The objective of this article is to conduct a review about the non-invasive analysis of cardiac involvement due to sarcoidosis, emphasizing the importance of advanced imaging methods in the clinical evaluation of this highly challenging disease.

Diagnostic criteria for CS

The first international guideline on the diagnosis of CS was published in 2014, by experts appointed by the Heart Rhythm Society (HRS), with representatives from several other societies.⁸ Previously, the diagnostic criteria of the Japanese Ministry of Health and Welfare (JMHW) had been published in 2006.⁹ They did not include FDG-PET, and they attributed less importance to late gadolinium enhancement (LGE) on CMR, consequently offering less ability to identify these patients. Subsequently, the Japanese Circulation Society (JCS)⁷ published a new guideline, with recommendations very close to those put forth by the HRS (highlighting the importance of FDG-PET and CMR), while admitting the possibility of diagnosing CS without histopathological documentation of sarcoidosis (Table 1).

Currently, the most used diagnostic criteria are those developed by the HRS and JCS. Although both include the same complementary exams in their approaches, such as ECG/Holter, echocardiogram, FDG-PET, and CMR, there appears to be low concordance between these criteria.¹⁰ Faced with this diagnostic difficulty, some centers have created multidisciplinary teams to evaluate suspected cases, using the aforementioned criteria as a guide, without being limited to them.¹¹ This type of approach requires experience on the part of the team and a high degree of familiarity with the main alterations in cardiovascular imaging methods associated with CS.

Cardiovascular imaging in the assessment of CS

Among the complementary exams used in the assessment of patients with suspected CS, CMR and FDG-PET/CT stand out, due to the possibility of identifying changes still in the initial phase of the disease, with minimal or absent cardiovascular manifestations,⁸ which is known as the silent form of CS. ECG and echocardiography, although they are less accurate, can also suggest diagnosis of CS in a probable clinical context, with the advantage of being widely available.^{7,8}

Role of electrocardiography

ECG can assist in the diagnosis of CS, both as a screening tool for cardiac involvement, in patients with a previous diagnosis of non-CS, and by raising the suspicion of sarcoidosis as the etiology of specific cardiac alterations.⁸

Review Article

Table 1 – Diagnostic guidelines for CS

HRS 2014 Expert Consensus	JCS 2016 Guidelines
1. Histological diagnosis of myocardial tissue	1. Histological diagnosis group
CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains, if applicable)	CS is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas, and granulomas due to other causes and local sarcoid reactions can be ruled out
2. Clinical diagnosis based on invasive and non-invasive exams	2. Clinical diagnosis group (negative myocardial biopsy findings or patients not undergoing myocardial biopsy)
a) There is diagnosis of extracardiac sarcoidosis b) One or more of the following are present: - Steroid +/- immunosuppressant responsive cardiomyopathy or heart block - Unexplained decrease in LVEF (40%) - Unexplained sustained VT (spontaneous or induced) - Mobitz type II second-degree heart block or third-degree heart block - Irregular uptake on dedicated cardiac PET (in a pattern consistent with CS) - Late gadolinium enhancement on CMR (in a pattern consistent with CS) - Positive gallium uptake (in a pattern consistent with CS)	1. When epithelioid granulomas are found in organs other than the heart, and clinical findings strongly suggestive of cardiac involvement are present 2. When the patient presents clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis, and at least 2 of the following 5 laboratory findings characteristic of sarcoidosis: - Bilateral hilar lymphadenopathy - Elevated serum angiotensin-converting enzyme activity or elevated serum lysozyme levels - Elevated serum soluble interleukin-2 receptor levels - Significant tracer accumulation in gallium-67 citrate scintigraphy or 18F-FDG-PET - A high percentage of lymphocytes with a CD4/CD8 ratio of > 3.5 in BAL fluid

18F-FDG-PET: positron emission tomography with 18F-fluorodeoxyglucose; CMR: cardiac magnetic resonance imaging; CS: cardiac sarcoidosis; HRS: Heart Rhythm Society; JCS: Japanese Circulation Society; LVEF: left ventricular ejection fraction; PET: positron emission tomography; TV: ventricular tachycardia. Adapted from Shrivastav et al.⁹

Several electrocardiographic changes have already been described in patients with CS. Nonspecific changes, when present in individuals with prior diagnosis of sarcoidosis, should raise the suspicion of myocardial involvement. These changes may vary from ventricular or atrial arrhythmias, varying degrees of atrioventricular block (AVB), bundle branch blocks, hemiblocks, QRS fragmentation, and T wave changes, such as inversion, alternation, and increased amplitude.¹²

