

## THE CHARACTERISTICS OF JAPANESE GUIDELINES ON DIAGNOSIS AND TREATMENT OF CARDIAC SARCOIDOSIS COMPARED WITH THE PREVIOUS GUIDELINES

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**ABSTRACT.** Sarcoidosis in Japanese sarcoidosis is characterized by a high prevalence of cardiac involvement. In this regard, cardiac sarcoidosis (CS) continues to be an important focus of study among physicians caring for sarcoidosis in Japan. The Japanese Ministry of Health, Labor and Welfare (MHLW) and Japan Society of Sarcoidosis and other Granulomatous Disorders (JSSOG) have published clinical guidelines aiming to assist clinical practices. Recently, the Japanese Circulation Society (JCS) has published new clinical guidelines for the diagnosis and treatment of CS that contain several new insights compared to previously published guidelines in Japan and other countries.

**KEY WORDS:** Guidelines, Diagnosis, Isolated cardiac sarcoidosis

### INTRODUCTION

Over the past thirty years, three major guidelines for the diagnosis and/or treatment of cardiac sarcoidosis (CS) have received international attention. The first one is the guidelines issued in Japan in 1992 and revised in 2006 (1,2). The second one is the guideline document published by the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) in 1999 as the sarcoido-

sis assessment instrument developed by the steering committee of A Case Control Etiologic Study of Sarcoidosis (ACCESS), and revised in 2014 (3). The third one is the expert consensus document proposed by the Heart Rhythm Society (HRS) in the United States in 2014 (4).

In 2016, new guidelines were developed by the Japanese Circulation Society (JCS), incorporating several new insights and technologic advances; these were subsequently published in 2017(5, 6). We herein summarize the main contents of the JCS guideline with special reference to the comparison with the previous guidelines.

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## DIAGNOSTIC CRITERIA OF CS

In both the 2014 revised version of WASOG guidelines (3) and the HRS guidelines (4), the clinical diagnosis group criteria for CS is expected to be applied to patients with histologically-proven sarcoidosis in organs other than the heart. On the other hand, the criteria of clinical diagnosis, in which histological proof is not necessarily required, was a key feature of the original JMHW guideline (1, 2). In the updated JCS guideline, CS can be diagnosed clinically when: (1) epithelioid granulomas are detected in organs other than the heart, and clinical findings strongly suggestive of cardiac involvement

are present; or (2) when the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis, including at least two of the five characteristic laboratory findings of sarcoidosis, along with clinical findings strongly supporting cardiac involvement (5) (Tables 1,2). Comparisons between the JCS and HRS guidelines are summarized in Table 3.

## DIAGNOSTIC CRITERIA FOR ISOLATED CS

There have been reported cases of non-caseating epithelioid cell granulomata found in myocardial bi-

**Table 1:** Diagnostic guidelines for cardiac sarcoidosis. (Cited from JCS 2016 guideline (5)).

### 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 in the five major criteria (a) to (e) and two or more of the three minor criteria (f) to (h) are satisfied.

### Criteria for cardiac involvement

#### 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%) or focal ventricular wall asynergy
- d. <sup>67</sup>Ga citrate scintigraphy or <sup>18</sup>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

### Diagnostic guidelines for cardiac sarcoidosis

Histological diagnosis group (those with positive myocardial biopsy findings)

1. 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 cardiac sarcoidosis (1) when epithelioid granulomas are found in organs other than the heart, and clinical findings strongly suggestive of the above-mentioned cardiac involvement are present; or (2) when the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least 2 of the five characteristic laboratory findings of sarcoidosis (Table 2); and clinical findings strongly suggest the above-mentioned cardiac involvement.

