Introduction
In 1875, Jonathan Hutchinson published a case of an odd disease that he “believed, had hitherto escaped special recognition.” In retrospect, this likely represented the first published case of sarcoidosis. However, Hutchinson would have to await his 1898 publication of a case of cutaneous sarcoidosis (famously dubbed Mortimer’s Malady after the afflicted patient)1 and similar reports by Ernest Besnier and Caesar Boeck2 before the medical community began to acknowledge the presence of this singularly challenging disease.

While our understanding of sarcoidosis has certainly expanded since Dr. Hutchinson’s time, much about this disease remains unknown. There exist many excellent, comprehensive reviews of sarcoidosis as a multisystemic disease.3,4 However, given the oft dire consequences of cardiac involvement with sarcoidosis and the rapid acceleration of cardiac imaging technology, we feel that a review encompassing this topic will be valuable and timely. In this focused review, we provide a brief discussion of the epidemiology and clinical presentation of cardiac sarcoidosis followed by a discussion of imaging modalities employed in its assessment and therapeutic approaches.

Supplement: structural heart disease: research and practice in coronary, structural, adult congenital and peripheral vascular cardiology

Cardiac Sarcoidosis: Clinical Manifestations, Imaging Characteristics, and Therapeutic Approach

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ABSTRACT: Sarcoidosis is a multi-system disease pathologically characterized by the accumulation of T-lymphocytes and mononuclear phagocytes into the sine qua non pathologic structure of the noncaseating granuloma. Cardiac involvement remains a key source of morbidity and mortality in sarcoidosis. Definitive diagnosis of cardiac sarcoidosis, particularly early enough in the disease course to provide maximal therapeutic impact, has proven a particularly difficult challenge. However, major advancements in imaging techniques have been made in the last decade. Advancements in imaging modalities including echocardiography, nuclear spectroscopy, positron emission tomography, and magnetic resonance imaging all have improved our ability to diagnose cardiac sarcoidosis, and in many cases to provide a more accurate prognosis and thus targeted therapy. Likewise, therapy for cardiac sarcoidosis is beginning to advance past a “steroids-only” approach, as novel immunosuppressant agents provide effective steroid-sparing options. The following focused review will provide a brief discussion of the epidemiology and clinical presentation of cardiac sarcoidosis followed by a discussion of up-to-date imaging modalities employed in its assessment and therapeutic approaches.

KEYWORDS: cardiac sarcoidosis, cardiac imaging, cardiac MRI

SUPPLEMENT: Structural Heart Disease: Research and Practice in Coronary, Structural, Adult Congenital and Peripheral Vascular Cardiology

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Clinical Presentation and Diagnostic Criteria
Sarcoidosis is a chronic multisystem disorder of unknown etiology. It is universally characterized by the accumulation of T-lymphocytes and mononuclear phagocytes into the sine qua non of the disease — the noncaseating granuloma.

There exist many excellent, comprehensive reviews of sarcoidosis as a multisystemic disease. However, given the oft dire consequences of cardiac involvement with sarcoidosis and the rapid acceleration of cardiac imaging technology, we feel that a review encompassing this topic will be valuable and timely. In this focused review, we provide a brief discussion of the epidemiology and clinical presentation of cardiac sarcoidosis followed by a discussion of imaging modalities employed in its assessment and therapeutic approaches.
non pathologic structure of the noncaseating granuloma.\textsuperscript{3,5} Other organ systems may be involved, though those most commonly affected include the lung, lymph nodes, skin, eye, and the central nervous system. Given the multisystem nature of the disease, its systemic presentations are myriad. Even the cardiac manifestations of the disease vary widely from patient to patient. Most common cardiac presentations can be divided into arrhythmic, cardiomyopathic, and pericardial groups (Table 1).\textsuperscript{3–8} Other rarely reported manifestations include direct granulomatous involvement of any of the four cardiac valves,\textsuperscript{9} coronary artery granulomatous disease causing myocardial ischemia,\textsuperscript{10} constrictive pericarditis,\textsuperscript{11} and intracardiac masses. Of note, the presence of cardiomyopathy with left ventricular ejection fraction (LVEF) <50% and clinical heart failure carries a particularly poor prognosis.\textsuperscript{12,13}

Given the multifaceted clinical manifestations of this disease, diagnosis is challenging. In 2006, the Japanese Ministry of Health and Welfare established guidelines for diagnosis based on either histology or clinical characteristics (Table 2).\textsuperscript{14} While useful, these guidelines are not universally accepted and are often maligned as lacking specificity and sensitivity while also failing to account for advances in diagnostic techniques.\textsuperscript{15,16}

