

Successful treatment of cardiac sarcoidosis based on clinical suspicion and advanced cardiac imaging

A case report

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Abstract

Introduction: Confirming the diagnosis of cardiac sarcoidosis (CS) is a challenging task as we often do not count with histopathologic evidence. However, prompt initiation of treatment is sometimes necessary, and advanced cardiac imaging along with key clinical findings can play a crucial role in the diagnostic workup.

Patient concerns: A 77-year-old male with a history of heart failure presented with chest pain and shortness of breath. He was found to have an acute drop in left ventricular ejection fraction associated with frequent premature ventricular contractions and nonsustained ventricular tachycardia. Coronary angiogram was negative for acute coronary syndrome. Advanced cardiac imaging with cardiac magnetic resonance raised suspicion of CS, and steroids were started empirically. Endomyocardial biopsy was attempted but was not successful.

Diagnosis: The patient's presentation was highly suggestive of cardiac sarcoidosis.

Interventions: Corticosteroids, diuresis, guideline-directed medical therapy for heart failure.

Outcomes: The patient's symptoms and ventricular arrhythmias improved on steroids. Subsequent FDG-PET revealed increased uptake in a pattern consistent with CS.

Conclusion: This clinical scenario highlights the importance of advanced cardiac imaging and clinical findings for the diagnosis of CS and exposes the practical need for a standardized, noninvasive strategy to the diagnosis of CS.

Abbreviations: CMR = cardiac magnetic resonance, CS = cardiac sarcoidosis, FDG-PET = fluorodeoxyglucose-positron emission tomography, GDMT = guideline-directed medical therapy, HRS = Heart Rhythm Society, JCS = Japanese Circulation Society, LGE = late gadolinium enhancement, LVEF = left ventricular ejection fraction, PVC = premature ventricular contraction.

Keywords: advance cardiac imaging, cardiac FDG-PET, cardiac magnetic resonance, cardiac sarcoidosis, endomyocardial biopsy

1. Introduction

Cardiac sarcoidosis (CS) is traditionally a histologic diagnosis. However, performing a myocardial biopsy comes with multiple limitations. The sensitivity of endomyocardial biopsy for CS is only around 20%–30%, even in patients with high clinical suspicion.^[1,2] This is a result of the patchy nature of cardiac involvement, with samples often showing fibrosis and lymphocytic infiltration without characteristic giant cells or epithelial granulomas.^[3] Furthermore, histopathologic features on their own are not enough to differentiate sarcoidosis from other granulomatous diseases. Histologic findings include granulomas,

which involve concentric layers of immune cells with a center of macrophages and multinucleated giant cells, and an outer layer of sparse lymphocytes and occasional dendritic cells. However, these features can be shared by other clinical entities including tuberculosis, berylliosis, malignancies, autoimmune disorders, giant cell myocarditis, and other bacterial and fungal infections.^[3] As a result, the decision to start treatment for CS cannot depend exclusively on tissue. The advent of advanced imaging techniques has played an important role in the development of clinical criteria to diagnose or highly suspect CS in the absence of a tissue sample. This is a case where a non-invasive strategy led to the decision to initiate treatment for CS.

The patient provided informed consent for case publication.

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2. Case report

A 77-year-old male patient with a past medical history of heart failure with reduced ejection fraction (45%), coronary artery disease, lung cancer on remission with partial right lung resection, and chronic obstructive pulmonary disease presents after an episode of pressure-like, pleuritic, nonradiating substernal chest pain that lasted for 1 h. It was associated with shortness of breath, as well as a 1-week history of fatigue.

On admission, he was found to have bradycardia with 54 beats per minute, elevated blood pressure of 150/80 mmHg, and normal oxygen saturation on room air. Physical exam was notable for bibasilar lung crackles and bilateral pitting edema in lower extremities. Labs were notable for a mildly elevated troponin 0.034 ng/mL, elevated brain natriuretic peptide 504 pg/mL, normal creatinine 1.05 mg/dL, normal white blood cell count $8.8 \times 10^3/\mu\text{L}$, and normal hemoglobin 13.8 g/dL.

