Cardiac Sarcoidosis: An Important Cause of Cardiomyopathy

Steven Sigman, M.D., FACC, FASNC
Director of Nuclear Cardiology, Piedmont Hospital and Piedmont Heart

Although less common than other causes of cardiomyopathy, cardiac sarcoidosis is an important disorder associated with high rates of morbidity and mortality, including sudden cardiac death. The early recognition of this disorder can be life saving. Although generally part of a systemic process involving the lung, lymph nodes, liver, spleen, skin, and bones, pathologic studies demonstrate the infiltrative pattern of scarring and inflammation with the presence of the noncaseating granulomas in the cardiac tissue in as many as 25% of these patients. Importantly, isolated cardiac sarcoidosis, with no other manifestations of systemic disease, has also been identified in certain patients, and is generally associated with a more malignant course.

Generally presenting with symptoms typical of congestive heart failure such as dyspnea, orthopnea and swelling, cardiac sarcoidosis can also present with arrhythmic symptoms such as palpitations, syncope, or near syncope. This is due to infiltrative predilection for involvement of the cardiac conduction system. Unexplained heart block, particularly in a younger patient, is a common presentation. A high index of suspicion by the health care provider for cardiac sarcoidosis is of utmost importance.

Diagnosis
Initial identification of this disorder is generally based on ECG findings of conduction abnormalities, including right bundle branch or complete heart block, and abnormal CXR findings in the presence of new onset, unexplained congestive heart failure. A careful history - even the mildest complaint of lightheadedness on direct questioning - can be of critical importance in the identification of important arrhythmias.

Lab work may demonstrate elevation of angiotensin converting enzyme (ACE) levels as well as hypercalcemia, particularly in widely systemic disease. Non-contrast CT scanning of the chest looking for lymphadenopathy may be important. Echocardiographic findings include: reduced left and right ventricular function in the presence of multiple non-contiguous wall motion abnormalities, aneurysms, and thinning of the basal portion of the septum. Valvular abnormalities, particularly mitral and tricuspid regurgitation may be present if the infiltrative process effects the papillary muscles. Occasionally, evidence of scarring on conventional nuclear myocardial perfusion imaging studies (MPI) using technetium agents or thallium suggest the diagnosis, particularly when in distributions not typical of usual coronary artery disease.

Advanced Cardiac Imaging
Multimodality cardiac imaging with a team approach is the key to best diagnosis, prognosis, and management of this complex disorder, and is an example of where both cardiac magnetic resonance imaging with late gadolinium hyperenhancement (CMR) and using F-18 Fluorodeoxyglucose positron emission tomography and computerized tomography (FDG-PET/CT) can be useful, and more importantly, complementary.

CMR
For most patients, CMR is the favored method of initial diagnosis of cardiac sarcoidosis. This is primarily due to its superior sensitivity and ability to localize even small areas of sarcoid infiltration. Typical CMR findings include dense, patchy areas of fibrosis representing scarring, particularly at the base of the anteroseptal, inferior, or inferolateral walls, which are not typical of coronary distributions. Involvement of the right ventricle has been noted as well, and when present, portends a particularly poor prognosis. CMR provides for exacting measurement of both right and left ventricular EF, as well as associated wall motion abnormalities. Degree of valvular disease can be carefully assessed as well.

FDG-PET/CT
Improvements in imaging techniques and an evolving body of research over the past few years have brought PET imaging to the forefront for both initial diagnosis and especially management of cardiac sarcoidosis. This type of imaging is based on the principle of uptake of radio labeled glucose in areas of intense inflammation characteristic of active sarcoidosis. Lack of uptake of radioisotope suggests scarring, or inactive “burnt out” disease. Performed in a manner
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very similar that which is done for the diagnosis and management oncologic diseases, the PET image is registered to the CT image, for exacting localization. Again, akin to cancer imaging, changes in the intensity of FDG uptake, defined in terms of standard uptake values (SUV), can be used to help monitor response to treatment.

A key component to optimal performance is meticulous adherence to a pre-procedure diet high in protein and fat, and low in glucose. The resultant low glucose/low insulin milieu suppresses uptake of glucose in the normal myocardium, and enhances imaging of uptake in areas of active sarcoidosis. PET can also be the primary modality of diagnosis in patients with relative contraindications to MRI, including older model pacemakers, renal insufficiency, obesity, or claustrophobia.