### Epidemiology

The annual incidence of sarcoidosis in the United States is 10.9 per 100,000 in whites and 35.5 per 100,000 in African Americans.\textsuperscript{17} Women between the ages of 20 and 40 carry the highest incidence of systemic sarcoidosis, though myocardial involvement seems to carry no gender predilection. Based on autopsy studies, 20–30% of all patients with sarcoidosis have pathologic cardiac involvement, though only approximately 3–5% of all sarcoid patients will have clinically evident cardiac involvement.\textsuperscript{18} It is thus likely that many cases of CS go clinically unrecognized. This is not without prognostic implications – cardiac involvement accounts for as much as 25% of all deaths from sarcoidosis in the United States and as much as 85% of deaths in Japanese patients with sarcoidosis (where CS has an unusually high incidence, up to 58% of all sarcoid patients in Japan have cardiac involvement).\textsuperscript{19}

### Imaging

**Echocardiography.** Echocardiographic abnormalities are reported in 24–77% of CS patients.\textsuperscript{13,16,20} While echocardiographic findings are often nonspecific (dilated cardiomyopathy, mild wall thickening, diastolic dysfunction, pericardial effusions, ventricular aneurysms), the presence of abnormalities in a patient with known extracardiac sarcoidosis should strongly suggest CS. Even subtle abnormalities in diastolic flow patterns in a patient with extracardiac sarcoidosis should prompt further investigation. One study found that 14% of patients with pulmonary sarcoidosis (and no known cardiac involvement) had diastolic dysfunction ultimately attributed to CS.\textsuperscript{21} The same small series suggested that the most common echocardiographic pattern of diastolic dysfunction seen in early CS (prolonged isovolumic relaxation time and reversed E:A Doppler ratio) points toward an abnormality of left ventricular (LV) active relaxation rather than merely diminished compliance, and that diastolic dysfunction often precedes any systolic impairment.\textsuperscript{21} Some more specific findings include focal thinning of the basal anterior septum (Fig. 1), regional wall motion abnormalities not in a coronary artery distribution, or a focal intracardiac mass (caused by a large granuloma).

While the presence of the above-noted echocardiographic abnormalities (prolonged isovolumic relaxation time and reversed E:A Doppler ratio) is diagnostically and prognostically important if seen in a patient with known extracardiac sarcoidosis, they lack both specificity and sensitivity to accurately diagnose early cardiac involvement when therapy holds the greatest benefit. Recently, cyclic variation of integrated backscatter has been used to evaluate the acoustic properties of the myocardium and detect CS.\textsuperscript{23} Impaired longitudinal strain and strain rate have also been reported as valuable diagnostic clues to the early diagnosis of CS.\textsuperscript{24–26} Despite these advances, no single echocardiographic abnormality is specific enough to diagnose CS – further diagnostic studies are invariably required.

**Radionuclide studies.** Resting perfusion scintigraphy employing either thallium-201 (\textsuperscript{201}Tl) or technetium-99 m (\textsuperscript{99m}Tc) may show areas of decreased uptake in patients with CS\textsuperscript{27} (Fig. 2). Fibrogranulomatous replacement,\textsuperscript{28} regional metabolic abnormalities,\textsuperscript{29} or microvascular vasoconstriction\textsuperscript{30} may all play a role in these defects. CS may demonstrate the property of reverse perfusion – defects related to CS often improve with exercise or vasodilator infusion.\textsuperscript{27,31} In one study of 13 patients, the degree of reverse perfusion was correlated with the degree of clinical and imaging improvement after

| **Table 1. Clinical Manifestations of Cardiac Sarcoidosis.** |
|-----------------|-----------------|
| **Arrhythmias** | **REPORTED PREVALENCE** |
| AV block | 26–62% |
| Bundle Branch Block | 12–61% |
| Supraventricular Tachycardia | 0–15% |
| Ventricular Tachycardia | 2–42% |
| Sudden Cardiac Death | 12–65% |
| **Cardiomyopathy** | **10–30%** |
| Congestive heart failure - Left ventricular systolic failure | |
| Heart failure with preserved ejection fraction or restrictive disease | |
| Right ventricular failure secondary to pulmonary disease | |
| **Pericardial** | **20%** |
| Pericardial effusion detected by echo (common) | |
| Pericarditis (rare) | |
Cardiac sarcoidosis

The sensitivity with 99mTc appears superior to 201Tl (65% vs 46% in one direct comparison study). Both appear quite specific, with one study reporting 100% specificity when comparing 99mTc radionuclide studies with the earlier Japanese Ministry of Health and Welfare guidelines from 1993.