**Table 2:** Characteristic laboratory findings of sarcoidosis. (Cited from JCS 2016 guideline (5)).

1. Bilateral hilar (or mediastinal) 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 <sup>67</sup>Ga citrate scintigraphy or <sup>18</sup>F-FDG PET
5. A high percentage of lymphocytes with a CD4/CD8 ratio of > 3.5 in BAL fluid

**Table 3.** Category of cardiac sarcoidosis in the different guidelines.

Involvement organ of sarcoidosis				CS diagnosis	
Heart		Other organs		JCS 2016 guideline	HRS 2014 expert consensus
Positive biopsy findings	Clinical sign manifestations	Positive biopsy findings	Clinical sign manifestations		
○		○		Systemic CS (Histological CS)	Histological CS
○			○	Systemic CS (Histological CS)	Histological CS
○				Isolated CS (Histological CS)	Histological CS
	○	○	○	Systemic CS (Clinical CS)	Clinical CS as probable CS
	○			Systemic CS (Clinical CS)	Undefined
	○			Isolated CS (Clinical CS)	Undefined

Systemic CS: cardiac sarcoidosis plus extracardiac involvement

opsy, and cases of clinical findings consistent with CS in patients with no organ involvement other than the heart. These cases are referred to as “isolated CS” (7). In the new JCS guidelines, the diagnostic criteria for isolated CS are addressed for the first time by a guideline. The prerequisites are satisfied by either: (1) histologic diagnosis of isolated CS by myocardial biopsy or surgical specimens demonstrating non-caseating epithelioid granulomas; or (2) clinical diagnosis of isolated CS when criterion (d) and at least three other criteria of the major diagnostic criteria (a) to (e) in Table 1 are satisfied (5) (Table 4).

In this rubric, the importance of fluorine-18 fluorodeoxyglucose (<sup>18</sup>F-FDG) positron emission tomography (PET) and cardiac magnetic resonance

imaging (cMRI) are emphasized based on several published reports (8-10). When the criterion (d) plus at least three other diagnostic criteria of major criteria in Table 1 are satisfied, most of heart diseases other than CS can be considered extremely unlikely. It is crucial, however, to recognize that the absence of a gold standard for CS has led to uncertainty about the precision of specificity estimates for either PET or cMRI. The range of human disease that can cause abnormalities in PET and cMRI is not yet fully elucidated, so clinicians must maintain an extremely high degree of circumspection when using these imaging studies as the linchpin for diagnosis of isolated CS.

One area of uncertainty is how to deal with hilar and/or mediastinal lymph node involvement. In some

**Table 4.** Diagnostic guidelines for isolated cardiac sarcoidosis. (Cited from JCS 2016 guideline (5))

#### 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. <sup>67</sup>Ga scintigraphy or <sup>18</sup>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 lung or hilar and mediastinal lymphadenopathy (minor axis >10mm).

#### 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 (a) to (e) are satisfied (Table 1)

articles, hilar or mediastinal lymphadenopathy seems to be permitted at the diagnosis of isolated CS (11). Our criteria may be more rigorous, insofar as hilar and/or mediastinal lymphadenopathy is considered as one organ involvement. Even when the short axis is less than 10mm, accessible lymph nodes may provide a means for cytologic confirmation of sarcoidosis (12). It is clear that diagnosis of isolated CS is challenging and further study is indispensable (13).

#### PHARMACOLOGICAL THERAPY (IMMUNOSUPPRESSIVE THERAPY)

Although no prospective and placebo-controlled studies confirm improvement in the long-term prognosis of CS, a relatively large number of published clinical experiences support the clinical benefits of steroid therapy. The “Views on the treatment of sarcoidosis-2003” published in Japan suggest that systemic corticosteroid therapy should be considered for patients with CS who have high-grade atrioventricular block, ventricular arrhythmias, or cardiac dysfunction (14).

The treatment protocol of prednisolone for CS proposed in the JCS guidelines is similar to that of the “Views on the treatment of sarcoidosis-2003”. The optimal starting dosing of prednisone is yet to be determined, however a previous retrospective study showed no significant difference in prognosis in those patients treated with greater than 40 mg/day of prednisone compared to those treated with 30 mg of prednisone or less (15).