Chest X-ray was unremarkable. Electrocardiogram was notable for first-degree atrioventricular block and multiple premature ventricular contractions (PVCs), which were present very frequently in telemetry monitoring. The echocardiogram was notable for a left ventricular ejection fraction (LVEF) of 35%, corresponding to a 10% drop from prior. It was also notable for left ventricle dilation and paradoxical septal motion. The patient underwent a coronary angiogram which revealed non-obstructive coronary artery disease. The patient subsequently underwent cardiac magnetic resonance (CMR) revealing late gadolinium enhancement at the basal midventricular septum, inferior wall, and posterior right ventricular insertion with spared subendocardium (Fig. 1). It also confirmed an LVEF of 34%.

The pattern of myocardial scarring on CMR raised suspicion for cardiac sarcoidosis. To treat cardiac rhythm abnormalities, the patient underwent PVC ablation with intracardiac echocardiography and electroanatomic mapping with pace mapping. There was successful ablation of one PVC morphology; however, the patient persisted with PVCs of different morphology, as well as runs of nonsustained ventricular tachycardia. The patient also persisted with symptoms of shortness of breath.

The patient subsequently received empiric treatment for sarcoidosis with oral steroids and amiodarone. The patient also received guideline-directed medical therapy (GDMT) for heart failure, including metoprolol, torsemide, and sacubitril/valsartan. Transjugular right ventricular endomyocardial biopsy was attempted. However, the procedure was aborted due to unfavorable anatomy. After a few days of treatment, there was

improvement in PVCs and no further runs of non-sustained ventricular tachycardia. There was also improvement in shortness of breath.

Subsequent CMR fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed bilateral hilar uptake, as well as diffuse uptake in cardiac basal inferior, medial anteroseptal regions (Fig. 2), and papillary muscle. Placement of implantable cardioverter-defibrillator was planned as outpatient, and the patient was continued on oral steroids, amiodarone, and GDMT for heart failure.

3. Discussion

Diagnosis of CS can be challenging, especially considering that attempts to obtain histologic evidence can be of low yield, technically difficult, or impractical. Nevertheless, it can sometimes be crucial to promptly start treatment with corticosteroid or device implantation, even without biopsy results. As a result, advanced cardiac imaging, namely FDG-PET and CMR have become crucial for the diagnosis of CS.

FDG-PET detects areas of inflammation that results in pathologically increased glucose uptake, something characteristic of active CS.^[3] In a study comparing FDG-PET to posttransplant cardiac histologic assessment as gold standard, findings associated with high probability of CS had a sensitivity of 83.3% and a specificity of 100% for CS.^[4] Findings associated with high probability of CS included multiple, noncontiguous perfusion defects with associated FDG uptake as well as multiple areas of focal FDG uptake and extracardiac FDG uptake. In the same study, sensitivity was 100% and specificity 33% when the cutoff was lowered to any probable or highly probable finding. In another study comparing FDG-PET to the clinical diagnosis criteria of the Japanese Ministry of Health, Labor, and Welfare (MHLW) as gold standard, overall sensitivity of FDG-PET was 89% (95% CI, 79%–96%), and specificity 78% (95% CI, 68%–86%).^[5]

CMR with late gadolinium enhancement (LGE) detects perfusion defects and fibrosis, which are characteristic of a later stage of CS.^[3] Findings that strongly suggest CS include intense LGE and prominent involvement of insertion points, along with contiguous and direct extension across the septum, with no alternative diagnosis.^[4] In a metaanalysis that included 649 patients, CMR had an overall sensitivity of 0.93 (95% CI, 0.87–0.97) and specificity of 0.85 (95% CI, 0.68–0.94) in the diagnosis of CS.^[6] Another study of 58 patients that compared LGE-CMR with diagnostic criteria from the Japanese MHLW as gold standard, the sensitivity was 100% (95% CI, 78%–100%) and the specificity was 78% (95% CI, 64%–89%) for the diagnosis of CS.^[7]