Gallium-67 (67Ga) accumulates in areas of active inflammation, and thus, has been employed in the detection of CS. However, as noted above, many areas of cardiac involvement are free of inflammation and consist only of fibrogranulomatous scar (which will not be detected by 67Ga). The sensitivity of 67Ga scintigraphy is thus lower than other radionuclides – estimated at 18–50%.

Also, uptake from near the heart (mediastinal lymph nodes or lung) is sometimes problematic. In a study of 25 patients with CS, active 67Ga uptake was more common in patients with ventricular tachyarrhythmias. Similar findings have been described for atrioventricular (AV) block. Recently, cardiac MRI and PET imaging techniques have replaced radionuclide studies because of their superior diagnostic performance.

**Positron emission tomography.** Inflammatory cells demonstrate increased metabolic requirements and glucose uptakes. PET scanning using 18F-fluorodeoxyglucose (FDG) takes advantage of this property to detect areas of active myocardial inflammation in cases of CS (Fig. 3). Simultaneous perfusion stress imaging is often conducted to exclude

### Table 2. Guidelines for CS according to the Japanese Ministry of Health and Welfare, 2006.

| DIAGNOSTIC CATEGORY | CRITERIA | COMMENTS |
|----------------------|----------|----------|
| **Histologic Diagnosis Group** | Endomyocardial biopsy demonstrates noncaseatingepithelioid cell granulomata with histological or clinical diagnosis of extracardiac sarcoidosis | |
| **Clinical Diagnosis Group** | • Negative endomyocardial biopsy | |
| | • Presence of histologic or clinical extracardiac sarcoid | |
| **Major Clinical Criteria** | Advanced atrioventricular block | • Unclear what constitutes “advanced” (II? III?) or if paroxysmal block is included. |
| | • First degree block also commonly seen in CS** | |
| | Basal thinning of the interventricular septum | • Imaging modality not specified (Echo? MR? Nuclear imaging?) |
| | • Specific thickness not specified (11 mm? 12 mm?) | |
| | Positive cardiac gallium uptake | • Not used commonly – now routinely replaced by PET |
| | Depressed left ventricular ejection fraction (<50%) | • Modality not specified |
| **Minor Clinical Criteria** | Abnormal ECG findings | • Atrial arrhythmias (sinus tachycardia or sinus exit block) commonly seen in CS excluded |
| | • Ventricular arrhythmias | • Abnormal repolarization excluded |
| | • Right bundle branch block | |
| | • Axis deviation | |
| | • Abnormal Q-wave | |
| | Abnormal echocardiography | • Valvular abnormalities excluded |
| | • Regional wall motion abnormalities | • Pericardial abnormalities excluded |
| | • Morphologic abnormality | |
| | Nuclear perfusion defect detected | • Reverse perfusion pattern (commonly seen) excluded |
| | Delayed gadolinium enhancement noted on cardiac MRI | • Localization and early enhancement not mentioned |
| | Endomyocardial biopsy showing interstitial fibrosis or monocyte infiltration over moderate grade | • “Moderate grade” not defined |

**Notes:** *Requires two or more major criteria, or one major criterion and two or more minor criteria. **CS = cardiac sarcoidosis.

![Figure 1. Echocardiogram, parasternal long axis view, of a 33-year-old patient with CS. Note the thinned, notched aneurysmal segment in the basal anteroseptal wall (red arrow).](image-url)
significant coronary artery disease. Studies have shown that 18F-FDG PET is superior to 201Th, 99mTc, and gallium scanning in detecting early stages of cardiac involvement. In several small studies, PET has been found to have an excellent sensitivity (82–100%), though it carries a highly variable specificity (39–91%) when compared to the 2006 Japanese Ministry criteria. The high variation in specificity may be related to the poor performance of the Japanese Ministry criteria as a gold standard. Small case series also support the notion that an improvement (reduction) in 18F-FDG uptake on PET scanning after therapy is correlated with a clinical improvement.

