HEART FAILURE

REVIEW ARTICLE

Cardiac Sarcoidosis: Recent Advances in Diagnosis and Treatment and an Argument for the Need for a Systematic Multidisciplinary Approach to Management

JASON P. EVANCHAN, DO, ELLIOT D. CROUSER, MD and STEVEN J. KALBFLEISCH, MD

Division of Cardiovascular Medicine, and Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, Columbus, OH

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Introduction

Sarcoidosis is an idiopathic disease characterized by the presence of non-caseating granulomas in the involved organs. Systemic sarcoidosis affects the respiratory system or mediastinal lymph nodes in more than 90% of cases, but any organ system can be involved. Cardiac involvement is common and significantly alters the patient’s prognosis. Manifestations of cardiac sarcoidosis (CS) include congestive heart failure, conduction abnormalities, atrial and ventricular arrhythmias, and sudden death. Cardiac complications are the second leading cause of sarcoidosis-related death, after respiratory complications, in the United States. The following case exemplifies the clinical challenges represented by CS:

Case

Ms. B is a 53-year-old female with a history of hypertension and hyperlipidemia who presented with a 4-week history of intermittent palpitations, dyspnea on exertion, and fatigue. Her physical examination was unremarkable. An electrocardiogram (ECG) in the office showed normal sinus rhythm with a prolonged PR interval of 440 ms and a normal QRS duration. Holter monitoring demonstrated sinus bradycardia with intermittent 2:1 atrioventricular (AV) block. An echocardiogram was normal with a left ventricular ejection fraction (LVEF) of 60–65%. During exercise stress testing she developed complete heart block with a junctional escape rhythm (Figure 1). She was admitted to the general cardiology service for further evaluation.

Cardiac catheterization demonstrated no coronary artery disease. However, she had enlarged mediastinal lymphadenopathy on her chest X-ray, prompting concerns of an infiltrative or inflammatory process. This suspicion was supported by cardiac magnetic resonance imaging (CMR) showing late gadolinium uptake of the basal interventricular septum and fludeoxyglucose (FDG)-18 positron emission tomography (PET) computed tomography (CT) scan demonstrating intense FDG-18 uptake in the mediastinal lymph nodes and basal interventricular septum (Figure 2). Mediastinal lymph node biopsy showed non-caseating granulomas consistent with sarcoidosis (Figure 3). The electrophysiology and pulmonary services were consulted to assist with management. The treatment plan included placement of a dual-chamber implantable cardioverter-defibrillator (ICD) and immunosuppressive therapy with low-dose prednisone and methotrexate.

Case discussion

The above case demonstrates some of the typical findings of a patient with CS. Although the diagnosis
seems obvious in retrospect, the diagnosis is often elusive as there is no readily available, definitive test for CS. Specialized cardiac imaging techniques such as CMR or PET scanning are usually required to detect the inflammation or scarring attendant to CS. Despite advanced imaging modalities, the diagnosis of CS is typically presumptive due to the inherent risks and low sensitivity of cardiac biopsy.

Once a presumptive diagnosis of CS is made the clinician is then confronted with uncertainties relating to treatment. For instance, there is a lack of formally agreed upon guidelines to direct immunosuppressive therapy or to risk-stratify patients for cardiac device therapy. The lack of consensus regarding the best methods for diagnosing and treating CS was highlighted in a recent survey of sarcoidosis experts. In this study the overall agreement between the experts was graded as only low to moderate, and there was considerable variability in the frequency and type of testing used to evaluate sarcoid patients. This review will consider the merits of

Figure 1: Exercise stress electrocardiogram demonstrating sinus tachycardia with complete heart block and a junctional escape rate at 48 bpm.

Figure 2: Coronal (a) and transverse (b) views of a positron emission tomography computed tomography with focal fludeoxyglucose uptake seen in the myocardium, located in the anteroseptal wall (long arrows) with hypermetabolic lymphadenopathy throughout the mediastinum (short arrow).
different diagnostic modalities and management strategies for CS and highlight the need for a systematic multidisciplinary approach for treating these patients.

Epidemiology

The reported incidence and prevalence of sarcoidosis varies widely and is strongly influenced by race, gender, and geographical location. A large epidemiological study conducted in the United States documented the annual incidence of sarcoidosis to be 10.9/100,000 in white people to 35.5/100,000 in African Americans. Sarcoidosis is more common in women than in men by a 1.3:1 margin, with a peak incidence in those between 20–49 years old. The overall prevalence of sarcoidosis is largely unknown but is estimated by the Rare Disease Network, a subsidiary of the National Institutes of Health, to be 15/100,000. A recent study conducted in Columbus, OH, the demographics of which closely matches that of the US population as a whole, indicates that the regional prevalence of disease is closer to 50/100,000 and has increased twofold within the past 15 years. The observed increase in prevalence and recent reports showing increasing disease-related mortality may be explained by improved detection or changes in the exposure to disease-causing antigens. Regardless of the explanation, it is evident that sarcoidosis is a growing health concern.