The Japanese Circulation Society (HCS) and the Heart and Rhythm Society (HRS) identified clinical findings that strongly

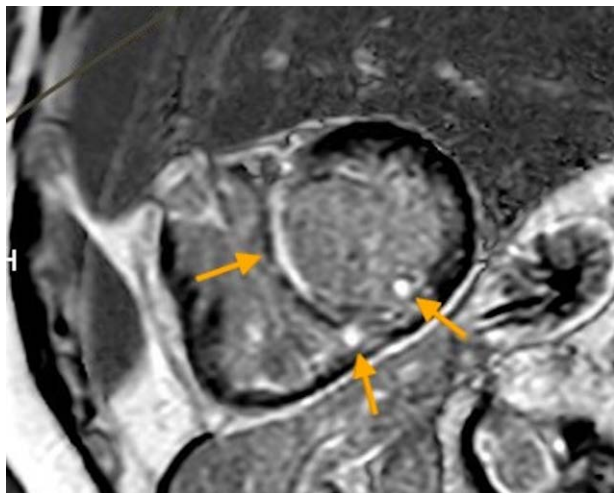


Figure 1. Cardiac magnetic resonance. Late gadolinium enhancement at the basal and midventricular septum, posterior right ventricular insertion, and papillary muscle (arrows). The subendocardium is spared.

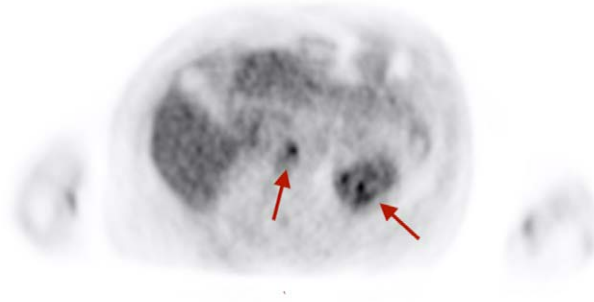


Figure 2. Cardiac magnetic resonance FDG-PET. Increased uptake in the cardiac segments predominantly seen in basal inferior and medial anteroseptal regions (arrows).

Table 1**Clinical criteria suggestive of cardiac sarcoidosis.**

Japanese Circulation Society 2016 ^[3]	Heart Rhythm Society 2014 ^[8]
<i>Major criteria</i>	
1. High-grade atrioventricular block or fatal ventricular arrhythmias such as sustained ventricular tachycardia and ventricular fibrillation	1. Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
2. LVEF <50% or focal ventricular wall asynergy	2. Unexplained reduced VEGF (<40%)
3. Basal thinning of the ventricular septum or abnormal ventricular wall anatomy.	3. Unexplained sustained (spontaneous or induced) VT
4. ⁶⁷ Ga citrate scintigraphy or ¹⁸ F-FDG PET with abnormally high tracer accumulation in the heart.	4. Mobitz type II 2 nd degree heart block or 3rd-degree heart block
5. CMR with late contrast enhancement of the myocardium. ^[1]	5. Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
<i>Minor criteria</i>	
1. Ventricular arrhythmias (NSVT, multifocal or frequent PVCs), bundle branch block, axis deviation, or abnormal Q waves	6. Late Gadolinium Enhancement on CMR (in a pattern consistent with CS) Positive gallium uptake (in a pattern consistent with CS)
2. Perfusion defects on myocardial perfusion scintigraphy	
Endomyocardial biopsy with monocyte infiltration and moderate or severe interstitial fibrosis	

CMR = cardiac magnetic resonance, CS = cardiac sarcoidosis, FDG PET = fluorodeoxyglucose-positron emission tomography, LVEF = left ventricular ejection fraction, NSVT = nonsustained ventricular tachycardia, PVCs = premature ventricular contractions, VT = ventricular tachycardia.

suggest cardiac involvement of sarcoidosis (Table 1).^[3,8] These societies have established a “clinical diagnosis” group of CS, which defines criteria to confirm diagnosis of CS in patients with negative findings on myocardial biopsy or in whom biopsy was not performed.