There are no established protocols regarding how to taper or maintain prednisolone therapy in patients with CS. Early initiation of corticosteroids is essential to prevent progression of cardiac dysfunction and thereby improve prognosis. However, it is still unknown when we should start and how long we should continue corticosteroids. Some patients may discontinue corticosteroid therapy (16), but many patients continue low-dose corticosteroid therapy for a long period of time in Japan because of the risk of recurrence and poorer prognosis (17,18). Since there are no reliable biomarkers that reflect the activity of CS, physicians determine the doses of corticosteroids for individual patients comprehensively based on symptoms, ECG changes, echocardiography and  $^{18}\text{F}$ -FDG PET. On the

other hand, it has been experienced and reported that ventricular tachycardia (VT) develop after introduction of steroid therapy in some patients particularly in the early period (19). It is important to emphasize that there are no data supporting the benefit of treating all PET evidence of active inflammation.

Low-dose methotrexate (MTX) is most commonly used in Japan and has been given for patients who cannot tolerate or are refractory to corticosteroids. The effectiveness of combination therapy consisting of low-dose corticosteroids with weekly MTX was reported in patients with CS in whom long-term therapy is required (20). MTX is often administered at doses of 5 to 8 mg/week in Japan. In contrast, the recommended dose in Western countries is 10 to 20 mg/week.

#### NON-PHARMACOLOGICAL THERAPY (DEVICE AND CATHETER ABLATION)

As an initial symptom, cardiac arrhythmia is commonly observed in CS. Atrioventricular (AV) block is the most common (26-67%) in CS (21), therefore pacemakers are required in such patients. Among them, cardiac resynchronization therapy (CRT) should be considered for patients who have a poor left ventricular (LV) function with AV block, because high frequency ventricular pacing is expected. Serious ventricular arrhythmias [VT/ventricular fibrillation (VF)] is the second most common arrhythmia (2-42%) in CS (21). Implantable cardioverter defibrillator (ICD) is sometimes required to prevent sudden death in such patients. In the new JCS guideline, ICD for primary prevention is recommended in the following scenarios, (1) history of syncope of unknown origin, (2) LV dysfunction (LV ejection fraction of  $\leq 35\%$ ), (3) nonsustained VT, (4) inducibility of arrhythmias, (5) pacemaker indication, (6) late gadolinium enhancement (LGE) in cMRI, and (7) positive findings of  $^{18}\text{F}$ -FDG PET or gallium-67 ( $^{67}\text{Ga}$ )-scintigraphy.

Catheter ablation should be considered for patients in whom VT cannot be controlled with corticosteroids or antiarrhythmic drugs, patients who cannot tolerate drug treatment or VT/VF storms. Because of high recurrence after catheter ablation (22),

ICD implantation is important even after successful ablation (23).

### CARDIAC MRI

In the new JCS guidelines, both LGE on cardiac MRI and a positive uptake on  $^{18}\text{F}$ -FDG-PET scan were upgraded to major criteria in the diagnosis of CS. The WASOG 2014 and HRS 2014 consensus statements both mentioned LGE on cardiac MRI as one of the characteristic findings of CS, but it is in the JCS guidelines where the imaging method as well as the interpretation of LGE on cardiac MRI was explicitly described. Cine images can be used to comprehensively evaluate LV function and other morphological changes (i.e. ventricular aneurysm, thinning of LV wall, and focal myocardial hypertrophy). Histopathologic changes such as myocardial fibrosis and edema can be evaluated using early Gadolinium enhancement (EGE), LGE, and T2-weighted short tau inversion recovery black-blood (T2w-STIR-BB) images. In particular, T2w-STIR-BB images may be used in combination with EGE images to evaluate disease activity of CS by visualizing myocardial edematous changes. The treatment strategy for CS is guided by the confirmation of the diagnosis of CS (including healed or remission) and evaluation of disease activity using the LGE images. It is important to emphasize that the presence of LGE is not equivalent to irreversible scarring, unlike the commonly held conception of the importance of LGE in ischemic heart disease. Cardiac MRI may be considered a useful screening tool for cardiac involvement in patients with sarcoidosis of other organs, as was mentioned in JCS guidelines (24).