In older observational studies, sarcoidosis was estimated to affect the heart in approximately 5% of patients. These estimates were based on the presence of overt clinical manifestations, such as symptomatic...
arrhythmias or heart failure, and the detection of abnormalities on relatively insensitive screening tools (ECG, telemetry, echocardiography) in patients with known systemic sarcoid. However, autopsy studies indicate that cardiac involvement is present in up to 25–30% of patients with systemic sarcoidosis.7 Thus, CS is often clinically silent and difficult to detect with routine screening tools. This is an important point because unrecognized cardiac involvement can have lethal implications.

Clinical presentation of cardiac sarcoidosis

CS can be clinically silent or can present with vague constitutional symptoms, heart failure, palpitations, presyncope, or syncope.8 The clinical manifestations of CS depend not only upon the location and extent of granulomatosus inflammation, but also on the stage of the disease process. Sarcoidosis granulomas can affect any part of the heart but there is a clear predilection for certain areas. The most common areas of involvement are the basal segment of the inferolateral left ventricular free wall and the basal interventricular septum, followed by the atrium, papillary muscles, the right ventricle and the pericardium.9 In its early stages, sarcoid is an active inflammatory disorder that causes myocardial swelling and edema, progressing in later stages to fibrosis (myocardial scarring).

Conduction system disease

Given the predilection for involvement of the anterior basal interventricular septum, conduction system abnormalities are relatively common, occurring in up to half of the cases of CS.7 Conduction system involvement can manifest as either a bundle branch block or AV block of any degree (first, second or third). Detection of any type of conduction system abnormality in a patient with systemic sarcoidosis should alert the clinician the possibility of cardiac involvement. In the early inflammatory stages the conduction changes may be transient or fluctuate, especially in response to immunosuppressive therapy, whereas in the subsequent fibrotic stages the conduction changes are irreversible.

Complete heart block (CHB) is a common presentation, reported in up to a third of patients with CS.10 The presence of CHB in a patient with known systemic sarcoidosis is essentially pathognomonic for cardiac involvement. In young to middle-aged and otherwise healthy adults presenting with CHB a strong consideration has to be given to the possibility of CS as the cause. Kandolin et al11 evaluated cases of idiopathic CHB in patients between the ages of 18 and 55 years, and 19% were determined to have CS, of which approximately two-thirds were felt to have isolated CS. CHB complicating CS has been found to be a strong predictor of sudden death. Thus, it is important to confirm the diagnosis and initiate proper treatment for these patients, as will be discussed below.

Congestive heart failure

Congestive heart failure (CHF) is now recognized as a leading cause of death from cardiac sarcoidosis.5 The development of CHF usually indicates extensive myocardial infiltration and can be caused by either systolic or diastolic dysfunction. Diastolic dysfunction typically predominates during the early inflammatory phase of the disease when more tissue edema is present. In these cases echocardiographic imaging typically demonstrates preserved contractility and the only detectable abnormality may be subtle wall thickening relating to tissue swelling. These changes may be difficult to appreciate on echocardiographic imaging and are best visualized on cardiac MRI, a more sensitive imaging modality. In the later fibrotic stages of the disease, reduction of right and/or left ventricular systolic function associated with chamber dilatation and wall thinning may be readily detected by echocardiographic testing, although at this point the prognosis and response to immunosuppressant therapy has been significantly altered. When patients with an ejection fraction (EF) of <40% caused by either CS or idiopathic dilated cardiomyopathy (IDCM) were compared, CS was distinguished by localized abnormalities of both wall motion and wall thickness (both thinning and thickening). This is presumably the result of the more focal nature of the sarcoid disease process. CS was further characterized by a greater incidence of conduction abnormalities and a much worse prognosis than the IDCM patients, with 37% versus 60% 5-year survival rates for CS and IDCM, respectively.12

Other common features of CS patients presenting with CHF include ventricular aneurysms and mitral regurgitation. Ventricular aneurysms have been reported to occur in up to 10% of CS patients with the anterior and septal walls being most commonly affected.9 While active granulomas can be found in the aneurismal tissue, the aneurysms are more commonly composed of fibrotic tissue, indicating that this is a late manifestation of the disease.13 Mitral regurgitation commonly occurs in CS and may be secondary to either left ventricular dilatation or direct granulomatous involvement of the papillary muscles.9

Sudden cardiac death

Sudden cardiac death (SCD) is the cause of death in up to 67% of CS cases. SCD is second only to respiratory complications as the cause of disease-related death in patients with systemic sarcoidosis. Ventricular tachyarrhythmias (VTs) are the most common cause of SCD; however, high-grade AV block has also been reported.9 High-risk markers of SCD in patients with CS include documented VTs, syncope, symptomatic CHF, high-grade AV block, and both right and left ventricular dysfunction. Unfortunately, these predictors are less than perfect and may not be sensitive enough to reliably predict adverse outcomes. Thus, the challenge lies in risk-stratifying patients with evidence of CS in the absence of high-risk features. More sensitive imaging modalities (e.g., PET scanning) or the propensity for
inducible VT on electrophysiology (EP) testing may provide direction for subsequent interventions as will be discussed below under the “Cardiac device therapy and electrophysiology testing” section.