Interestingly, the JCS established one set of clinical criteria that do not require extracardiac histologic diagnosis. It involves a combination of cardiac and pulmonary or ophthalmic clinical findings that strongly suggest sarcoidosis, together with highly suggestive laboratory findings. However, the diagnosis CS without histologic evidence came into question in a study that found low concordance between JCS and other major diagnostic tools for CS.^[9]

There is great need for more research on new modalities for the effective and practical diagnosis of CS, regardless of the involvement of an invasive procedure. Performing simultaneous FDG-PET and CMR to diagnose CS is promising, as it exploits the key advantages of each imaging modality.^[10] Fusion of different types of imaging can provide additional information, such as by studying the relationship between increased tracer uptake and fibrosis. Endomyocardial biopsy assisted by cardiac imaging including CMR and PET had an increase in sensitivity from 32% to 55% in a study on patients who had a prior biopsy without the assistance of imaging.^[11] Magnetic resonance imaging with T2 mapping also shows promise and is undergoing investigation.^[12]

New techniques of robotic-assisted myocardial biopsy guided by electroanatomic mapping, which involves the integration of multiple imaging modalities, have the potential for increased accuracy and lower complication rates.^[13]

Author contributions

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References

- [1] Sekiguchi M, Numao Y, Imai M, Furuie T, Mikami R. Clinical and histopathological profile of sarcoidosis of the heart and acute idiopathic myocarditis concepts through a study employing endomyocardial biopsy I. Sarcoidosis: symposium on secondary myocardial disease. *Jpn Circ J*. 1980;44:249–63.
- [2] Uemura A, Morimoto S-i, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J*. 1999;138:299–302.
- [3] Terasaki F, Azuma A, Anzai T, et al. JCS 2016 guideline on diagnosis and treatment of cardiac sarcoidosis — digest version —. *Circ J*. 2019;83:2329–88.
- [4] Divakaran S, Stewart GC, Lakdawala NK, Padera RF, Zhou W, Desai AS, et al. Diagnostic accuracy of advanced imaging in cardiac sarcoidosis. *Circ Cardiovasc Imaging*. 2019;12:e008975.
- [5] Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. *J Nucl Med*. 2012;53:241–8.
- [6] Zhang J, Li Y, Xu Q, Xu B, Wang H. Cardiac magnetic resonance imaging for diagnosis of cardiac sarcoidosis: a meta-analysis. *Can Respir J*. 2018;2018:7457369–7457369.
- [7] Smedema J-P, Snoep G, van Kroonenburgh MPG, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol*. 2005;45:1683–90.
- [8] Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1304–1323.
- [9] Ribeiro Neto ML, Jellis C, Hachamovitch R, Wimer A, Highland KB, Sahoo D, et al. Performance of diagnostic criteria in patients clinically judged to have cardiac sarcoidosis: Is it time to regroup? *Am Heart J*. 2020;223:106–109.
- [10] White JA, Rajchl M, Butler J, Thompson RT, Prato FS, Wisenberg G. Active cardiac sarcoidosis. *Circulation*. 2013;127:e639–41.
- [11] Kandolin R, Lehtonen J, Graner M, et al. Diagnosing isolated cardiac sarcoidosis. *J Intern Med*. 2011;270:461–8.
- [12] Trivieri MG, Robson P, LaRocca G, et al. Abstract 16511: hybrid magnetic resonance imaging and fluorodeoxyglucose (FDG) positron emission tomography (PET) guided cardiac sarcoidosis treatment. *Circulation*. 2018;138(Suppl_1):A16511–A16511.
- [13] Bhimaraj A, Trachtenberg B, Valderrábano M. Robotically guided left ventricular biopsy to diagnose cardiac sarcoidosis. *Circ Heart Fail*. 2018;11:e004627.