

Multimodality Imaging to Diagnose Isolated Cardiac Sarcoidosis and Determine Regional Inflammatory Activity Levels

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INTRODUCTION

Cardiac sarcoidosis is one of the uncommon causes of cardiac failure and is associated with poor prognosis if untreated.^{1,2} Early diagnosis of cardiac sarcoidosis is of great clinical importance, as corticosteroid therapy can provide symptomatic relief and improve the long-term prognosis for patients with cardiac sarcoidosis.³ There is increasing recognition of isolated cardiac sarcoidosis in recent years, although its diagnosis remains challenging.¹ Here we report the case of a 71-year-old woman with isolated cardiac sarcoidosis using a noninvasive diagnostic approach and discuss the role of current imaging modalities in the diagnostic algorithm for cardiac sarcoidosis and its therapeutic approaches.

CASE PRESENTATION

A 71-year-old woman presented with a 2-day history of nonradiating dull chest pain on a background of exertional dyspnea (New York Heart Association class II) and bilateral edema of the lower extremities over the past few months. She had a history of factor V Leiden with a pulmonary embolus and deep venous thrombosis, as well as asthma, hypertension, and hypothyroidism, but no history of cardiac symptoms. On examination, the patient was hypertensive with moderate dependent edema. Electrocardiography demonstrated sinus rhythm with left atrial overload, premature ventricular complexes, left ventricular hypertrophy, and T-wave inversion in leads III and aVF (Figure 1). Sequential serum high-sensitivity troponin levels were stable at 17 ng/L (normal range, <14 ng/L). Serum N-terminal pro-brain natriuretic peptide was elevated at 4,417 ng/L (normal range, <900 ng/L) and serum angiotensin-converting enzyme level was normal (37 U/L; normal range, 20–70 U/L). Computed tomography showed no pulmonary embolism and no significant axillary, mediastinal, or hilar lymphadenopathy, with only mild atherosclerotic coronary plaque. There was no evidence of significant coronary artery disease demon-

strated on computed tomographic coronary angiography at presentation and previous invasive coronary angiography.

Transthoracic echocardiography demonstrated a mildly dilated left ventricle with severe regional systolic dysfunction (ejection fraction 29%; Figure 2). Wall motion abnormalities involved the septal and inferior walls, crossing typical coronary distribution territories (Figure 3F, Videos 1A–1C). There was septal hypokinesia (Figure 3D, Video 1A). There was moderately severe mitral regurgitation with mild pulmonary hypertension (right ventricular systolic pressure 46 mm Hg). There was evidence of significant diastolic dysfunction with borderline shortened mitral deceleration time (166 msec), reduced septal and lateral e'/e' -wave values (0.04 m/sec), and markedly elevated filling pressures (E/e' ratio 22). Transpulmonary gradient was normal, as indicated by an echocardiographic pulmonary-to-left atrial ratio (tricuspid regurgitation maximum velocity divided by the E/e' ratio) of 0.14 m/sec, suggesting postcapillary pulmonary hypertension.⁴

Cardiac magnetic resonance imaging (MRI), positron emission tomography (PET) using ^{18}F -fluorodeoxyglucose (FDG), and resting myocardial perfusion imaging using $^{99\text{Tc}}$ tetrofosmin were subsequently performed to characterize the tissue abnormalities in the ventricle. Cardiac MRI demonstrated patchy, nodular areas of left ventricular enhancement, predominantly in the basal left ventricle inferior and lateral wall (Figure 3E, Videos 2 and 3), corresponding to the akinetic areas on echocardiography (Figure 3F). There was subepicardial late gadolinium uptake in the distal septal wall (Figure 3C).

Nuclear medicine imaging with $^{99\text{Tc}}$ tetrofosmin and FDG PET revealed a significant focal perfusion defect in the inferior wall of the left ventricle (Figure 3A) with concordant significant reduced FDG uptake (Figure 3B). There was a significant focal perfusion defect in the anterior septal wall (Figure 3A) with mismatched preserved FDG uptake (Figure 3B). These combined techniques suggested combination of patchy active and chronic cardiac sarcoidosis, with no extracardiac sarcoidosis identified. Specifically, there was no FDG uptake in the mediastinum to suggest hilar lymphadenopathy involvement (Figure 3G). Initial conservative management without immunosuppression was chosen by the patient. Repeat echocardiography in the 3-month interval showed stable ventricular function.