Ventricular arrhythmias

Ventricular arrhythmias are common in patients with CS and can range from isolated ventricular ectopy to episodes of sustained VT. The mechanisms of ventricular arrhythmias are proposed to relate to abnormal automaticity during the acute inflammatory stages and are caused by re-entry in the later fibrotic stages. In patients with known systemic sarcoidosis an abnormal Holter monitor study demonstrating frequent ventricular ectopy (>10 premature ventricular contractions (PVCs)/h) was found in approximately 30% of patients ultimately diagnosed with CS. During the early stages of the disease frequent ectopy is thought to be due to myocardial irritability as a result of the acute inflammatory process and may be reversible with immunosuppressive therapy. An important unanswered question is whether the degree of ventricular ectopy can serve as a marker for disease activity and help to guide immunosuppressive therapy.

In larger autopsy series conducted on patients with CS, sustained VT was reported in approximately 20% of patients ante mortem. The majority of CS patients presenting with sustained VT have significant left ventricular dysfunction and inducible VT in the EP laboratory. These findings indicate that most of the patients with sustained VT are in the later stages of the disease and have significant degrees of myocardial fibrosis, which serves as the substrate for ventricular re-entry. Patients with sustained ventricular arrhythmias are at a high risk for sudden death and require ICD implantation. In the majority of these patients the scarring is fixed and the process is not reversible with immunosuppressive therapy.

Notably, there are reports of patients with CS presenting with sustained monomorphic VT in whom the EF is relatively preserved (≥45%) and who are not inducible in the EP laboratory. These patients usually have evidence of active cardiac inflammation on gallium or PET scanning, and their arrhythmias may be responsive to immunosuppressive therapy. These case reports indicate that the degree of active cardiac inflammation may be an independent predictor of VT and sudden death. This notion is supported by a study where CS patients with relatively preserved EFs (≥35%) who received appropriate ICD therapy for VT where likely to have an abnormal cardiac PET scan, although the number of patients was too small to draw firm conclusions.

Supraventricular arrhythmias

Supraventricular arrhythmias, most commonly atrial fibrillation or atrial tachycardia, can be associated with CS. The mechanism for these arrhythmias can be multifactorial, including direct involvement of the atria with the sarcoid granulomas, or secondary to pressure changes in the atria due to heart failure or core pulmonale as a result of sarcoid lung disease. The reported incidence of atrial arrhythmias in cardiac sarcoid is approximately 20%. In patients where the inflammatory process directly affects the atrial myocardium, traditional antiarrhythmics may be ineffective, and steroid therapy may be required to control the arrhythmia.

Pericardial effusion

Pericardial effusions are reported to occur in 2–12% of patients with CS. Typically these are small and asymptomatic, but occasionally they can be large and hemodynamically significant, especially when there is active granulomatus involvement of the pericardium. Patients with recurrent large effusions despite immunosuppressive therapy may benefit from the creation of a pericardial window to facilitate drainage.

Prognosis

The prognosis for surviving sarcoidosis is primarily dependent upon the degree of lung and cardiac involvement, and the prognosis changes substantially in patients with symptomatic CS. As previously stated, cardiac involvement is the second leading cause of death and accounts for up to 25% of disease-associated mortality, primarily by either progressive heart failure or cardiac arrhythmias. Sudden death, presumably as a result of ventricular arrhythmias, is the cause of cardiac death in approximately two-thirds of these patients. Younger age (25–44 years) and black race appear to be risk factors for SCD in the setting of CS.

Diagnosis

The accuracy of measures to establish the diagnosis of CS is predicated upon a high index of clinical suspicion. The pretest probability of CS differs significantly for patients with known systemic sarcoid versus those presenting with a cardiac manifestation without a previously established diagnosis of sarcoid. Overt clinical symptoms relating to CS are present in only approximately 5% of cases, whereas nearly a third of the patients have cardiac involvement on necropsy. Early detection of CS is critical because SCD can be the first manifestation of cardiac involvement and early appropriate treatment is often protective.

Given these serious clinical implications, it is essential to screen for cardiac involvement in patients with sarcoidosis. However, the optimal screening approach is controversial and varies greatly among physicians, a fact which was highlighted in a recent survey of experts in the field. Specific guidelines for the detection of CS were proposed by the Japanese ministry of health in 1993 (Table 1) and then again in 2006, but these guidelines fail
to consider recent innovations such as cardiac PET-CT. While conducting advanced cardiac imaging on every patient with sarcoidosis is impractical, these modalities may be ultimately cost-effective and less risky than other diagnostic approaches (e.g., myocardial biopsy).