Another role of ECG in this pathology is due to the fact that CS is an important cause of advanced AVB and sustained ventricular tachycardia, initially seen as idiopathic in middle-aged adults. In some samples, CS was responsible for up to 30% of idiopathic cases of AVB and sustained ventricular tachycardia in this age group (< 60 years).^{13,14} It is worth highlighting that the identification of CS as the cause of AVB has prognostic importance, since immunosuppressive treatment has the potential to reverse the block.¹⁵

Another change already described in individuals with CS is the epsilon wave. This change is classically observed in individuals with arrhythmogenic right ventricular cardiomyopathy. There are case reports of patients who met the criteria for arrhythmogenic right ventricular cardiomyopathy according to the task force criteria, but who were subsequently diagnosed with CS after endomyocardial biopsy.^{16,17} Signs such as advanced AVB, important left ventricular dysfunction, septal LGE, absence of family history, and mediastinal lymphadenopathy should raise the suspicion of CS.¹⁸

In general, patients with CS and cardiovascular symptoms present some degree of electrocardiographic alteration. Nonetheless, a normal ECG does not rule out myocardial involvement, but it reduces the likelihood, especially in patients without cardiovascular symptoms.¹⁹

Role of echocardiography

Echocardiography, as it is practical and easily accessible, is generally the first imaging test to be requested when screening for CS. It is usually altered in symptomatic patients, but frequently normal in patients with the silent form.²⁰

Its findings vary, including increased ventricular wall thickness (resulting from focal areas of edema or granulomatous infiltration) or, in more advanced phases of the disease, thinning (most commonly septal, in the basal portion), akinesia, dyskinesia, or even aneurysms.²¹ The most commonly affected regions are the left ventricular free wall and the interventricular septum. The ejection fraction may be reduced or preserved, with varying degrees of diastolic dysfunction. However, unlike reduced ejection fraction, changes in diastolic function have not yet been included in the diagnostic criteria for CS.²¹

Echocardiography has limited sensitivity when compared to advanced imaging exams such as CMR and F-FDG-PET. In a study including 321 patients with a histopathological diagnosis of sarcoidosis, echocardiography showed a sensitivity of less than 30%.²² Therefore, in patients with extracardiac sarcoidosis and cardiovascular symptoms, even with a normal echocardiogram, clinical investigation with advanced imaging methods is recommended.⁸

More recently, the use of techniques such as speckle tracking appears to have improved the sensitivity of echocardiography in identifying myocardial injury due to sarcoidosis, with some studies showing reduced global longitudinal strain in patients with sarcoidosis, normal ejection fraction, and evidence of myocardial injury on FDG-PET/CT and CMR.²³ In the evaluation of 23 patients with CS (compared to controls), the global longitudinal strain was $-15.9\% \pm 2.5\%$ versus -18.2%

$\pm 2.7\%$. Worsening of this parameter was also associated with the development of heart failure and hospital admission.

Furthermore, echocardiography is also a valuable tool for assessing cardiovascular alterations secondary to severe lung disease caused by sarcoidosis, such as pulmonary artery pressure and changes in the right ventricle. These cardiological alterations should not be confused with cardiac involvement caused by the granulomatous infiltration of sarcoidosis.²⁴

Papel do 18F-FDG-PET/CT

¹⁸F-FDG is a glucose analogue labeled with radioactive fluorine, which remains inside the cell, contributing to the generation of the PET image. It is frequently used in association with CT for attenuation correction and anatomical correlation.

The rationale behind this method lies in the fact that the inflammatory cells involved in sarcoidosis granuloma have avidity for uptake of glucose and glucose analogues, thus making it possible to identify regions with active inflammation.²⁵

The usual pattern of the image generated by FDG in CS is focal and irregular, which can appear as areas of hyper-uptake in a myocardium with physiological uptake completely suppressed or merely reduced; in the latter case, it generates a pattern of focal hyper-uptake in a myocardium with diffuse uptake (focal on diffuse) (Figure 1).