DISCUSSION

Sarcoidosis is a systemic disease characterized by noncaseating granulomatous disorder of unknown etiology. Sarcoidosis most commonly affects the respiratory system, but the clinical presentation is highly variable.⁵ Approximately 5% of patients have cardiac symptoms, but cardiac involvement is likely to be underdiagnosed, with 27% of patients with sarcoidosis identified to have pathologic

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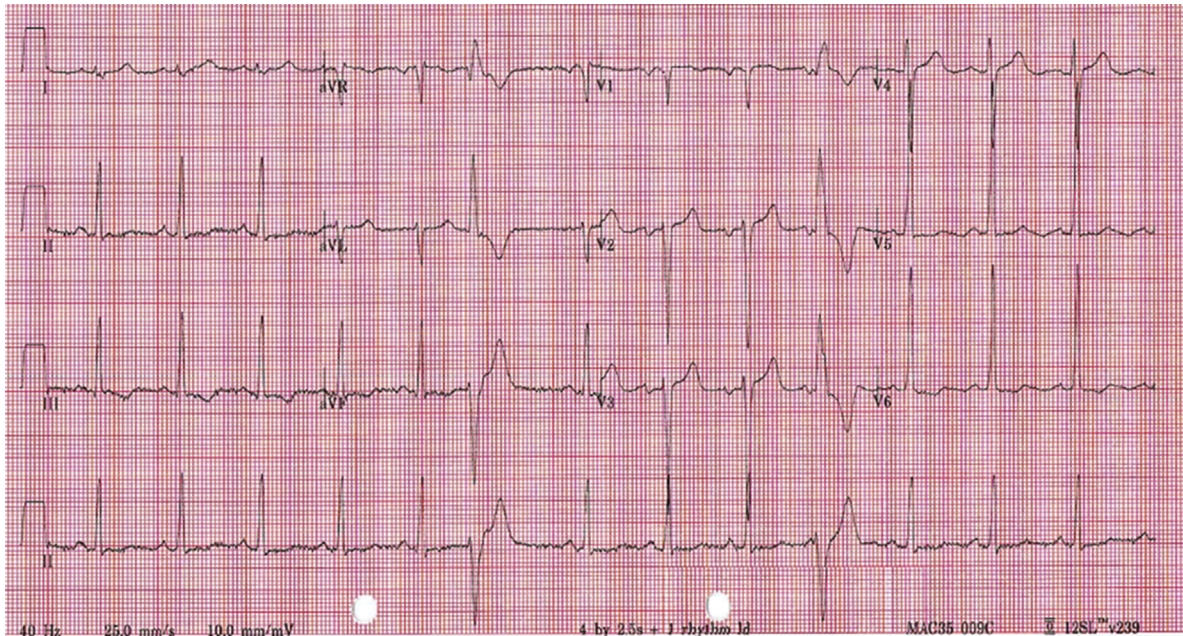


Figure 1 Twelve-lead electrocardiogram showing sinus rhythm with a vertical axis and normal PR and QTC intervals. The QRS duration is normal, and there is inferolateral T-wave inversion. Left atrial overload and left ventricular hypertrophy are also demonstrated.