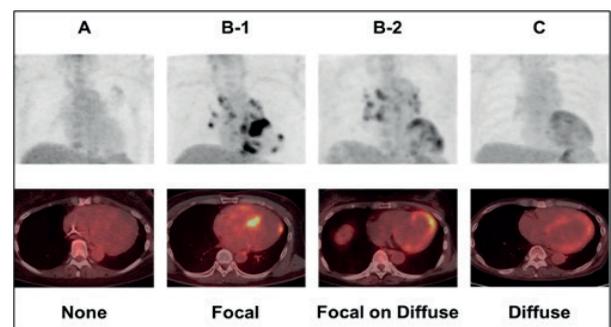
The limitations of cardiac MRI examinations include image artifacts related to arrhythmias and poor breath hold, patients who are difficult to examine after device implantation, and those with contraindications to gadolinium contrast media due to chronic kidney disease (CKD). Emerging techniques such as T1 mapping may be useful in this regard. Also, current CS disease activity evaluation with T2w-STIR-BB and EGE images needs  $^{18}\text{F}$ -FDG PET comparison.

### $^{18}\text{F}$ -FDG PET

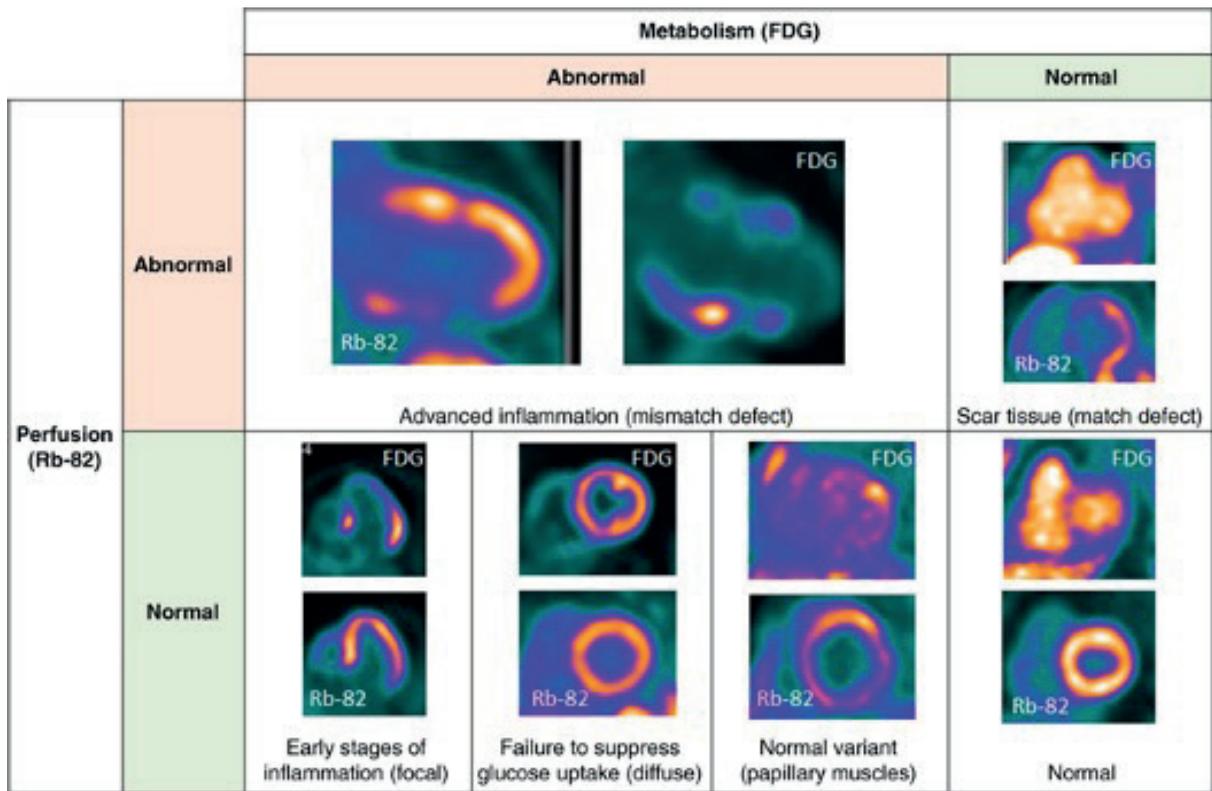
Previous Japanese guidelines update in 2006 included positive inflammatory imaging as one of the major diagnostic criteria (1). However, the inflammatory radionuclide approach was limited to  $^{67}\text{Ga}$ -scintigraphy;  $^{18}\text{F}$ -FDG PET findings was defined as one of minor diagnostic criteria, which may have been due to lack of evidence and uncertain diagnostic specificity at that time (25).