Generally, cardiac PET is associated with whole-body PET, assisting in the identification of areas suggestive of extracardiac involvement.²⁶

One of the challenges of this method is that the myocyte is also usually avid for glucose (and consequently FDG) uptake. Therefore, for the exam to be interpretable, preparation must be carried out in order to suppress this physiological uptake of the radiotracer by the myocardium. Protocols may vary

between services, but, in general, a high-fat diet restricted in carbohydrates is recommended during the 24 hours preceding the exam, associated with 12 hours of fasting.²⁷ However, in spite of this, in up to approximately 25% of cases, adequate suppression of myocardial FDG uptake does not occur, making it impossible to interpret the exam.²⁸ In some centers, it is also common to administer unfractionated heparin with the aim of increasing the circulation of free fatty acids, which could potentially contribute to suppressing myocyte avidity for glucose.²⁷

It is important to remember that myocardial FDG uptake is not synonymous with CS. Other conditions can also generate myocardial uptake of FDG, such as physiological uptake itself (which will normally appear as diffuse uptake), different etiologies of myocarditis, cardiac involvement due to rheumatological diseases, hibernating myocardium, and even some genetic cardiomyopathies.²⁹ Therefore, the exam needs to be interpreted within the clinical context, seeking to rule out differential diagnoses, especially ischemic disease. The presence of extracardiac uptake appears to significantly increase the specificity of CS.²⁹

Given that F-FDG-PET assesses active inflammation, a normal exam does not rule out the presence of CS; it only indicates that there is no inflammatory process active in the myocardium at that time.²⁷ The intensity of uptake is quantified using the standardized uptake value (SUV), whose calculation considers the concentration of radioactivity in the region of interest, the dose injected, and the patient's weight.

The sensitivity and specificity described in the literature are approximately a little over 80%. Kim et al., in a meta-analysis with 891 patients from 17 studies, observed a sensitivity of 84% and specificity of 83%.³⁰ An important limitation of these data is that they did not use histopathology as a reference method, but rather the JMHW criteria, published in 2006.

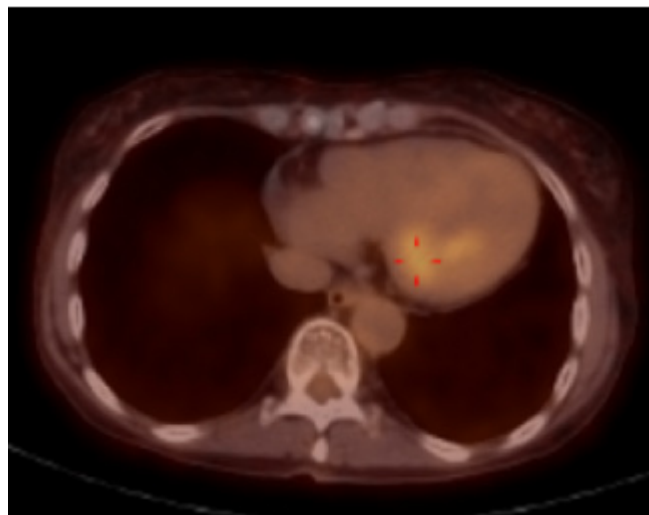


Figure 1 – Cardiac ¹⁸F-FDG-PET/CT with heterogeneous distribution of FDG in the left ventricular walls, showing focal areas with greater uptake in the inferior wall (middle and basal segment) in a 46-year-old female patient, with endomyocardial biopsy suggestive of CS. Author's data. ¹⁸F-FDG-PET/CT: positron emission tomography with ¹⁸F-fluorodeoxyglucose combined with computed tomography.

In addition to the great usefulness of F-FDG-PET in the diagnostic evaluation of CS, the test also has therapeutic and prognostic implications.

The main guidelines on this topic (HRS and JCS) recommend immunosuppression in patients with clinical manifestations attributed to CS when there are signs of inflammation detected by PET-FDG.^{7,8} Reduced FDG uptake after immunosuppression seems to be a predictor of improved ejection fraction; thus, this method has also been used as a parameter to evaluate therapeutic response.^{31,32}

The persistence of FDG uptake in serial exams is strongly associated with worse prognosis, increasing the risk of major cardiovascular events by up to 20-fold in patients who do not respond to immunosuppression.³³

Another important predictor of worse prognosis is FDG uptake in the right ventricle, associated with increased mortality, ventricular arrhythmias, and a decline in left ventricular ejection fraction.^{34,35}

Perfusion study, when associated with PET-FDG, also adds prognostic information; thus, patients with myocardial FDG uptake associated with perfusion alterations in these regions (which would be a mismatch) appear to have worse prognosis than those with myocardial inflammation but normal perfusion.³⁶ Perfusion studies can be performed by means of PET/CT using radiotracers such as ammonia labeled with nitrogen-13 and rubidium-82, which are rarely used due to their high cost, or with perfusion scintigraphy.³⁷

