RAPID COMMUNICATIONS

New Guidelines for Diagnosis of Cardiac Sarcoidosis in Japan

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Abstract

In recent years, advancements in diagnostic imaging modalities, such as cardiac magnetic resonance (CMR) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET), as well as the accumulation of cases, have allowed a more accurate diagnosis of cardiac sarcoidosis (CS). In addition, emerging cases of "isolated CS" in which no obvious lesions are present in organs other than the heart have been reported, and the clinical importance of CS has become recognized. Many issues including etiology, pathology, diagnosis, and treatment of CS remain to be solved. Considering this situation, guidelines for the diagnosis and treatment of cardiac sarcoidosis were recently updated by the Japanese Circulation Society and were published in February 2017.
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In the diagnosis and management of cardiac sarcoidosis (CS), there are a number of critical issues. Because of a low histological diagnostic rate of CS by endomyocardial biopsy (EMB), a definitive diagnosis is not always easy. Also, CS is difficult to distinguish from some other conditions such as dilated cardiomyopathy. Corticosteroid therapy improves cardiac function and prognosis, and, in particular, earlier intervention is considered to provide better therapeutic results. Treatment involving the insertion of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices has markedly improved the prognosis for CS. However, prognosis remains poor in patients with advanced cardiac dysfunction or heart failure. Occasionally, cardiac dysfunction may progress rapidly—within a few months or one year. All of these factors indicate that accurate early diagnosis and timely treatment intervention are extremely important for the management of CS. This being the case, the Guidelines for Diagnosis and Treatment of Cardiac Sarcoidosis (Chair: Fumio Terasaki) (1) were published in February 2017 by the Japanese Circulation Society (JCS) and its collaborative organizations, including the Japanese Society of Nuclear Cardiology (JSNC). Considering current circumstances and trends, we feel it important for us to share our up-to-date knowledge regarding the diagnostic criteria for CS.

Diagnostic guidelines for cardiac sarcoidosis

There have been only a few guidelines that address how to diagnose and treat CS. Many healthcare professionals have followed the "Diagnostic standard and guidelines for sarcoidosis," which were created in 1992 and revised in 2006 in Japan (2, 3), and "The WASOG Sarcoidosis Organ Assessment Instrument," which originated as A Case Control Etiology of Sarcoidosis Study (ACCESS) sarcoidosis organ assessment instrument in 1999 and was revised in 2014 by the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) (4). In 2014, the Heart Rhythm Society (HRS) proposed an expert consensus statement on the diagnosis of CS (5). The revision of these guideline documents was required to reflect the current situation and recent developments in diagnostic approaches.

In the updated guidelines for the diagnosis and treatment of CS, the JCS has further revised criteria for cardiac

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Table 1 Criteria for cardiac involvement of sarcoidosis

1. Major criteria
(a) High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e. g., sustained ventricular tachycardia and ventricular fibrillation)
(b) Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening)
(c) Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50%)
(d) ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET reveals abnormally high tracer accumulation in the heart
(e) Gadolinium-enhanced MRI reveals delayed contrast enhancement of the myocardium
2. Minor criteria
(f) Abnormal ECG findings: Ventricular arrhythmias (nonsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves
(g) Perfusion defects on myocardial perfusion scintigraphy (SPECT)
(h) Endomyocardial biopsy: Monocyte infiltration and moderate or severe myocardial interstitial fibrosis

（Note: English translation of tables has been provided by the authors.）

Table 1 (cont.)
Clinical findings defining cardiac involvement

Cardiac findings should be assessed based on the major criteria and the minor criteria. Clinical findings that satisfy the following 1) or 2) strongly suggest the presence of cardiac involvement.
1) Two or more of the five major criteria (a) to (e) are satisfied .
2) One of the five major criteria (a) to (e) and two or more of the three minor criteria (f) to (h) are satisfied.

（Note: English translation of tables has been provided by the authors.）

Table 2 Diagnostic guidelines for cardiac sarcoidosis

1) Histological diagnosis group (those with positive myocardial biopsy findings) Cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas.
2) Clinical diagnosis group (those with negative myocardial biopsy findings or those not undergoing myocardial biopsy) The patient is clinically diagnosed as having sarcoidosis (1) when epithelioid granulomas are found in organs other than the heart, and clinical findings strongly suggestive of the above-mentioned cardiac involvement (Table 1) are present; or (2) when the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least two of the five characteristic laboratory findings of sarcoidosis (Table 4); and clinical findings strongly suggest the above-mentioned cardiac involvement (Table 1).