2014 was an important year for  $^{18}\text{F}$ -FDG PET in terms of diagnosis of CS because the HRS expert statement raised the importance of  $^{18}\text{F}$ -FDG PET to detect CS, and the Japanese MHLW approved  $^{18}\text{F}$ -FDG PET use for detecting disease location in patients with an existing diagnosis of CS (26). At that time,  $^{18}\text{F}$ -FDG PET still had two major issues such as lower diagnostic specificity related to physiological myocardial  $^{18}\text{F}$ -FDG uptake and lack of diagnostic criteria of  $^{18}\text{F}$ -FDG imaging. In this regard, the Japanese Society of Nuclear Cardiology (JSNC) made recommendations for standardization of patient preparation before  $^{18}\text{F}$ -FDG PET imaging, resulting in reducing physiological myocardial  $^{18}\text{F}$ -FDG uptake and improved diagnostic specificity (27). In addition, JSNC established diagnostic criteria for  $^{18}\text{F}$ -FDG PET imaging in CS (Figure 1) (8, 28).

Combining FDG PET scan with a perfusion tracer (typically rubidium or ammonium) allows more detailed assessment of scar burden and probably improves the specificity of the test (29). Depending on the combination of findings, there are different interpretations including examples of failure to suppress



**Figure 1.** Diagnostic criteria of  $^{18}\text{F}$ -FDG PET imaging in cardiac sarcoidosis. (Cited from Kumita S, et al. J Nucl Cardiol (8, 28))



**Figure 2.** Interpretation of cardiac positron emission tomography scan findings according to perfusion and metabolism results. FDG = fluorodeoxyglucose; Rb-82 = rubidium-82. (Cited from Ribeiro Neto ML, et al. *Ann Am Thorac Soc* (29)).

glucose uptake (Figure 2).

A thorough clinical work-up of patients with suspected sarcoidosis including whole-body  $^{18}\text{F}$ -FDG PET guided sampling of (mediastinal/hilar) lymph nodes increases diagnostic accuracy for histologically confirmed CS (30). The issue is that sometimes heart failure patients can get lymph node enlargement, so that confirming the diagnosis may be more important if there is a lymph node that can be accessed (31).

## DISCUSSION

None of the diagnostic guidelines for CS have been validated. The performance of all three major diagnostic guidelines is fairly similar for patients with extracardiac disease, but only the more recent JCS guideline specifically addresses the thorny issue of isolated cardiac sarcoidosis. All of the current diagnostic strategies rely heavily on MRI and PET scan

(32). Although we tend to believe that we understand the causes of abnormal MRI or abnormal PET scan, in fact we do not really know all of the cardiac etiologies that can cause abnormalities. For example, in addition to CS, diverse types of cardiovascular disorders have been reported to cause abnormal tracer accumulation in  $^{18}\text{F}$ -FDG PET. These disorders include cardiovascular inflammation and infection (myocarditis, endocarditis, pericarditis, and vasculitis) (33-35), arrhythmogenic right ventricular cardiomyopathy (36), hypertrophic cardiomyopathy (37,38), takotsubo cardiomyopathy (39), and coronary artery disease (40). Physicians sometimes jump to a diagnosis of isolated CS in a patient with senile heart block, modest cardiomyopathy and a nonspecific finding on an imaging study in a patient with hypertension and a remote history of sarcoidosis. We must always be suspicious when relying on a non-histologic diagnosis.

## CONCLUSION

We addressed the summary of main contents of new JCS guidelines with special reference to the characteristics and advances compared with the prior guidelines. The major new insights of the JCS guidelines include the diagnostic criteria for isolated CS (Table 5). We very much hope that new Japanese guidelines contribute to the development of this academic field, and anticipate further development in international understanding and collaborations (32).

**CONFLICTS OF INTEREST:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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