Cardiac magnetic resonance imaging. Given its high spatial resolution and excellent performance characteristics, cardiac magnetic resonance imaging (CMR) with gadolinium enhancement is increasingly being shown to be the technique of choice for the evaluation of CS. It is capable of demonstrating both active inflammation and areas of myocardial scar. Acute myocardial inflammation is evidenced by increased signal intensity on T2-weighted images representing edema (most commonly used) and early gadolinium-enhanced images (used rarely). Late gadolinium enhancement representing fibrogranulomatous scarring is often found in the midmyocardium and epicardium (as opposed to the endocardial predomiance seen in ischemic disease), and shows a predilection for the basal and lateral segments of the left ventricle and the papillary muscles. Patchy, discrete lesions in a noncoronary distribution are particularly suggestive of CS in the appropriate clinical context. Given the high spatial resolution of CMR, areas of inflammation on T2-weighted imaging or either early or delayed gadolinium enhancement can be targeted for future endomyocardial biopsy if tissue diagnosis is required. Similar to PET, improvement in gadolinium-enhanced and T2-weighted inflammation using CMR on post-therapy imaging studies is associated with clinical improvement.

CMR readily outperforms radionuclide imaging in terms of sensitivity. In small case series, CMR provided a similar sensitivity for detection of CS when compared to PET, with a highly improved specificity. In fact, it may be that CMR functions as a superior gold standard to the revised Japanese Ministry criteria. In a cohort of 81 patients with extracardiac sarcoidosis, Patel et al found that 26% were diagnosed with CS by CMR, while only 12% fulfilled 1993 Ministry criteria. Likewise, Cheong et al showed that in a cohort of 31 patients with systemic sarcoidosis, 8 patients had late gadolinium enhancement on CMR but none met guideline criteria for CS diagnosis employing the more recent (2006) guidelines. It is likely that a future iteration of diagnostic criteria for CS will rely heavily on CMR findings.

Therapy

Corticosteroids. As noted above, cardiac involvement with sarcoidosis carries a poor prognosis if untreated and warrants immediate initiation or escalation of immunosuppressive therapy at the time of diagnosis. Despite a paucity of randomized controlled trial data, it is widely accepted that initial therapy of CS should consist of systemic corticosteroids at moderate to high doses. Small cohort studies suggest that an initial dose of at least 30 mg/day (and some authors suggest a starting dose of 1 mg/kg/day) of oral prednisone for two to three months with a gradual tapering over the course of a year to a minimum maintenance dose of 10–20 mg every other day results in clinical improvement and reduction in negative ventricular remodeling and the risk of ventricular arrhythmia or heart block. The initial dose remains controversial; however, a retrospective analysis failed to show any difference in clinical outcome between low-dose (<30 mg/day) and
high-dose (>40 mg/day) regimens. Some authors advocate starting with a low-dose strategy (30 mg/day) with close clinical and imaging follow-up. Regardless of starting dose, it is clear that steroids are effective in altering the clinical course of CS. Yazaki et al found that 75 patients treated with steroids had a significantly better five-year survival compared with untreated patients (75% vs 10%).

Historically, corticosteroid therapy was reserved for CS patients with LVEF <50%, advanced AV block, or ventricular tachyarrhythmias. However, this approach may lead to a harmful delay in therapy. Several retrospective cohort analyses have suggested that corticosteroid therapy holds the most benefit for patients who do not yet have severe LV dysfunction and patients with signs of active inflammation on imaging (edema on T2-weighted CMR or positive ⁶⁷Ga scans). Early detection and treatment of CS improves clinical outcomes; once patients progress to the burned out or fibrogranulomatous scarred phase of the disease, immunosuppressant therapy has little ability to alter the dire course of this disease. These findings argue for early and aggressive therapy with corticosteroids in patients with signs of CS and active inflammation, even in the absence of LV dysfunction or high-grade arrhythmias.

Finally, it is not uncommon for CS symptoms and signs to recur during a taper of steroids. If this occurs, experts recommend an immediate return to the initial dose (often 1 mg/kg/day of oral prednisone) until symptoms are again controlled.

Steroid-sparing immunosuppressant agents. Long-term therapy with corticosteroids is, of course, rife with side effects, making the use of steroid-sparing agents attractive. Also, CS patients may demonstrate clinical manifestations, such as worsening arrhythmias or myocardial inflammation, by imaging that are refractory to steroid therapy. Several other immunosuppressant agents have been used with varying reports of success; none have been tested in clinical trials. Cyclophosphamide, methotrexate, mycophenolate mofetil, and cyclosporine have all been reported in the treatment of CS, however, with little evidence-based data on efficacy and superiority to date. Given the relatively prolonged onset of action of these medications, however, it is recommended to start therapy while continuing concomitant steroids with eventual weaning of steroids as sparing agents demonstrate efficacy in symptom abatement.

Recently, the pathophysiological importance of tumor necrosis factor-α (TNF-α) in the formation of granulomata has become evident, prompting trials of infliximab (a TNF-α antagonist) in CS with improvement reported in myocardial inflammation by imaging as well as improved clinical outcomes. Infliximab poses a not insignificant risk of infection, and in fact, cases of fatal disseminated cryptococcosis have been reported with the use of infliximab in a CS patient.

