

SUPPLEMENTAL MATERIAL

Supplemental Material

Supplemental Table 1: Heart Rhythm Society Consensus Document: Clinical Diagnosis from Invasive and Non-Invasive Studies ¹:

THERE ARE TWO PATHWAYS TO A DIAGNOSIS OF CARDIAC SARCOIDOSIS

1. HISTOLOGICAL DIAGNOSIS FROM MYOCARDIAL TISSUE

2. CLINICAL DIAGNOSIS FROM INVASIVE AND NONINVASIVE STUDIES
IT IS PROBABLE THAT THERE IS CS IF:
 - A) There is a histologic diagnosis of extra-cardiac sarcoidosis
AND
 - B) One or more of the following is present
 - Steroid +/- immunoresponsive cardiomyopathy or heart block
 - Unexplained reduced LVEF < 40%
 - Unexplained sustained (spontaneous or induced) VT
 - Mobitz Type II 2nd degree heart block or 3rd degree block
 - Patchy uptake on dedicated ¹⁸F-FDG 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)
 - AND
 - C) Other causes for the cardiac manifestation(s) have been reasonably excluded

CMR=Cardiac magnetic resonance imaging; CS=Cardiac sarcoidosis; ¹⁸F-FDG PET=Positron emission tomography scan; LVEF=Left ventricular ejection fraction, VT=Ventricular tachycardia

Supplemental Table 2: Japanese Circulation Society Diagnostic Guidelines for Cardiac Sarcoidosis²

Diagnostic Guidelines for Cardiac Sarcoidosis

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 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) ⁶⁷Ga citrate scintigraphy or ¹⁸F-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 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. ⁶⁷Ga scintigraphy or ¹⁸F-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) to (e) are satisfied.

¹⁸F-FDG PET =Positron emission tomography scan; ⁶⁷Ga=Gallium

Supplemental Table 3: ECG and Ambulatory Monitor Abnormalities Suggesting Possible Cardiac Sarcoidosis in Patients with Extracardiac Disease

| ECG-Abnormalities | Ambulatory-Monitor-Abnormalities |
|--|---|
| Any atrioventricular block | High premature ventricular contractions burden (>10 per hour) |
| Bundle branch block (right or left, but right is more common) | Non-sustained or sustained ventricular tachycardia |
| Supraventricular tachyarrhythmia, including atrial fibrillation or flutter | Atrial tachycardia or frequent atrial ectopy |
| Pseudo-infarct Q-waves | |
| QRS fragmentation | |

ECG=Electrocardiogram

Supplemental Table 4: Heart Rhythm Society Expert Consensus Recommendations for ICDs in Patients with Cardiac Sarcoidosis¹

CLASS I ICD implantation IS RECOMMENDED in patients with CS and one or more of the following:

1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest
2. LVEF \leq 35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation)

CLASS IIa ICD implantation CAN BE USEFUL in patients with CS, independent of ventricular function, and one or more of the following:

1. An indication for permanent pacemaker implantation
2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology
3. Inducible sustained ventricular arrhythmias ($>$ 30 seconds of monomorphic VT or polymorphic VT) or clinically relevant VF

CLASS IIb ICD implantation MAY BE CONSIDERED in patients with LVEF in the range of 36–49% and/or an RV ejection fraction $<$ 40, despite

optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation)

CLASS III ICD implantation IS NOT RECOMMENDED in patients with no history of syncope, normal LVEF/RV ejection fraction, no LGE on

CMR, a negative EPS, and no indication for permanent pacing. However, these patients should be closely followed for deterioration in ventricular function

ICD implantation IS NOT RECOMMENDED in patients with one or more of the following:

1. Incessant ventricular arrhythmias
2. Severe New York Heart Association Class IV heart failure

CMR=Cardiac magnetic resonance imaging; CS=Cardiac sarcoidosis; EPS=Electrophysiology study; ICD=Implantable cardioverter defibrillator; LGE=Late gadolinium enhancement; LVEF=Left ventricular ejection fraction; RV=Right ventricle; VF=Ventricular fibrillation; VT=Ventricular tachycardia

Supplemental Table 5: AHA/ACC/HRS Guideline for ICDs in Patients with Cardiac Sarcoidosis³

| COR | LOE | RECOMMENDATIONS |
|-----|------|--|
| I | B-NR | 1. In patients with CS who have sustained VT or are survivors of SCA or have an LVEF of 35% or less, an ICD is recommended, if meaningful survival of > 1 year is expected |
| Ila | B-NR | 2. In patients with CS and LVEF > 35% who have syncope and/or evidence of myocardial scar by CMR or ¹⁸ F-FDG PET, and/or have an indication for permanent pacing, implantation of an ICD is reasonable, provided that meaningful survival of > 1 year is expected |
| Ila | C-LD | 3. In patients with CS and LVEF > 35%, it is reasonable to perform an EPS and to implant an ICD, if sustained VA is inducible, provided that meaningful survival > 1 year is expected |
| Ila | C-LD | 4. In patients with CS who have an indication for permanent pacing, implantation of an ICD can be beneficial |
| Ila | C-LD | 5. In patients with CS, with frequent symptomatic VA and evidence of myocardial inflammation, immunosuppression in combination with antiarrhythmic medication therapy can be useful to reduce VA burden |

AHA/ACC/HRS=American Heart Association/American College of Cardiology/Heart Rhythm Society; COR=Class of recommendation; CS=Cardiac sarcoidosis; EPS=Electrophysiology study; ¹⁸F-FDG PET=Positron emission tomography scan; ICD=Implantable cardioverter defibrillator; LOE=Level of evidence; LVEF=Left ventricular ejection fraction; CMR=Cardiac magnetic resonance imaging; SCA=Sudden cardiac arrest; VA=Ventricular arrhythmia; VT=Ventricular tachycardia

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Supplemental References

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3. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ and Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e272-e391.