Cardiac Sarcoidosis

Subjects: Cardiac & Cardiovascular Systems
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Definition

Cardiac sarcoidosis (CS) is an unusual, but potentially harmful, manifestation of systemic sarcoidosis (SA), a chronic disease characterized by organ involvement from noncaseating and nonnecrotizing granulomas. Lungs and intrathoracic lymph nodes are usually the sites that are most frequently affected, but no organ is spared and CS can affect a variable portion of SA patients, up to 25% from post-mortem studies. The cardiovascular involvement is usually associated with a bad prognosis and is responsible for the major cause of death and complications, particularly in African American patients. Furthermore, the diagnosis is often complicated by the occurrence of non-specific clinical manifestations, which can mimic the effect of more common heart disorders, and imaging and biopsies are the most valid approach to avoid misdiagnosis.

1. Introduction

Sarcoidosis is a chronic disease characterized by organ involvement from noncaseating and non-necrotizing granulomas. Genetic predisposition and environmental risk factors were hypothesized as the main actors of the disease pathogenesis [1]. Lungs and intrathoracic lymph nodes are usually the sites that are most frequently affected [2][3] but no organ is spared as the involvement can be also cardiovascular, gastrointestinal, neurological and of the genitourinary system and skin [4][5][6][7].

The cardiovascular involvement is usually associated with a bad prognosis and is responsible for the major cause of death and complications, particularly in African American patients. The diagnosis is often complicated by the occurrence of non-specific clinical manifestations [8], which can mimic the effect of more common heart disorders, and imaging and biopsies are the most valid approach to avoid misdiagnosis.

2. Diagnosis of Cardiac Sarcoidosis

The diagnostic criteria of cardiac sarcoidosis were presented by many international scientific societies and an optimal diagnostic algorithm is still under discussion.

The JMHW guidelines of 2006 [9] have suggested that a diagnosis of cardiac sarcoidosis can be reached by (1) histological demonstration of the presence of noncaseating granulomas in the myocardium in a patient with a histological or clinical diagnosis of sarcoidosis in other organs or tissues, and (2) a clinical or histological diagnosis of extra-cardiac sarcoidosis in association with at least three major cardiac criteria: advanced atrioventricular block (AVB), basal interventricular septal thickening and cardiac uptake of gallium-67, left ventricular ejection fraction is less than 50% for four minor criteria: (1) ECG abnormalities (ventricular extrasystoles, ventricular tachycardia, right bundle branch block, Q wave abnormalities and axial deviation on the standard electrocardiogram); (2) echocardiographic abnormalities (segmental-type morphological or wall mobility abnormalities, ventricular aneurysms, or wall thickening); (3) perfusion defects revealed by thallium or technetium scintigraphy; (4) late gadolinium reinforcement on cardiovascular magnetic resonance imaging; (5) diffuse infiltration or interstitial fibrosis in the myocardium on the biopsy.

The JMHW guidelines emphasize the importance of an endomyocardial biopsy to demonstrate cardiac involvement by sarcoid tissue. However, this approach has the great limitation of being extremely invasive in the clinical practice. Furthermore, myocardial involvement in cardiac sarcoidosis is patchy and multifocal and, when combined with the limitations of current sampling techniques, many patients can have nondiagnostic biopsies [10]. Despite its high specificity, therefore, an endomyocardial biopsy can have a low sensitivity for the diagnosis of cardiac sarcoidosis. Another limit of the JMH guidelines is that

the uptake of Gallium-67 (67 Ga), still considered among the diagnostic criteria, is not currently used in most centers due to its limited diagnostic accuracy, as demonstrated by several studies [10][11][12][13].

In the latest update, fatal ventricular arrhythmias (e.g., sustained ventricular tachycardia and ventricular fibrillation) and anatomic abnormalities of the ventricular wall (e.g., aneurysm of the ventricular wall, midbasal septum thickening) were included in the major criteria, and diagnostic methods such as the 18F-FDG PET and CMR were included in the major criteria as diagnostic tools [14].

