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Imaging for Diagnosis and Monitoring of Cardiac Sarcoidosis

Ghazaleh Mehdipoor (MD)[1,*], Sabahat Bokhari (MD)[2], Martin R. Prince (MD, PhD)[3, 4]

[1] Cardiovascular Research Foundation (CRF), New York, NY, USA
[2] Division of Cardiology, New York Presbyterian Hospital and Columbia University Medical Center, New York, NY, USA
[3] Department of Radiology, Weill Cornell Medicine
[4] Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY, USA

** Corresponding author: Ghazaleh Mehdipoor (MD), Cardiovascular Research Foundation (CRF), New York, NY, USA. E-mail: Ghazaleh.mehdipoor@gmail.com*

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Abstract

Sarcoidosis is a granulomatous condition, primarily affecting the lungs and thoracic lymph nodes. Clinical cardiac involvement might occur in 2 to 5% of patients with sarcoidosis, and can be associated with serious complications including heart block, cardiomyopathy, ventricular arrhythmias, and potentially death. Timely diagnosis helps initiate treatment before cardiac damage becomes irreversible. In this brief review, we discuss imaging updates for diagnosis and monitoring of cardiac sarcoidosis.

INTRODUCTION

Sarcoidosis is a chronic granulomatous disorder. Although primarily affecting the lungs and thoracic lymph nodes, clinically it involves the heart in up to 5% of patients causing serious morbidity and mortality.[1, 2] Autopsy data suggest cardiac involvements in up to 25%, emphasizing that there may be an underestimation due to the difficulty in diagnosis.[3, 4] Signs and symptoms depend on the site and extent of cardiac involvement, and include conduction abnormalities, and heart failure.[5] The diagnosis is usually made by existing recommendations, including those from the Japanese Ministry of Health and Welfare Criteria for Diagnosis of Cardiac Sarcoidosis (Revised 2006) and Heart Rhythm Society Expert Consensus Statement.[6, 7] Timely diagnosis can help direct specific treatments to ameliorate the disease course and avoid unnecessary interventions. Suggestive findings include increased myocardial wall thickness, regional wall motion abnormalities, systolic or diastolic dysfunction, and pericardial effusions on transthoracic echocardiography.[8] However, transthoracic echocardiography is not, in isolation, diagnostic for cardiac sarcoidosis. Historically, the diagnosis was made by endomyocardial biopsy. However, cardiac involvement could be patchy and missed by a single biopsy. Multiple biopsies are not feasible because of the increased procedural risks, and long-term complications such as tricuspid regurgitation.[9, 10] Use of cardiac magnetic resonance (CMR) imaging, and positron emission tomography (PET) have redefined the timeliness of diagnosis, and have provided avenues for monitoring the response to treatment. Here we briefly review these imaging advances in diagnosis and monitoring of sarcoidosis.

Diagnosis

Endomyocardial biopsy is the gold standard diagnostic method. However, focal involvement of the heart is one the limitations of biopsies. Increasing the sensitivity of biopsy by sampling multiple sites increases procedural risk. Thus, diagnostic utility of endomyocardial biopsy is limited. CMR imaging can evaluate the entire myocardium for sarcoid involvement and also evaluates cardiac structure, perfusion, and function.[11] CMR can show wall thickness abnormalities, edema, patchy involvement, and chronic fibrotic scar with delayed gadolinium enhancement.[8, 12] T_1-weighted images can demonstrate structural changes and T_2-weighted images can detect the acute phase of inflammation.[13] Cine MR sequences assess wall motion abnormalities (hypokinesia or akinesia) due to scar or inflamation.[14] In the appropriate clinical context, the diagnosis of sarcoidosis is based upon the presence of patchy, subepicardial late gadolinium enhancement (LGE), which identifies fibrosis, or advanced disease.[14] MRI can also provide information about the mediastinum and possible

extracardiac signs. Cardiac sarcoidosis without known or apparent extracardiac sarcoidosis has been reported previously, but is relatively rare.[15-18] Fluid sensitive sequences can also provide valuable information about the myocardial edema at earlier stages, but the role in the diagnosis of cardiac sarcoidosis is not clear.[7, 19] Since diagnosing sarcoidosis required gadolinium (typically a double dose), limitations include a risk of nephrogenic systemic fibrosis when GFR < 30 ml/min as well as allergic reactions to the gadolinium-based contrast agents. [20, 21] PET imaging is also commonly used to assess active cardiac sarcoidosis (Table 1).