（Note: English translation of tables has been provided by the authors.）

involvement of sarcoidosis (1) over those presented in the 2006 guideline (Table 1). New guidelines describing how to diagnose CS for the histological diagnosis group (those with positive myocardial biopsy findings) and for the clinical diagnosis group (those with negative myocardial biopsy findings or those not undergoing myocardial biopsy) have been developed (Table 2). Guidelines on diagnosing isolated CS were also created (6) (Table 3).

New feature of the updated CS guidelines

Criteria for cardiac involvement were revised from the 2006 version in the following ways: 1) Fatal ventricular arrhythmia (e. g., sustained ventricular tachycardia and ventricular fibrillation), which is considered important, was included in the major criteria where high-grade atrioventricular block is listed. 2) Abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening), which is considered clinically significant in diagnosing cardiac involvement, was moved from the minor criteria to the major criteria where basal thinning of the ventricular septum is listed. 3) Abnormally high tracer accumulation in the heart with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is considered an important finding that reflects the activity of inflammation in CS and was moved from the remarks to the major criteria. 4) The late-gadolinium enhancement (LGE) of the myocardium in gadolinium-enhanced magnetic resonance imaging (MRI) was moved from the minor criteria to the major criteria as it is considered an important index of tissue damage and fibrosis in CS.

Importance of imaging modalities

As epithelioid granulomas in CS develop sporadically in the myocardium, it has been reported that only 20% of patients with epithelioid granulomas can be correctly diagnosed with an EMB because biopsy samples do not contain granulomatous tissues. The low sensitivity of EMB in CS may be partly due to preferential location of myocardial injury in the mid-

Table 3 Diagnostic guidelines for isolated cardiac sarcoidosis

Prerequisite
1. No clinical findings characteristic of sarcoidosis are observed in any organs other than the heart. (The patient should be examined in detail for respiratory, ophthalmic, and skin involvements of sarcoidosis. When the patient is symptomatic, other etiologies that can affect the corresponding organs must be ruled out.)
2. ^{67}Ga scintigraphy or ^{18}F-FDG PET reveals no abnormal tracer accumulation in any organs other than the heart.
3. A chest CT scan reveals no shadow along the lymphatic tracts in the lungs or no hilar and mediastinal lymphadenopathy (minor axis > 10 mm).
1) Histological diagnosis group Isolated cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas.
2) Clinical diagnosis group Isolated cardiac sarcoidosis is diagnosed clinically when the criterion (d) and at least three other criteria of the major criteria (a)-(e) are satisfied (Table 1).

（Note: English translation of tables has been provided by the authors.）

Table 4 Characteristic laboratory findings of sarcoidosis

1. Bilateral hilar lymphadenopathy
2. High serum angiotensin-converting enzyme (ACE) activity or elevated serum lysozyme levels
3. High serum soluble interleukin-2 receptor (sIL-2R) levels
4. Significant tracer accumulation in ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET
5. A high percentage of lymphocytes with a CD4/CD8 ratio of >3.5 in BAL fluid
Clinical diagnosis of sarcoidosis is supported when at least two of the above five characteristic findings are observed. (Source: Japan Society of Sarcoidosis and other Granulomatous Disorders. 2015)

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layer or epicardial layer rather than endocardial layer that is suggested by LGE on cardiac magnetic resonance (CMR).

As the positive detection rate in EMB is much lower in patients with normal heart function, a correct histological diagnosis is difficult to make in patients at an early stage of CS. However, it is critically important to diagnose the disease at an early stage to ensure effective treatment and positive outcomes.

In this regard, reliable, precise clinical diagnostic criteria must be established without delay. As currently there are no specific biomarkers available to diagnose CS, clinicians place expectations on imaging modalities such as CMR and ^{18}F-FDG PET. CMR has good spatial resolution enough to discern the location of LGE not only horizontal distribution but also vertical involvement of myocardial layer. Although only LGE is included in the criteria for cardiac involvement, the usefulness of T2 weighted imaging and T1 mapping should be investigated in the future. Significant positive tracer accumulation with ^{18}F-FDG PET is listed in the characteristic laboratory findings associated with sarcoidosis (Table 4). These findings reflect the active inflammation in sarcoidosis and are useful in evaluating treatment efficacy. In the past few years, many studies have shown the diagnostic utility of ^{18}F-FDG PET in patients with CS, and evaluation involving ^{18}F-FDG PET is therefore included as an important component in the “Criteria for cardiac involvement of sarcoidosis” (Table 1) and in the “Diagnostic guidelines for isolated cardiac sarcoidosis” (Table 3). While ^{18}F-FDG PET is considered mandatory by the clinical diagnosis group, it has been pointed out that physiological ^{18}F-FDG uptake in the myocardium should be prevented in order to make a correct diagnosis, and specific points regarding its use have also been noted (3). Further improvements to and advancements in imaging modalities are being sought to ensure timely and accurate diagnosis of CS.

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Conflicts of interest

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