The consensus statement from the Heart Rhythm Society (HRS), in association with the American College of Chest Physicians (ACCP), the American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) in 2014 recognized both histological (defined) and clinical (probable) criteria for the diagnosis of cardiac sarcoidosis. These guidelines have included both the use of LGE-CMR and 18F-FDG PET in the diagnostic criteria [15].

2.1. Patient Screening for Cardiac Involvement

The first evaluation of patients with suspected CS should include a baseline ECG, which is useful to reveal the most common alterations. A normal ECG, however, does not exclude the presence of even minimal cardiac involvement, but is most often altered in overt CS. Echocardiography is important to reveal the most frequent, although nonspecific, abnormalities such as segmental-type morphological or wall-thickening wall hypomobility abnormalities. Such findings, however, can be found in other cardiac disorders, and are not specific to CS, but can be useful for the first screening of the severity of the disease [9].

Some abnormalities such as the cardiac right ventricular involvement can lead to the misdiagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). The 2010 ARVC task force criteria failed to differentiate between CS and hereditary ARVC. Some authors have recently demonstrated how prolonged PR interval, advanced AVB, long duration of QRS associated with reduced LVEF, right involvement of the ventricular apex and positive findings on the 18F-FDG PET should be considered as suspected for CS [16].

2.2. Cardiac MRI

CMR allows a rapid, accurate and non-invasive evaluation of clinical or sub-clinical cardiac sarcoidosis, thanks to the high spatial and soft-tissue resolution [17]. At present, it is one of the preferred techniques for evaluating cardiac sarcoidosis [18][19], having a high sensitivity and specificity of 75–100% and 76–78%, respectively [11], and thanks to the lack of ionizing radiation. Bright blood cine sequences allow an accurate evaluation of biventricular volume and function, mass and myocardial segment thickness (Figure 1c,d).

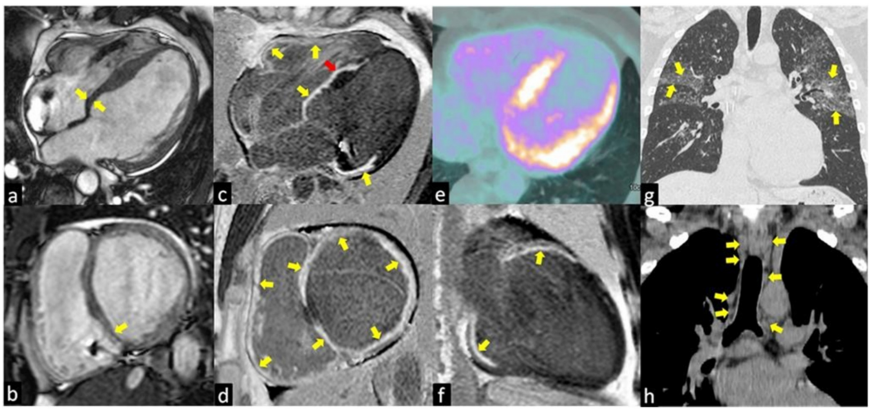

Figure 1. The images show a case of typical Cardiac Sarcoidosis characterized by the presence of LGE of all basal segments of both ventricles (yellow arrows in **c**,**d**,**f**) with the predominantly transmural distribution involving more than one coronary territory and the right ventricular side of the

interventricular septum (red arrow in **c**). Bright blood cine sequences show the thinning of the basal septum (yellow arrows in **a**,**b**). Coronal computed tomography (CT) scans show the typical perilymphatic distribution of micronodules with upper lobe predilection (yellow arrows in **g**) and hilar and mediastinal bilateral lymphadenopathy (yellow arrows in **h**). The 18F-fluorodeoxyglucose positron emission tomography (**e**) revealed an increased uptake in the septal and lateral left ventricle myocardial segments in a patient with systemic sarcoidosis.

With the T2-weighted images and the evaluation of early gadolinium uptake, it is possible to reveal respectively the focal presence of acute inflammation (edema) (Figure 2a) and myocardial hyperemia in the thickened myocardium where the granulomas infiltration is located (Figure 2a,b) [20]. Instead, the chronic phase is characterized by ventricular systolic dysfunctions and dilatation often associated with basal septum wall thinning (Figure 1c,d) [21].