The cornerstone of screening sarcoid patients for cardiac involvement continues to be a search for clinically manifest signs or symptoms of CS. Even subtle cardiac symptoms warrant a thorough evaluation. A baseline ECG should be obtained at the time of diagnosis of sarcoidosis and should be repeated if any concerning symptoms arise at any time in a patient with established sarcoidosis. The reported sensitivity of ECG for detecting CS is up to 65–70% for detecting cardiac involvement, the most common finding being conduction system abnormalities. Holter monitoring is an effective screening tool in detecting atrial and/or ventricular arrhythmias, as well as transient AV conduction abnormalities which may be missed on baseline ECG. Using a threshold of 100 PVCs/day, Holter monitoring had a reported sensitivity of 67% and a specificity of 80% for detecting CS in the setting of established sarcoidosis elsewhere.

While echocardiography lacks sensitivity for the detection of myocardial involvement, it can help risk-stratify patients with suspected CS by quantifying right and left ventricular function. Furthermore, echocardiography is useful for assessing the response to immunosuppressive therapy in patients with documented ventricular dysfunction. Other meaningful findings on echocardiography include abnormalities of wall thickness (either thinning or thickening reflecting myocardial fibrosis or edema, respectively), localized regional wall motion abnormalities, pericardial effusions, papillary muscle involvement manifesting as mitral regurgitation, and pulmonary hypertension.

When used together, ECG, Holter monitor, and echocardiogram are highly sensitive for detecting cardiac involvement, but these modalities are not specific for CS. In a patient with systemic sarcoidosis without cardiac symptoms in whom the ECG, Holter, and echocardiogram are normal, the prognosis from a cardiac standpoint is very good and further immediate testing is unnecessary. On the other hand, abnormalities detected during any of these screening tests should lead to more definitive imaging with either CMR or cardiac PET-CT, as detailed below, and treatment decisions can be based on the information gained from this imaging.

**Advanced cardiac imaging with CMR and PET-CT**

The role of imaging in the diagnosis of CS has evolved significantly over the past decade. For instance, the 1993 Japanese Ministry criteria recommend screening with low-sensitivity cardiac imaging such as gallium-67, thallium-201 or technetium-99m myocardial scintigraphy, or abnormal accumulation by gallium-67. With the emergence of CMR and cardiac PET-CT, these older modalities have largely been replaced. **Table 2** compares the various imaging modalities used in evaluating for CS.

CMR has become a cornerstone for establishing the diagnosis of CS. This test is now readily available at most tertiary care centers, is low-risk and highly sensitive. CMR should be considered when pretest probability is high, based on a patient with established systemic sarcoidosis. CMR can often differentiate CS from other disease processes, such as ischemic heart disease and arrhythmogenic right ventricular dysplasia (ARVD). However, the pattern of ARVD and CS can overlap in some cases and a tissue biopsy may be necessary to differentiate between the two. When compared to older imaging modalities, as recommended in the 1993 guidelines from the Japanese Ministry of Health and Welfare, CMR was more than twice as sensitive for the detection of CS in patients with biopsy-proven pulmonary sarcoidosis. In this study, CMR findings of late gadolinium enhancement were detected in 33% of patients, which more closely matches the percentage found in autopsy series. Because of the superiority of CMR for detecting CS it has now been included in the most recent screening recommendations from the Japanese Ministry of Health (2006).

The appearance of CS on CMR depends upon the stage of the disease. The acute inflammatory and potentially reversible stage of CS is associated with myocardial thickening and increased signal intensity on T2-weighted images, indicating the presence of edema. Technical limitations including myocardial motion artifacts have limited the sensitivity and the widespread use of T2-weighted imaging, and T2 mapping is increasingly used...
as a more reliable and sensitive method for detecting myocardial edema in these patients. The chronic stage of CS is characterized by focal areas of scar formation, myocardial thinning, and left ventricular dysfunction, and is best detected with delayed gadolinium enhancement (DGE). The DGE pattern can be linear or nodular and, in contrast to ischemic disease, is often mid-myocardial or subepicardial. In patients with sarcoidosis, the presence of DGE on CMR was associated with an 11-fold higher rate of cardiac death compared with those without evidence of disease. On average, DGE abnormalities were restricted to only 6% of the myocardium in this study, demonstrating that even a small amount of cardiac involvement may have prognostic significance.

PET-CT using 18-FDG is also useful in assessing organ involvement in patients with sarcoidosis, and may provide complementary information. Macrophage-dense regions, such as active CS, have high metabolic activity as reflected by increased myocardial FDG uptake on PET-CT.