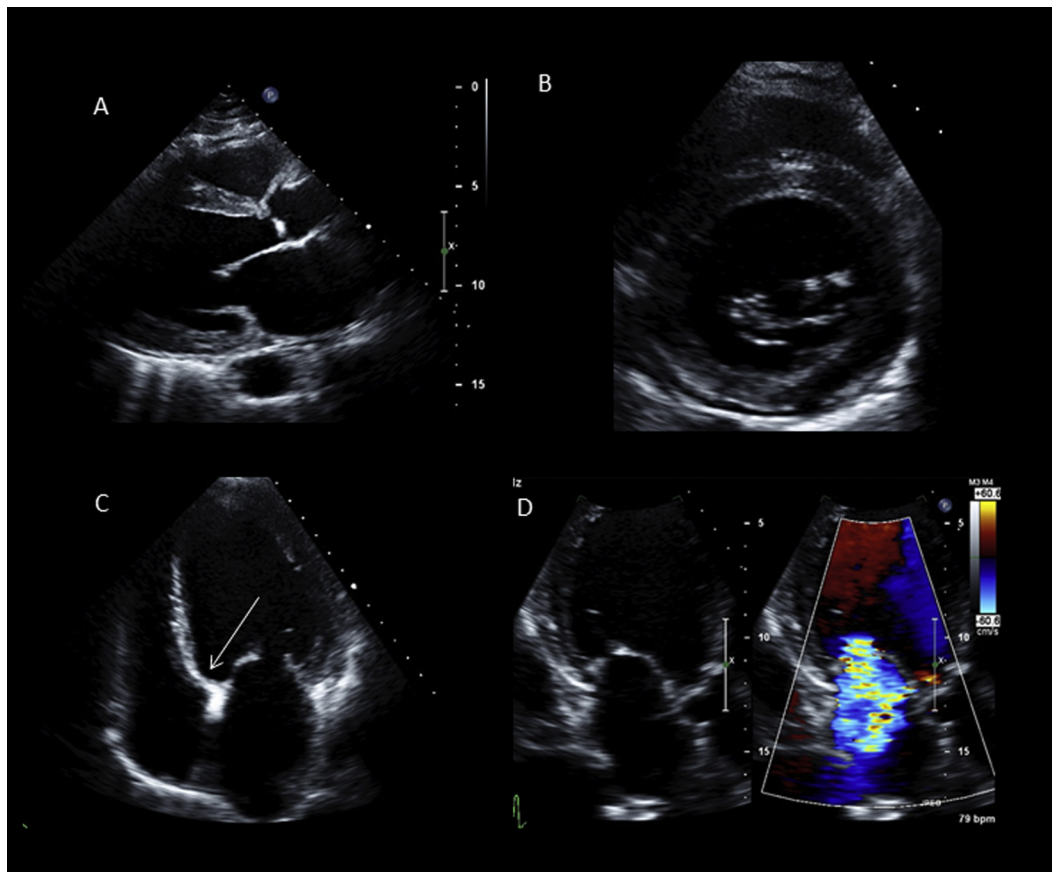


Figure 2 Transthoracic echocardiogram demonstrating dilated left ventricle on parasternal images (A,B), with septal thinning (white arrow) on the apical four-chamber view (C). There was moderately severe functional mitral regurgitation (D).