A general approach to management may use both techniques: CMR to make the initial diagnosis, and PET to document an active inflammatory process as well as monitor response to therapy. Again, the important concept is that CMR and PET can be complementary (Figure 1).

Diagnostic Guidelines

Recent expert consensus guidelines (Heart Rhythm Society, 2014) propose the following criteria for diagnosis of cardiac sarcoidosis: (1) presence of non-caseating granulomas on histological examination of myocardial tissue by biopsy in the absence of other etiologies, or (2) a combination of positive histology from a non-cardiac source (lung biopsy) and either unexplained EF <40%, unexplained sustained ventricular tachycardia, Mobitz II second or third degree heart block, abnormal cardiac imaging or clinical evidence of steroid responsive improvement in CHF or heart block. However, as far as the first criterion is concerned, it should be noted that due to the patchy nature of myocardial involvement, the yield of cardiac biopsy is low (<20%).

Management

Management of cardiac sarcoidosis requires a team approach, with close cooperation among primary cardiologists, congestive heart failure

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Figure 1: Panel A - Axial (four chamber) cardiac MRI with late gadolinium enhancement at the level of the heart demonstrating fibrosis in the mid and basal septum, base of lateral wall, and portions of the right ventricle (white areas, arrow). Panel B - Axial PET/CT scan at same level with corresponding areas of inflammation (orange areas, arrow).
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specialists, electrophysiologists, radiologists, and pulmonologists experienced in the treatment and monitoring of therapy in this complex disorder.

Treatment with standard recommended therapy for CHF including beta blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, low dose diuretics, and aldosterone blockers, is initiated early on.

Immunosuppression with prednisone is the cornerstone of treatment, usually starting with a high dose, with very slow tapering over a period of months to years. Adjunctive treatment with methotrexate may also be recommended, keeping in mind the meticulous monitoring required with use of this medication. Follow up PET FDG/CT is often repeated 6-12 months after initiation of treatment to assess response to therapy. Again emphasized is the need for careful follow up by a team well familiar with management of this disorder.

Use of Implantable Cardioverter Defibrillator (ICD)

Sudden cardiac death (SCD) is the most feared complication of cardiac sarcoidosis and with incidence 10% or higher in most series of 3-5 years episodes of prolonged ventricular tachycardia (VT) with syncope are also frequent. Further complicating the situation is that these arrhythmias can occur (and commonly do) in patients with left ventricular ejection fraction (LVEF) ranges of 35% to 50%, higher than those required for primary prevention of SCD in patient with coronary heart disease.

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Diagnostic Guidelines

Recent expert consensus guidelines (Heart Rhythm Society, 2014) assign a Class I indication (“is recommended”) for placement of ICD in patients with cardiac sarcoidosis who have experienced sustained VT or cardiac arrest, or for patients with LVEF <35% despite optimal medical therapy and a period of immunosuppression. Class Ila (“can be useful”) recommendations are made for the implantation of ICD in patients with cardiac sarcoidosis independent of LVEF if there is an indication for permanent pacemaker for heart block, unexplained syncope or near syncope, or inducible VT on electrophysiology study. The development of broader indications for placement of ICD in patients with ejection fractions between 36% to 49% is an area of strong clinical interest and research.

Prognosis

Due to the wide variability in cardiac involvement, LVEF, treatment protocol and follow up methodology, prognostic information is limited, although studies over the last 5-10 years tend to indicate a better prognosis than previously thought. One recent series of 110 patients from Finland treated with immunosuppressants, contemporary treatments for CHF, and ICDs, found 97%, 90% and 83% transplant free survivals at 1,5, and 10 years, respectively.

Of note, the patients with lower EF (<35%) had worse outcomes, with a transplant free survival at 10 years as low as 53%.

Summary

Cardiac sarcoidosis is an important and perhaps underappreciated cause of cardiomyopathy, characterized by elements of congestive heart failure, as well as cardiac conduction disturbances such as complete heart block, and malignant arrhythmias including sudden cardiac death. Optimal diagnosis and treatment relies strongly on a high clinical index of suspicion. Treatment of this disorder exemplifies the importance of careful collaboration between cardiologists, electrophysiologists, cardiac imagers, and pulmonologists to provide the best care possible for these complex patients.

References