### Table 2:

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity/specificity</th>
<th>Findings</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Endomyocardial biopsy</td>
<td>Low/high</td>
<td>Non-caseating granulomas</td>
<td>Rarely necessary with known extracardiac sarcoidosis. Low sensitivity from patchy involvement limits use. Image guided techniques improve the yield.</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Low to intermediate/intermediate</td>
<td>AV block, IVCD/BBB, PVCs, sinus tachycardia, pseudoinfarct pattern, LVH.</td>
<td>Useful as a screening tool in patients with extracardiac sarcoidosis.</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Low–intermediate/intermediate</td>
<td>LV or RV dysfunction, abnormalities in wall thickness, Mitral regurgitation, aneurysms, pericardial effusion, pulmonary hypertension.</td>
<td>Low sensitivity as sole imaging modality. Widely available, safe, and relatively low cost. Prognostic information via ejection fraction. Can monitor EF over time.</td>
</tr>
<tr>
<td>Myocardial perfusion imaging (thallium-201 and 99 sestamibi)</td>
<td>Low–intermediate/intermediate</td>
<td>Segmental areas of perfusion defects not in a typical coronary distribution. The defects are better on stress than rest (reverse redistribution).</td>
<td>Low sensitivity limits use as a screening tool. Widely available. Can be used to follow treatment response. Low sensitivity and exposure to radiation significantly limits use. When positive usually indicates active inflammation that is responsive to therapy. Can be used in conjunction with myocardial perfusion imaging.</td>
</tr>
<tr>
<td>Gallium-67</td>
<td>Low/high</td>
<td>Myocardial gallium uptake.</td>
<td></td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td>High/intermediate-high</td>
<td>Increased signal intensity on T2-weighted image indicates edema. Delayed gadolinium enhancement in areas consistent with known sarcoid pattern of cardiac involvement.</td>
<td>Test of choice for diagnosing CS. No exposure to radiation. Has prognostic implications. Correlates with disease activity. Cannot be done in patients with ICDs or PPM limiting its use in following patients over time.</td>
</tr>
<tr>
<td>Cardiac PET</td>
<td>High/intermediate</td>
<td>Focal or focal on diffuse myocardial FDG uptake.</td>
<td>Test of choice for diagnosing CS. Simultaneous assessment for myocardial perfusion defects increases specificity. Can be done in patients with implanted cardiac devices. Useful in monitoring treatment response.</td>
</tr>
</tbody>
</table>

AV: atrial-ventricular; BBB: bundle branch block; CS: cardiac sarcoid; EF: ejection fraction; FDG: fluorodeoxyglucose; ICD: implantable cardioverter-defibrillators; IVCD: intraventricular conduction delay; LV: left ventricular; LVH: left ventricular hypertrophy; MRI: magnetic resonance imaging; NSVT: non-sustained ventricular tachycardia; PET: positron emission tomography; PPM: permanent pacemaker; PVCs: premature ventricular contractions; RV: right ventricular.
PET-CT. Thus, enhanced 18-FDG uptake correlates with the active inflammatory stage of CS. In a meta-analysis by Youssef et al. PET-CT was estimated to have a sensitivity of 89% and specificity of 78% for the detection of CS. It is felt that PET scanning is at least as sensitive as CMR for detection of CS but may be less specific. Matching FDG uptake with myocardial perfusion imaging improves specificity by differentiating scar from active inflammation. The main advantage of PET-CT over CMR is that PET scanning can be performed in patients with implanted cardiac devices.

PET-CT scan is useful for predicting the likelihood of adverse events. In a recent series of CS patients in whom ICDs had been placed, 11 of 26 (42%) of patients with a positive PET scan had VT over the course of the study compared to 2/7 (28%) in those with a negative PET scan. This relationship was even more robust in CS patients with preserved left ventricular function; wherein four of seven (57%) patients with an EF >35% and a positive cardiac PET scan received appropriate ICD therapy for VT. Although the findings were not statistically significant, this study and other related ones suggest that active inflammation, as reflected by increased 18-FDG uptake, is a risk factor for VT.

Since PET-CT scanning detects the active inflammatory stage of the disease, it has proven useful in both monitoring and predicting response to immunosuppressive therapy. While perfusion defects on nuclear imaging or DGE on CMR often change only minimally with treatment, FDG uptake can improve dramatically with immunosuppressive therapy. PET-CT also has the advantage over CMR of evaluating the extent of systemic disease. The disadvantage to PET imaging relative to CMR is the exposure to radiation, lower spatial (anatomical) resolution, and the lack of standardization of protocols for CS detection. With regard to the last one, it is essential to tightly control glucose metabolism, particularly insulin levels, to avoid non-specific myocardial uptake on PET-CT.

The choice between CMR and cardiac PET-CT is influenced by the technical expertise of the medical center and patient-related variables. The tests are complimentary and obtaining both studies in single a patient, while expensive, can increase the detection rate of CS. In patients with suspected CS based upon preliminary screening, and provided the facility has adequate experience and the patient has no contraindications, CMR is the initial test of choice as it provides more information (e.g., edema, fibrosis, anatomical detail, left ventricular function) and is better for distinguishing CS from other cardiac diseases. Although the role of PET-CT remains to be defined, it is reasonable to postulate that PET-CT may be more sensitive for the detection of inflammation in the context of early-stage CS, and this imaging modality is preferred in a patient with an ICD or with other contraindications to MRI.