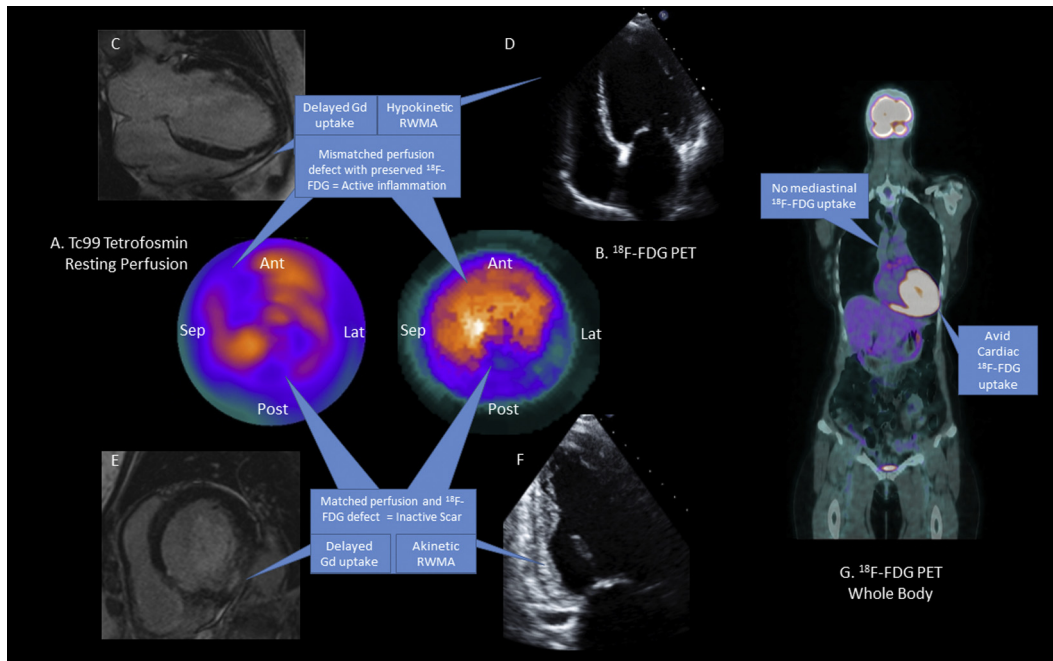


Figure 3 (A) Radionuclide resting ^{99m}Tc tetrofosmin scan demonstrating two distinct perfusion defects, in the inferior and septal (Sep) walls. FDG PET (B) shows a matching glucose uptake defect in the inferior wall and a mismatched preserved glucose uptake area in the Sep region. MRI (E) shows transmural gadolinium (Gd) uptake, and the echocardiographic images (F) show akinesia in the “matched defects” area. MRI (C) and the echocardiographic images (D) show subepicardial Gd uptake and hypokinesia in the “mismatched defects” area. Whole-body FDG PET (G) shows no mediastinal lymph node tracer uptake, suggesting isolated cardiac involvement. Ant, Anterior; Lat, lateral; Post, posterior; RWMA, regional wall motion abnormalities.

cardiac involvement in one autopsy study.¹ Preliminary retrospective data suggested that the rate of isolated cardiac sarcoidosis is 25%.¹ A recent study suggested that patients with isolated cardiac sarcoidosis may have a worse prognosis than patients with systemic sarcoidosis and cardiac involvement.² Granulomatous infiltration of the myocardium causes focal scarring in a noncoronary distribution, with a wide spectrum of clinical manifestations, including arrhythmias, cardiomyopathy, pericardial effusions, and coronary aneurysms.^{1,6} Complete heart block and ventricular arrhythmias are the most common forms of arrhythmia, which reflect granulomatous infiltration and disruption of conduction fibers and induction of abnormal automaticity. Progressive systolic and diastolic heart failure secondary to extensive granulomatous infiltration of the myocardium presents as either dilated or restrictive cardiomyopathy and is the second most common cause of death, behind sudden cardiac death.⁷

Unfortunately, there is a lack of universally accepted diagnostic criteria for cardiac sarcoidosis. In 2006, the Japanese Ministry of Health and Welfare revised the guidelines for the diagnosis of cardiac sarcoidosis, based on either histologic confirmation on myocardial biopsy or a clinical pathway consisting of major and minor criteria.⁵ These early guidelines lacked sensitivity and specificity and did not take the recent advancement of imaging modality into consideration. Recently, Birnie *et al.*⁷ published a consensus statement regarding diagnosis of cardiac sarcoidosis, which requires positive results on histologic examination either from myocardial tissue for definite diagnosis or extracardiac sarcoidosis for clinical diagnosis, along with other clinical criteria. This presents a diagnostic challenge for isolated cardiac sarcoidosis as the sensitivity of endomyocardial biopsy is still limited (approximately 20%) and is associated with complications,

despite recent advances in electrophysiologic mapping and image-guided protocols.⁶ Completely noninvasive diagnosis of cardiac sarcoidosis was proposed in 2015 by the Japanese Ministry of Health and Welfare in a novel guideline replacing histologic confirmation with PET and cardiac MRI as major criteria (see Table 1).⁸

Echocardiography is the investigation of choice for initial identification and for follow-up assessment of cardiac infiltrative conditions. Typical echocardiographic abnormalities for cardiac sarcoidosis include focal thinning of basal anterior septum, regional wall motion abnormalities in a noncoronary artery distribution, and ventricular systolic and/or diastolic dysfunction. Other findings include ventricular aneurysms, valvular abnormalities, and pericardial effusions. Contrast echocardiography allows further assessment for the presence of reduced perfusion in the associated underlying myocardium.⁹

Radionuclide scintigraphy with ^{201}Tl , ^{99m}Tc sestamibi, and ^{99m}Tc tetrofosmin has been used to differentiate fibrogranulomatous myocardium from fibrosis secondary to ischemia or infarction. As inflammatory cells demonstrate increased glycolytic demand, FDG PET can identify areas of active myocardial inflammation and has been shown to detect earlier stages of cardiac sarcoidosis than radionuclide scans alone.¹⁰ The combination of FDG PET with myocardial perfusion studies provides more precise assessment of active inflammation versus fibrosis¹¹:

- Increased FDG uptake with normal perfusion suggests an early phase of the disease.
- Increased FDG uptake with impaired perfusion implies active inflammation with myocardial damage.
- Decreased FDG uptake and perfusion are consistent with scarring of tissue (i.e., “burned out” sarcoid).