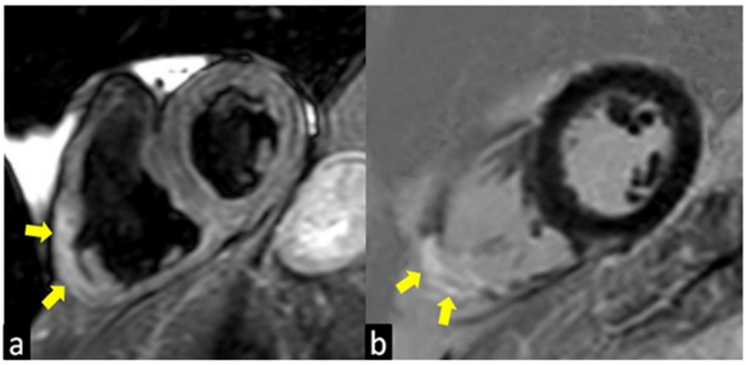

Figure 2. T2-weighted (**a**) and Late Gadolinium Enhancement (LGE; **b**) images show a case of atypical presentation of the acute phase of Cardiac Sarcoidosis, characterized by the presence of edema (yellow arrow in **a**) and LGE (yellow arrow in **b**) of the inferolateral wall of the right ventricle with the transmural distribution.

Gadolinium is a biologically inert tracer that diffuses freely into the extracellular space, but is unable to cross the intact cell membrane and exhibits a slow washout from damaged cardiomyocytes, identifying areas of myocyte necrosis during the acute phase of CS and areas of macroscopic interstitial fibrosis (scar) during the chronic phase of CS. It is important to underline that late enhancement with gadolinium is not specific for cardiac sarcoidosis but can be observed also in other infiltrative pathologies such as amyloidosis, cardiomyopathies (e.g., hypertrophic cardiomyopathy), myocarditis and ischemic lesions [22].

Typical aspects of cardiac sarcoidosis are: (1) presence of edema (acute phase) and LGE in the basal and mid interventricular septum (Figure 1c,f); (2) presence of both non-ischemic (intramyocardial or subepicardial) (Figure 1e) and ischemic (subendocardial or transmural) (Figure 1f,h) LGE patterns, the latter characterized by the involvement of more than one coronary territories [23]; (3) LGE of the right ventricular side of the interventricular septum (Figure 1e); (4) transmural LGE of thin and akinetic segments in the chronic phase of CS (Figure 1e,f) [22]. The presence of extensive LGE was associated with a poor prognosis by several studies, index of strong sarcoid activity. A meta-analysis including 7 studies and 694 subjects suggested that the presence of LGE among CS patients was associated with an increased risk of cardiovascular death or ventricular arrhythmia [24].

LGE, as well as T1 and T2 mapping techniques, can be used for monitoring the response to anti-inflammatory therapies.

CMR has some advantages over PET imaging, as there is no exposure to ionizing radiation, there is no need for patient preparation such as a specific diet prior to the image acquisition, and it also allows the assessment of cardiovascular morphology, ventricular function, valve and flow quantification [24][25] and the identification of several extracardiac collateral findings [26][27]. However, CMR imaging is limited in patients with pacemakers, or other recently implanted metal devices, and gadolinium is contraindicated in patients with advanced renal disease (estimated glomerular filtration rate [eGFR] < 30 mL/min) [28].

3. Conclusions

As systemic sarcoidosis, CS remains a challenging issue in the matter of diagnostics [29][30]. The evolution of diagnostic techniques in recent years has led to a significant improvement in the detection and classification of the severity of the disease.

Despite the fact that the present gold standard is represented by endomyocardial biopsies, the high invasiveness and risk of false negatives suggests the need for searching and validating new diagnostic algorithms including non invasive methods. As increasing information is available, there is less need for an invasive diagnostic approach to reach a definitive diagnosis of cardiac sarcoidosis. We think that the use of Hybrid PET/CMR imaging could change the global approach to this harmful and complex disease in the future.

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Keywords

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