**Role of endomyocardial biopsy**

Myocardial sarcoid involvement is patchy, often involving the left ventricle or the basal septum and sparing the endocardium. This typical pattern of involvement explains the low diagnostic yield (~20%) of a standard right ventricular endocardial biopsy in the setting of CS. With the emergence of advanced cardiac imaging, including CMR and cardiac PET-CT, patients with biopsy-proven extracardiac sarcoidosis rarely require an endomyocardial biopsy to establish a presumptive diagnosis of CS. In some cases, including isolated CS (discussed in detail below), cardiac biopsy can yield the appropriate diagnosis.
cardiac biopsy is contemplated, image-guided techniques can dramatically improve the yield. In some cases a tissue diagnosis of sarcoid is not possible and in these cases an empiric trial of steroid therapy with clinical improvement is felt to be highly suggestive of CS. Based upon the currently available published data, as outlined in this section, a proposed algorithm for screening patients with an established diagnosis of extracardiac sarcoidosis for cardiac involvement is shown in Figure 5.

### Diagnosis of isolated cardiac sarcoidosis

While isolated CS is relatively rare, there are certain clinical features that should raise suspicion of this disease variant. Patients with isolated CS tend to be younger (25–55 years old) and often present with unexplained high-grade AV block, VT, or CHF. In these patients a search for sarcoidosis should be undertaken as conventional antiarhythmic and CHF treatments may be ineffective. Given the propensity for sarcoidosis to involve the respiratory system and mediastinum, screening with chest imaging (CXR, and/or chest CT) is indicated. Likewise, a routine ophthalmological examination may reveal characteristic findings. In view of the potential side-effects of immune-modulating therapies, every effort should be undertaken to obtain diagnostic tissue from an extracardiac source prior to the initiation of treatment for presumed CS. When extracardiac sarcoidosis is not evident but suspicion for CS remains high, further investigation with advanced cardiac imaging (CMR and/or cardiac PET-CT) is indicated, looking for characteristic patterns, as described above. A cardiac biopsy may be necessary if diagnosis remains in doubt after all other measures have been undertaken to detect CS. A recommended algorithm for the diagnosis of isolated CS is provided in Figure 6.

### Treatment

The primary difference when treating patients with CS compared to most other cardiac conditions is that these patients usually require immunosuppressive therapy in addition to standard medical and device therapy. The cornerstone for immunosuppressive therapy is corticosteroid treatment; however, steroid-sparing agents are also commonly co-administered to reduce side-effects. Cardiac device therapy has evolved over time such that many more patients are now receiving ICDs for primary
prevention of sudden death, and CS patients often receive ICD therapy in favor of standard pacemaker therapy when high-grade AV block is present. Given that most patients with CS also have systemic involvement, including other vital organs, a team approach, including cardiologists, electrophysiologists, and those experienced with the management of extracardiac sarcoidosis (e.g., subspecialized pulmonologists or rheumatologists), is recommended for the treatment of these complex patients. Unfortunately, the lack of consensus among sarcoid experts that was highlighted in the diagnosis section also applies to the treatment and risk stratification of these patients. The following sections will summarize the major considerations for treating patients with CS.

**Corticosteroids**

Corticosteroids are the mainstay of immunosuppressive therapy in patients with CS. The data supporting steroid use are derived almost exclusively from retrospective trials. Consensus relating to the optimal dose and duration of therapy have not been established; however, no significant difference in outcomes was observed when comparing high- (>30 mg prednisone daily) and low-dose (<30 mg prednisone daily) steroid therapy. As expected, immunosuppressant therapy is most beneficial when initiated during the early inflammatory phase of the disease and is less efficacious once extensive fibrosis has developed. Steroids appear to prevent adverse ventricular remodeling in CS patients with preserved ventricular function, and can modestly improve the EFs in those with mild to moderate...
ventricular dysfunction.\textsuperscript{37} Likewise, steroids are protective in terms of reducing the incidence of refractory atrial and ventricular arrhythmias.\textsuperscript{38,39,13} The predictors of response to corticosteroid therapy in patients with sustained ventricular arrhythmias include preserved EF ($\geq$30\%) and evidence of active inflammation on cardiac imaging.\textsuperscript{38} As such, a trial of corticosteroid therapy is indicated in most patients with newly diagnosed CS. That being said, there have been no good prospective trials demonstrating that immunosuppressive therapy reduces the risk of sudden cardiac death or reduces the rate of ICD therapy in patients with devices.\textsuperscript{18} Thus, while steroids may suppress malignant ventricular arrhythmias or partially reverse high-grade AV block in some patients, they cannot be relied upon as the sole therapy and cardiac device therapy is recommended in nearly all of these patients.\textsuperscript{39}