Table 1 Clinical cardiac findings in the 2015 diagnostic standard and guideline for sarcoidosis of the Japanese Society of Sarcoidosis and Other Granulomatous Disorders

1. More than two of five major findings are satisfied
 2. One of five major findings and more than two of three minor findings are satisfied
- Major findings
- Advanced atrioventricular block (including complete atrioventricular block) or sustained ventricular tachycardia
 - Basal thinning of the interventricular septum or morphologic ventricular abnormality (ventricular aneurysm, wall thinning of other ventricular region, wall thickening)
 - Impaired left ventricular contraction (LVEF < 50%) or regionally abnormal wall motion
 - Abnormal cardiac uptake in ⁶⁷Ga citrate scintigraphy or FDG PET
 - Late myocardial enhancement on gadolinium-enhanced MRI
- Minor findings
- Nonsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions, bundle branch block, axis deviation, or abnormal Q wave on electrocardiography
 - Defect on myocardial perfusion scintigraphy
 - Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade

Reproduced with permission from Sano *et al.*⁸ LVEF, left ventricular ejection fraction.

Studies have shown that FDG PET has sensitivity of 87% to 89%, but specificity is variable (38.5%–79%) compared with Japanese Ministry of Health and Welfare 2006 guidelines.¹⁰

Cardiac MRI with gadolinium enhancement provides excellent functional and morphologic information, as well as analysis of disease activity level.¹² However, it is contraindicated in certain patients, such as those with pacemakers, implantable cardioverter-defibrillators, or severe renal impairment. The typical pattern of cardiac sarcoidosis on MRI involves nodules or linear foci of enhancement that most frequently occur in the interventricular septum or basal left ventricle.⁶ Late gadolinium enhancement therefore occurs in patchy areas that do not relate to coronary artery distribution. The subepicardium, followed by the midwall portions of the myocardium, are most frequently involved, allowing cardiac sarcoidosis to be distinguished from ischemic disease, which affects the subendocardial layer.¹³ The presence of myocardial enhancement is a poor prognostic indicator with a risk for cardiac death increased >11 times.⁶ Emerging magnetic resonance sequences of T1 mapping and texture analysis are likely to improve the sensitivity and prognostic value of cardiac MRI in the future.¹⁴

Corticosteroid therapy is traditionally regarded as the mainstay of treatment for cardiac sarcoidosis, though there is a lack of consensus regarding the optimal dosing regimen, when to commence therapy, and the evaluation of therapeutic response. Moreover, the adverse effects profile associated with prolonged corticosteroid use is of significant concern for chronic disease management, and thus the role of steroid-sparing agents has been increasingly recognized. Methotrexate is an antimetabolite drug that has been studied extensively in sarcoidosis and shown to have a moderate steroid-sparing effect.¹⁵ Recent recommendations by the World Association of Sarcoidosis and Other Granulomatous Disorders suggest that first-line methotrexate and corticosteroid combination therapy be considered in patients with cardiac sarcoidosis to avoid complications such as aneurysm formation secondary to high-dose corticosteroids.¹⁵ Infliximab, a tumor necrosis factor- α antagonist, can be considered in refractory cardiac sarcoidosis, but its use should be carefully considered in patients with signs of heart failure. Nonetheless, immunosuppressive therapy should be evaluated regularly for potential tapering as part of long-term management strategy. In addition, there is a lack of

clear data to support whether to use medical therapy alone or with primary preventive implantable cardioverter-defibrillator therapy in early stages of the disease.⁷

CONCLUSION

With advances in imaging modalities, the feasibility of diagnosis of isolated cardiac sarcoidosis using a noninvasive approach (i.e., without a histologic diagnosis) has improved greatly. Current diagnostic algorithms need to be further validated to strengthen the evidence-based framework to supplement a high index of clinical suspicion for the diagnosis of cardiac sarcoidosis in a timely manner.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.case.2017.06.002>.

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