For the future, we expect the use of radiotracers that are not usually captured by the normal myocardium, consequently making dietary preparations unnecessary, for example somatostatin analogues.²⁷

Role of cardiac magnetic resonance imaging

CMR is an indispensable exam in the assessment of patients with suspected CS. In addition to assessing morphological and functional details of the right and left ventricles with high accuracy, it also makes it possible to identify signs of inflammation, mainly necrosis and fibrosis.³⁸

CMR has the advantage of not using radiation and of using gadolinium, which is a contrast material with a low risk of adverse events.

One of the main resources of CMR is LGE analysis, detecting the expansion of the extracellular matrix, which suggests, especially in the more advanced phase of the disease, the presence of fibrosis (Figure 2).

Although there are no pathognomonic findings, the LGE patterns most commonly observed in CS are focal, mesocardial or subepicardial in basal regions of the septum and lateral wall.¹¹ These patterns are not specific and can be found in several other conditions of myocardial injury, especially inflammatory ones. However, even transmural patterns can occur.³⁹

An LGE pattern was recently described that initially appeared to be specific to CS, namely, the hug sign. This is characterized by LGE that extends from the interventricular septum towards the right ventricle, observed in cases of isolated CS with histopathological diagnosis.⁴⁰ Nonetheless, this pattern has already been observed in giant cell myocarditis.⁴¹

CMR can also suggest the presence of myocardial inflammation through the presence of T2 hypersignal, which indicates excess fluid in the myocardium. However, the absence of this alteration does not rule out the presence of inflammation when compared to PET.⁴² In CMR, it is also possible to estimate diffuse interstitial fibrosis through T1 and T2 maps, suggesting subclinical sarcoidosis, although the clinical usefulness of this parameter is still uncertain.⁴³

The real accuracy, sensitivity, and specificity of imaging tests in CS are still quite debatable, because, in most studies, these methods were not compared with the gold standard of endomyocardial biopsy, but rather with diagnostic criteria, generally those proposed by the HRS⁸ and the JMHW.⁹ These studies describe sensitivities ranging from 75% to 100% and specificities ranging from 77% to 85%.⁴⁴

Thus, in individuals with extracardiac sarcoidosis, the presence of LGE is indicative of probable CS; however, a negative test cannot rule out the presence of heart disease, for instance, still in the initial phase.

To date, no large prospective study has been designed with the objective of comparing the accuracy of CMR and PET in diagnosing CS. Some services, when there is a strong suspicion of CS, suggest that CMR investigation should be started before PET, for some reasons; for example, it does not depend on preparation, and it provides good structural and tissue characterization of the heart. However, the current impression is that these are exams that offer complementary information; PET shows signs of inflammatory activity, and CMR shows fibrosis⁴⁵ (Table 2).

In addition to its diagnostic usefulness, several studies have observed an important prognostic role. A meta-analysis with 694 patients observed higher cardiovascular mortality, all-cause mortality, and ventricular arrhythmias in patients with CS and LGE.⁴⁶ Specific LGE patterns, such as involvement of the right ventricle and multifocal pattern, also seem to be associated with worse prognosis.⁴⁷

Regarding the limitations of this exam, we highlight the at least relative contraindication in patients with glomerular filtration rate < 30 mL/min/1.73 m² and the difficulties in image interpretation (due to the presence of artifacts) in patients with cardiac devices, such as pacemakers and implantable cardioverter defibrillators, even though they are compatible with magnetic resonance devices.⁴⁸

Integrating imaging exams in the assessment of patients with suspected CS

When discussing the ideal diagnostic approach for individuals with suspected CS, it is essential to distinguish at least two main scenarios: patients who already have a previous diagnosis of extracardiac sarcoidosis and those who do not.⁴⁴

In the former case, any cardiovascular symptom or alteration on ECG/echocardiography increases the probability that the myocardium is also affected by sarcoidosis, indicating further investigation with CMR, generally followed by FDG-PET, and, in exceptional cases, endomyocardial biopsy⁸ (Figure 3).