PET requires a special patient dietary preparation to reduce glucose uptake by normal myocardium.[5] The patient must have a high protein, high fat, low carbohydrate diet for 24 hours prior to PET scanning. This reduces the glucose uptake by myocytes. Alternatively, unfractionated heparin could be administered to increase fatty acid availability. Upon arrival in nuclear cardiology laboratory, a rest N^{13} labeled ammonia PET is performed to identify myocardial perfusion defects. Then in the same setting F-18 Fluorodeoxyglucose (FDG) can be administered to identify sites of myocardial inflammation[22] as well as lymph nodes in the active phase of disease. Cardiac PET images are classified based on the perfusion defect and the corresponding FDG uptake into four categories of normal, early disease, progressive disease, and fibrous disease.[9, 23] The ability of FDG PET scan to identify inflammation can detect the disease at earlier stages, which is important for treatment before fibrosis happens.[9] Whole-body PET may be useful for detecting extracardiac involvement, especially in cases initially presenting with isolated cardiac sarcodosis.[17]

FDG PET can discover active cardiac sarcoidosis and is considered more sensitive than other radionuclide imaging tests. It assesses the hypermetabolic activity of myocardium due to inflammation. The most important advantage of FDG PET over MRI, is more accurate quantification of myocardial FDG uptake in sarcoidosis, which can assess response to therapy.[9] FDG is not accumulated in normal vascular structures. Neoplastic PET uptake could be differentiated since the uptake is more intense than other inflammatory diseases (including sarcoidosis).[24] On PET/computed tomography (CT), the manifestations may include patchy or diffuse hypermetabolic activity. Cross-sectional imaging studies are complementary for precise localization of anatomic involvement.[24] FDG PET is also a useful imaging tool for diagnosis, evaluating disease activity, and monitoring the response to treatment in patients with sarcoidosis.[9] PET/ CT scan using F-18 sodium fluoride has been tested in recent years but does not appear to detect myocardial inflammation caused by suspected cardiac sarcoidosis.[25] Nuclear imaging tests for diagnosis of cardiac sarcoidosis are generally performed with thallium, technetium pyrophosphate, and gallium. Coronary artery disease should be differentiated from cardiac sarcoidosis by further pharmacological assessment usually with dipyridamole. Perfusion-inflammation mismatch happens in cardiac sarcoidosis. Alternatively, in those with newly discovered cardiomyopathy, coronary disease might be interrogated by other modalities, including cardiac catheterization. Gallium is sensitive for cardiac sarcoidosis. However, the currently available gallium scans are not sufficiently clear to differentiate between mediastinal and lung disease versus cardiac involvement with sarcoidosis. [26] A combined approach using FDG PET and CMR can assess inflammation, scar, fibrosis and wall motion abnormalities. Combined imaging modalities may help in confirmation of the diagnosis with higher confidence, better tissue characterization, and prognostication. Recently, guided biopsy with CMR or PET has been shown to be helpful. However, a negative biopsy does not exclude the diagnosis.[8] Real-time MRI guided biopsy has been reported to provide a better tissue characterization for guided biopsy from the patchy involvements.[27, 28]

Table 1: Imaging Modalities for Assessment of Cardiac Sarcoidosis

	Transthoracic echocardiography	FDG PET	CMR
Test characteristics/ protocol	-Performed at beside with cardiac ultrasound probes	-Needs a special dietary preparation in advance, with or without administration of intravenous unfractionated heparin. Imaging is done after about 90 minutes of FDG uptake.	Cine short axis, 4-chamber and 3-chamber views; Gadolinium to assess patchy and late enhancement as well as T_1 and T_2 weighted images.
Role in diagnosis/ prognosis / follow up	-Can help identify new cardiomyopathy or wall-motion abnormality, ejection fraction, etc.	-A sensitive tool to assess the hypermetabolic activity of myocardium due to inflammation	-Can identify patchy and Late gadolinium enhancement in diagnosis of fibrosis -T_1-weighted images are useful for assessing structural changes and T_2-weighted images for acute phases of inflammation and edema
Strengths	-Relatively inexpensive, readily available, no adverse effects	-No immediate complications -helpful to assess extracardiac disease -A quantitative tool for assessment of response-to-treatment	-Can identify other cardiomyopathies or infiltrative diseases with similar presentations - No ionizing radiation -Prognostic utility -Provides valuable information about the lungs and thoracic lymph nodes
Limitations	-Insufficient for definite diagnosis	-Radiation	-Some patients may have intracardiac devices that are known to be incompatible with MRI -Length of imaging is long for patients -Risk of nephrogenic systemic fibrosis (if GFR < 30 ml/min) -Immediate type allergic reactions