**Steroid-sparing agents**

Steroid-sparing agents, such as methotrexate, azathioprine, cyclophosphamide, or hydroxychloroquine, are frequently used to treat CS. Steroid-sparing agents are typically employed in patients failing to respond to steroid therapy alone and in those with intolerance or contraindications to their use. Given the high risk of developing serious complications from chronic exposure to even moderate doses of corticosteroids (e.g., $>10$ mg of prednisone per day), it is logical to consider a steroid sparing agent to minimize the risk of potentially life-altering steroid-related complications. Methotrexate is the steroid-sparing agent with which the experience is greatest; however, some cases of CS are refractory to steroids and methotrexate and may require alternative treatment approaches, such as anti-tumor necrosis factor (TNF)-\textsubscript{x} therapy.\textsuperscript{40} Further studies are needed to determine if the efficacy of steroid-sparing agents are similar to that of corticosteroids alone for the treatment of CS and to better define the role of other immune-modulating agents.

**Monitoring therapy**

Unfortunately, specific guidelines for monitoring the response to immunosuppressive therapy in patients with CS are currently lacking. Recognizing the potentially life-threatening implications of undertreatment, initial therapy with high-dose oral steroid therapy (e.g., prednisone 1 mg/kg/day) is recommended followed by a slow tapering of the dose over a period of 6 months while closely monitoring the clinical response. Measurements of the therapeutic response include clinical symptoms, objective measures of arrhythmia burden (ECG, Holter monitor, implantable loop monitor, ICD interrogation), left ventricular and right ventricular function (echocardiogram), resolution of edema (CMR), or decreased metabolic activity (PET-CT). If the decision is made to stop immunosuppressive therapy, the patient should be reassessed frequently for disease reactivation, and treatment should be reinitiated at the first sign of clinical deterioration.

**Cardiac device therapy and electrophysiology testing**

The American College of Cardiology/American Heart Association guidelines list CS as a class IIa (level of evidence C) indication for ICD implantation for primary prevention of sudden death.\textsuperscript{41} Unfortunately no further guidance is available regarding risk stratification of CS patients. Given that up to 30\% of sarcoidosis patients have cardiac involvement, the routine placement of an ICD is impractical and is difficult to justify based upon the frequency of SCD in certain low-risk patients. Two recent retrospective studies of CS patients—with ICDs implanted for both primary and secondary prevention of sudden death—reported fairly consistent findings. The larger of these series was a multicenter evaluation of 112 CS patients with an implanted ICD, 83 of which were implanted for primary and 29 for secondary prevention of sudden death.\textsuperscript{42} Appropriate ICD therapy for ventricular arrhythmias occurred in 36 patients (32.1\%) over a mean follow-up of 29 months. The overall annualized appropriate ICD therapy rate for the entire group was $13.2\%/year$; $10.7\%/year$ for the primary and $21\%/year$ for the secondary prevention group. The multivariate adjusted predictors of appropriate therapy for both groups were the presence of either right or left ventricular dysfunction. In the primary prevention group, no patient with both normal right and left ventricular function received appropriate ICD therapy. In a separate single-center study involving 45 CS patients with an implanted ICD (29 for primary and 16 for secondary prevention), the appropriate ICD therapy rate for ventricular arrhythmias was $13\%/year$.\textsuperscript{18} The predictors of appropriate ICD therapy were left ventricular systolic dysfunction, the presence of CHB and a longer follow-up time. In this study the mean LVEF in the group with appropriate ICD therapies was $35.5\%$; however, seven (42\%) patients who received appropriate therapy had an EF greater than 35\%. These results indicate that employing the usual LVEF cut-off of 35\% for determining the indication for primary prevention ICD implantation, as is done for patients with either ischemic or non-ischemic cardiomyopathies, is inappropriate in this disease process. An important finding in this series was that patients with CHB were at increased risk for appropriate ICD therapies. This finding calls into question the use of standard pacemaker therapy for treating AV block in CS patients, and indicates that an ICD with appropriate pacing therapy is the preferred approach. These retrospective studies demonstrated that patients with CS who had an ICD implanted for primary prevention had a rate of appropriate ICD therapy that is roughly twofold greater than that reported in the Sudden Cardiac Death in Heart Failure Trial primary prevention ICD trial where the rate of appropriate ICD therapy was $5.1\%$ per year.\textsuperscript{43} Based on the high incidence of appropriate ICD therapies in these studies, the question of whether we are underutilizing ICD therapy in this population is raised. It should be noted up to 15\% of patients with ICDs suffered a device-related complication, demonstrating
that device therapy itself is not benign in these patients.\textsuperscript{18} In patients with normal right and left ventricular function and without a history of significant VT or high-grade AV block, the risk of SCD, at least over the short term, appears to be small, and ICD therapy may not be indicated. In patients with CS and no history of sustained ventricular arrhythmias or lacking the other high-risk features just listed, EP testing has been reported to be useful for risk stratification and may help guide the decision regarding ICD implantation.