The main diagnostic challenge is the second scenario, regarding patients with cardiovascular alterations such as heart

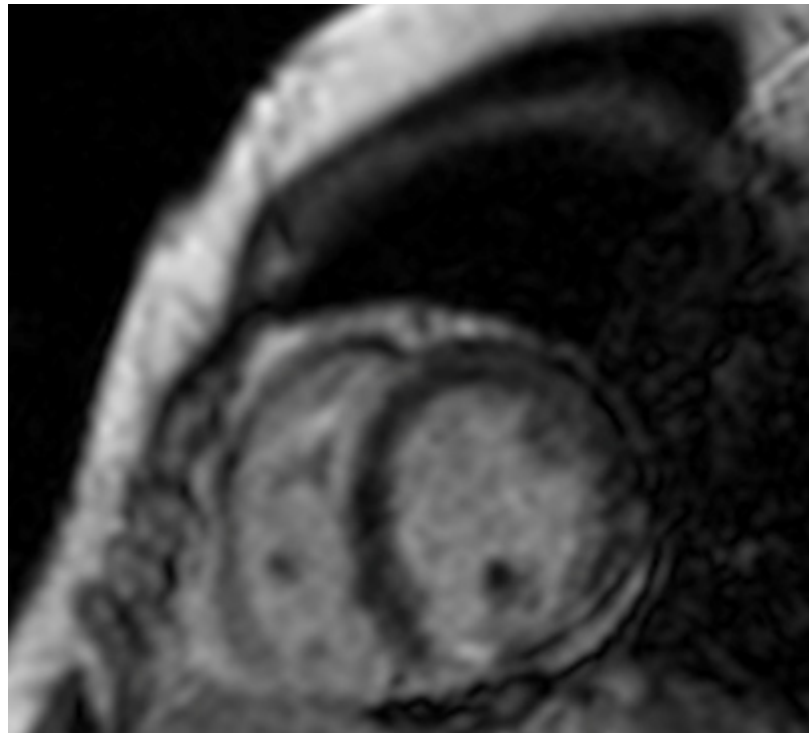


Figure 2 – CMR showing the presence of mesocardial late enhancement in the inferior wall of a 38-year-old male patient diagnosed with CS. Author's data. CMR: cardiac magnetic resonance imaging.

Table 2 – Diagnostic interpretation of combined data from CMR with 18F-FDG-PET

Interpretation	CMR findings	18F-FDG-PET findings
Active disease with the presence of scarring and inflammation	Presence of LGE	18F-FDG uptake observed
Scarring without active inflammation (inactive)	Presence of LGE	No 18F-FDG uptake observed
Normal (no disease)	Presence of LGE	Lack of 18F-FDG uptake
Early disease/false positive	Presence of LGE	18F-FDG uptake observed

18F-FDG-PET: positron emission tomography with 18F-fluorodeoxyglucose; CMR: cardiac magnetic resonance imaging; LGE: late gadolinium enhancement. Adapted from Shrivastav et al.⁹

failure, advanced AVB, or ventricular arrhythmias, without previous diagnosis of any systemic condition, in which the range of etiologies is immense, and CS is just one among dozens of possibilities. In these cases, the suspicion of CS should be raised mainly in cases of advanced AVB or ventricular tachycardia of unexplained cause in patients under 60 years of age, or even in patients with heart failure not justified by the most prevalent etiologies, especially with the presence of thinning of the basal septum and thinning or thickening of the ventricular wall.^{7,31} For these patients, the investigation must include both the characterization of the pattern of myocardial injury, with CMR and cardiac FDG-PET, searching for signs that may suggest CS, as well as whole-body FDG-PET, with the aim of identifying possible signs of extracardiac sarcoidosis. The search for signs of extracardiac sarcoidosis can be refined with ophthalmological,

dermatological, and pulmonary evaluation. In selected cases, endomyocardial biopsy will also be recommended.⁷

Take-home messages

- CS is a complex disease to diagnose.
- Generally, diagnosis is made without confirmation of myocardial histology, based on alterations in imaging tests.
- Most alterations observed in these tests are nonspecific findings that need to be interpreted in the patient's clinical context.
- The lack of studies that compare the accuracy of these tests with the gold standard (histopathology) makes it