The refinement of PET and CMR, and the finding that clinical status tends to correlate with improvement (or lack thereof) in CMR and/or PET imaging provide a powerful modality for assessing the efficacy of these novel immunosuppressant agents. For example, in any given patient, the recrudescence of FDG myocardial uptake on PET or inflammation on T2-weighted CMR after transitioning from corticosteroids to a steroid-sparing agent might prompt escalation of therapy or reintiation of corticosteroids before the occurrence of a dangerous clinical event. Also, improvement in myocardial FDG uptake (PET) or inflammation on T2-weighted MRI may provide a meaningful outcome in future clinical trials of novel immunosuppressant agents.

Traditional heart failure therapies. In the patient with CS with heart failure, pharmacologic therapy should be further directed by standard heart failure guidelines with some notable cautions. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used in patients with CS and reduced LV function. Similarly, it is reasonable to add hydralazine and nitrate therapy to the pharmacologic regimen if in line with the guidelines for a given patient. However, beta-blocker therapy has been associated with precipitation of heart block, and thus, requires a circumspect approach. In the patient with no evidence or history of AV nodal delay, a cautious trial of beta blockade with slow dose up-titration can be attempted. Likewise, antiarrhythmic therapy with amiodarone, often a mainstay of cardiomyopathic patients with significant ventricular or supraventricular arrhythmias, carries a panoply of potential respiratory side effects that may be particularly detrimental to patients with concomitant pulmonary sarcoid disease or right heart failure. When used, amiodarone (and other antiarrhythmic agents) should be only employed in addition to immunosuppressant therapy and/or implantable defibrillator therapy.

The use of implantable cardioverter-defibrillators (ICDs) should follow guideline recommendations for patients with LVEF <35%. For patients with preserved LV function, defibrillator therapy should be considered if they have established or strongly suspected ventricular tachyarrhythmias. Some case series suggest that programmed electrical stimulation (PES) can accurately risk stratify CS patients and predict the benefit of ICD implantation. In a CS patient with LVEF >35% and the absence of confirmed ventricular tachyarrhythmias, it is not unreasonable to perform PES as an arbiter of their need for ICD as primary prevention, particularly in those patients with extensive myocardial involvement on imaging. Radiofrequency ablation has shown only limited success in the prevention of recurrent ventricular tachyarrhythmias in CS. Implantation of a permanent pacemaker should be performed for patients with high-grade AV block.

Conclusion
Cardiac involvement remains a morbid and potentially mortal manifestation of sarcoidosis. Clinicians must maintain a high degree of suspicion for cardiac involvement in patients with extracardiac sarcoidosis and likewise should consider CS in the patient with unexplained ventricular tachyarrhythmias.
high-degree heart block, or cardiomyopathy. Based on its superior sensitivity, specificity, and spatial resolution, CMR should be considered the diagnostic imaging test of choice for CS in those patients who can undergo magnetic resonance imaging and gadolinium administration. 18F-FDG PET remains a highly sensitive, albeit less specific, imaging modality for CS. While other radionuclide tests ($^{201}$Tl, $^{99m}$Tc, and $^{67}$Ga) may fall short of the diagnostic capabilities of CMR and PET, they remain more widely available outside of tertiary referral centers and their utility should not be forgotten. Given the important prognostic and functional information it provides, two-dimensional echocardiography remains a mainstay of imaging modality for CS diagnosis and follow-up assessment. Doppler assessment of strain and strain rate by tissue Doppler sampling has shown early promise in assessing patients for cardiac sarcoid involvement and warrants further investigation.

Despite significant advances in immunosuppressant pharmacotherapy, the backbone of therapy for CS remains systemic corticosteroids. Further study is required comparing regimens of steroid-sparing agents for CS. Ventricular arrhythmias and heart block remain a significant source of morbidity and mortality in CS, and appropriate risk stratification and implantable device consideration are warranted in all CS patients. Ultimately, management of this complex disease is best when orchestrated among a multidisciplinary team of physicians experienced with its manifestations, diagnosis, and therapy at a high-volume specialized center.

Author Contributions

Conceived the concepts: BAH, MM. Analyzed the data: BAH, MM. Wrote the first draft of the manuscript: BAH. Contributed to the writing of the manuscript: BAH, MM. Jointly developed the structure and arguments for the paper: BAH, MM. Made critical revisions and approved final version: MM. Both authors reviewed and approved of the final manuscript.

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Cardiac sarcoidosis

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