There are multiple reports from a single center relating to the use of EP testing for risk stratification of CS patients.\textsuperscript{15,16,44} In one of their earlier reports, a retrospective study of 32 CS patients published in 2005, EP testing was used to determine the need for ICD implantation.\textsuperscript{16} In that study, all 12 patients that had either spontaneous (6) or inducible (6) sustained VT underwent ICD implantation. The mean EF in this ICD group was $33 \pm 17\%$. Four of the six (67\%) inducible and five of the six (83\%) spontaneous VT patients received appropriate ICD therapies. This compares to only two of 20 (10\%) who had a negative EP study and did not receive an ICD but developed either sustained VT or sudden death during follow-up. In this study the negative EP group had a mean EF of $34 \pm 21\%$. So although this report indicates that EP testing is good at predicting which CS patients are at highest risk for developing sustained ventricular arrhythmias, the negative predicitive value of EP testing in patients with left ventricular dysfunction appears inadequate to guide ICD implantation. A subsequent follow-up study from the same center reported on 67 patients with biopsy-proven sarcoid without cardiac symptoms but with evidence of cardiac involvement based on CMR or PET scanning who underwent EP testing.\textsuperscript{44} The EP study was positive for inducible VT in eight (11\%) patients, all of whom underwent ICD implantation. Compared to patients with a negative EP study the positive EP study patients had a lower mean EF ($36 \pm 4$ versus $56 \pm 2\%$) and greater risk of death or spontaneous VT over a 5-year follow-up (6 of 8 versus 1 of 59). This study indicates that patients with a negative EP study for VT and preserved cardiac function are at low risk for sustained VT or sudden death over at a moderate-term follow-up. It remains unclear from these studies what additional prognostic value EP testing adds in CS patients with preserved left ventricular function and no other high-risk markers. Another study from this same group reported that asymptomatic patients with preserved cardiac function incidentally found to have abnormalities CMR or PET scanning were at low risk of developing malignant arrhythmias over the short term.\textsuperscript{15}

In summary ICD implantation is clearly indicated in patients with CS presenting with spontaneous sustained ventricular arrhythmias or significant left ventricular dysfunction (EF <35\%). ICD implantation should also be strongly considered in patients with CS with mild left ventricular dysfunction (EF 35–50\%), evidence of right ventricular dysfunction or high-grade AV block. CS patients presenting with syncope concerning for a ventricular arrhythmia by history, should also be highly considered for an ICD. A more difficult decision is whether to implant an ICD in a patient with asymptomatic CS detected only by CMR or PET imaging and in the absence of the previously described high-risk features. EP testing may be useful in this low- to intermediate-risk subgroup, but further investigation is needed to confirm this. Given the unpredictable and progressive nature of the disease process, if it is decided not to place an ICD in a patient with CS, close follow-up is recommended to screen for the development of any high-risk features.

A proposed algorithm for treatment and risk stratification of CS patients is shown in Figure 7.

### Refractory arrhythmias

For patients presenting in the later stages of the disease, when myocardial scarring is more established, traditional antiarrhythmic therapy is usually the treatment of choice for recurrent ventricular arrhythmias. Patients with recurrent ventricular arrhythmias, evidence of active inflammation, and relatively preserved ventricular function (EF >30\%) are likely to respond to immunosuppressive therapy for arrhythmia control.\textsuperscript{45} In patients with VT refractory to medical therapy, catheter ablation can be effective.\textsuperscript{46} Given the diffuse nature of the disease, EP mapping of both the endocardial and epicardial surfaces of the right and left ventricle may be required to localize the circuit. Owing to the predilection of sarcoidosis for the basal septum, it is not surprising that the VT circuit is frequently localized to the tricuspid annulus.\textsuperscript{24}

### Cardiac transplantation

In CS associated with refractory heart failure or VT, cardiac transplantation may be the only treatment option. Sarcoidosis should not be a contraindication for transplantation. While recurrence of sarcoid in the transplanted heart has been described, the incidence is low and the 5-year survival after transplantation for cardiac sarcoidosis is similar to other disease processes.\textsuperscript{47}

### Conclusion

Recent studies indicate that the prevalence of sarcoidosis and the risk of mortality relating to cardiac involvement have been on the rise over the past several decades.\textsuperscript{2,6} With the emergence of advanced cardiac imaging, CS is being diagnosed earlier and more frequently than before. This leaves the clinician with the dilemma of risk stratifying these patients to provide the appropriate therapy. These difficult decisions are further complicated by the progressive and unpredictable nature of the disease process. The lack of prospective data relating to the natural history and effects of treatment leave us with many unanswered questions relating to the care of CS. Given the complexity and multisystem nature of the disease we feel that a systematic multidisciplinary team approach, including
strong imaging and electrophysiological capabilities, is required for the optimal care of these patients.

References