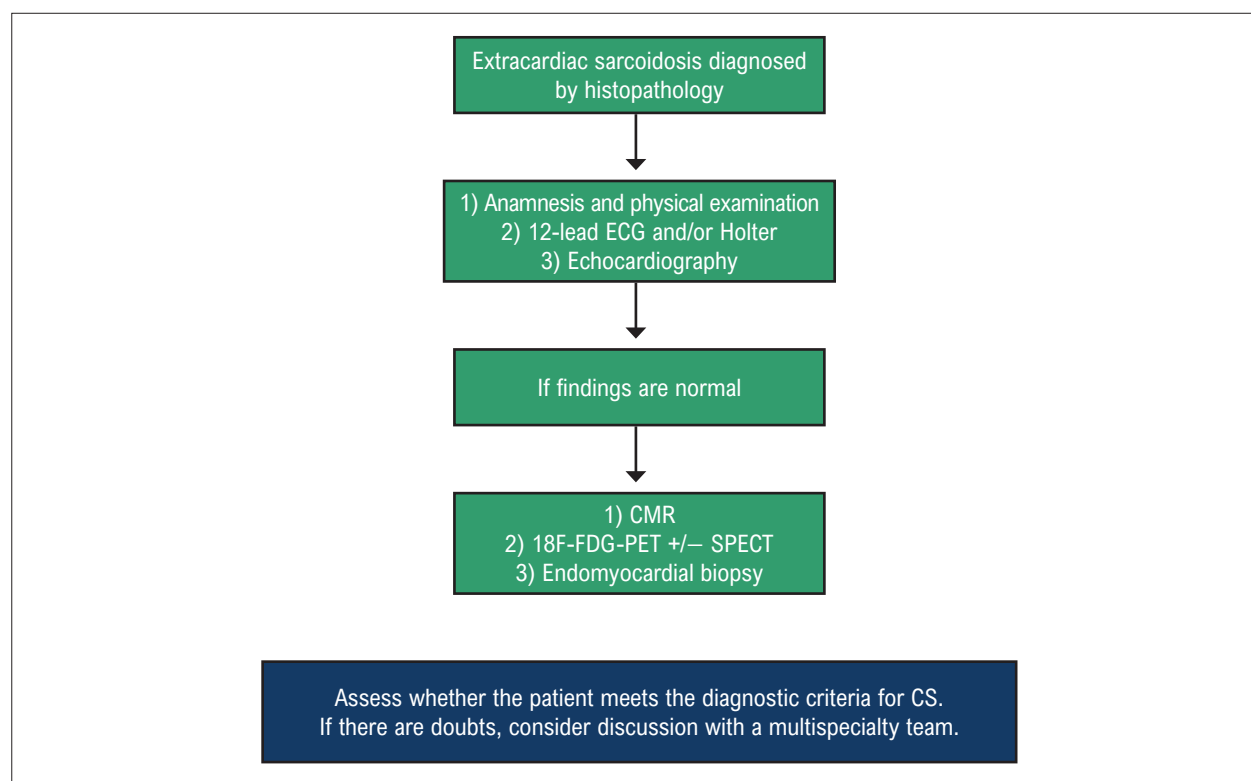


Figura 3 – Diagnostic investigation flowchart for CS in patients diagnosed with extracardiac sarcoidosis. 18F-FDG-PET: positron emission tomography with 18F-fluorodeoxyglucose; CMR: cardiac magnetic resonance imaging; ECG: electrocardiography; SPECT: single-photon emission computerized tomography. Adapted from Montero et al.⁴⁹

difficult to understand the real diagnostic capacity of each method, reinforcing the importance of using multimodal imaging in the investigation of suspected cases.

- CMR and PET appear to be the imaging tests with the greatest accuracy, providing complementary information regarding the presence and extent of fibrosis and inflammation, respectively.
- CS should always be suspected in the presence of significant rhythm disturbances or heart failure of unexplained cause, especially in middle-aged patients.

Conclusion

CS is a disease whose etiology is still little understood. Its diagnosis is challenging, with most diagnoses made without confirmation of myocardial histology, based on alterations in imaging tests. Despite the low prevalence, its identification is of fundamental importance due to its unfavorable prognosis, in addition to the fact that there are treatments with the potential to modify the natural history of this disease. Fortunately, in recent years there has been a major advance in cardiovascular imaging methods, allowing greater understanding of diagnostic and prognostic aspects. Nonetheless, it is still necessary to conduct further studies that involve direct comparison between imaging tests and histopathological findings of myocardia affected by sarcoidosis, in order to usher in a new era of more accurate diagnoses.

Author Contributions

Conception and design of the research and critical revision of the manuscript for intellectual content: Moura DM, Melo MDT, Fernandes F;

Acquisition of data and writing of the manuscript: Moura DM, Monteiro Neto AJO, Melo MDT, Fernandes F; image editing: Monteiro Neto AJO; article lead: Fernandes F.

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Ethics Approval and Consent to Participate

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

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