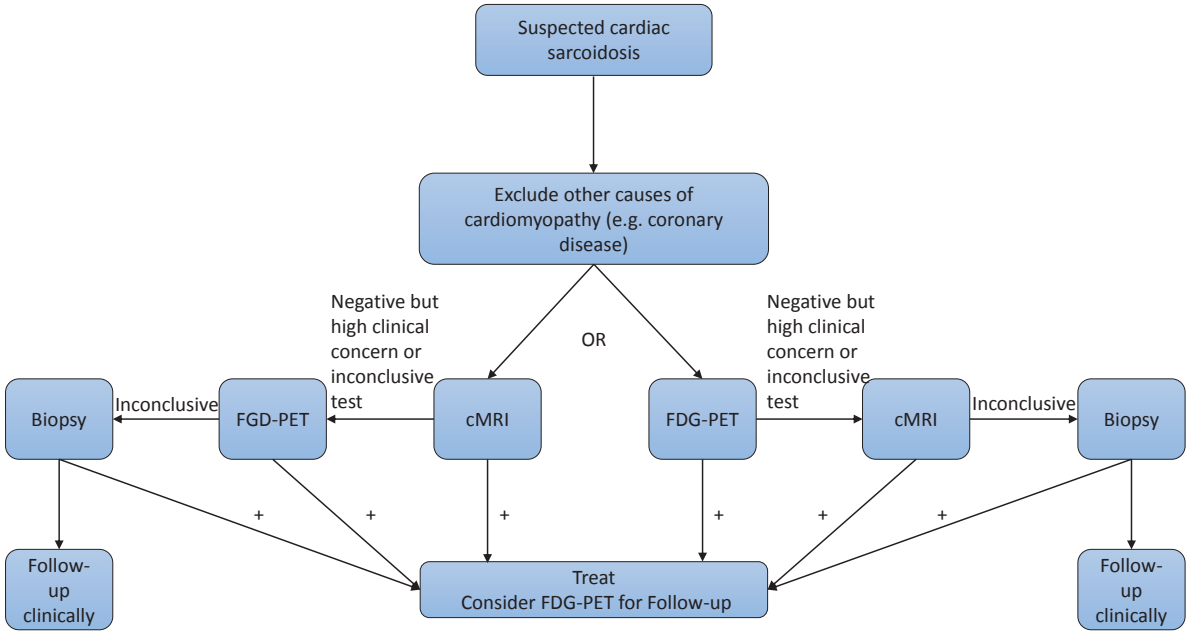

Figure 1: Flow Diagram for Diagnostic Evaluation for Suspected Cardiac Sarcoidosis

We should reemphasize that in patients with suggestive history and related cardiac findings, diagnosis of sarcoidosis should be considered once other common causes of cardiomyopathy, such as coronary disease, have been excluded and then an imaging modality would help for making the diagnosis (Fig 1).

Prognostic Significance

Initial echocardiographic assessment is helpful in prognostication and has been reported in a number of patients who are not responsive to immunosuppression therapy.[5, 15, 29] In CMR, late gadolinium enhancement has also been reported to be an important prognostic factor and is associated with sudden cardiac death, implantable cardioverter-defibrillator (ICD) discharge, and ventricular arrhythmias in patients with systemic sarcoidosis.[2, 5, 8, 29-31] In addition, in a prospective study of cardiac sarcoidosis in 118 patients, FDG PET abnormality was associated with sudden cardiac death or ventricular tachycardia.[23] Clinically overt heart failure and impaired LV function portends dismal outcomes.[15]

Monitoring Disease Activity

PET imaging is an option to monitor the response to immunosuppressive therapy.[32] Serial FDG-PET can show normalization of tissue uptake after treatment which is also associated with improved outcomes, or may show cases resistant to treatment that might require adjusting therapies.[33, 34] The data about the follow-up of patients with CMR, is probably limited due to incompatibility of intracardiac devices such as defibrillators, commonly recommended for these patients, and MRI. However, in a recent study assessing the safety of MRI in 1509 patients with pacemakers or implantable cardioverter defibrillator, no long term clinically significant adverse events were reported.[35] Therefore, it is likely that future studies can assess the potential impact of CMR on response to therapy, as well.

CONCLUSIONS

Cardiac sarcoidosis is a debilitating inflammatory cardiac myopathy that can lead into adverse outcomes including death. Although endomyocardial biopsy is the gold standard for diagnosis, existing and growing evidence and consensus statements[1] suggest that an algorithm of careful evaluation based on symptoms, signs, basic tests (such as electrocardiogram and echocardiogram) and advanced imaging modalities (such as CMR and FDG PET) can help make the diagnosis in most suspected patients. CMR and FDG-PET are complementary and provide valuable information for diagnosis and follow up. Hybrid imaging with PET-MR is a novel method to evaluate cardiac sarcoidosis and may improve the yield and timeliness of diagnosis.[36] Endomyocardial biopsy would be considered in selected cases, including those with inconclusive non-invasive test results, or those with high suspicion for the disease but without proven extracardiac disease.

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CONFLICTS OF INTEREST

None declared.

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