Curr Cardiol Rep (2014) 16:514
DOI 10.1007/s11886-014-0514-3

Cardiac Sarcoidosis

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Published online: 27 June 2014

Abstract Cardiac sarcoidosis (CS) is a rare and under-recognized clinical entity that requires a high level of suspicion and low threshold for screening in order to make the diagnosis. CS may manifest in a variety of ways, and its initial presentation can range from asymptomatic electrocardiographic abnormalities to overt heart failure to sudden cardiac death. The aim of this literature review is to provide a comprehensive overview of CS, with an emphasis on clinical manifestations and special diagnostic and management considerations, while highlighting recent studies that have provided new insights into this unique disease.

Keywords Cardiac sarcoidosis · Cardiomyopathy · Heart failure · Atrioventricular block · Arrhythmia · Sudden cardiac death

Introduction

Sarcoidosis is a rare multi-organ granulomatous disease in which the heart is frequently affected. The clinical course and prognosis of sarcoidosis are highly variable and dependent on involved organs. While the lungs and the thoracic lymph nodes are most commonly involved, myocardial involvement occurs in 20-30 % of patients, though only 5 % may be diagnosed antemortem [1, 2]. Isolated cardiac sarcoidosis(CS) can also present in the absence of clinically-evident extracardiac involvement, though this is somewhat less common [3]. Prognosis is highly variable in CS, with 5-year survival rates ranging from 60-90 % [4]. While more than a century has passed since the initial description of sarcoidosis, its underlying cause continues to be an enigma. The approach to diagnosis and management in these patients can be similarly enigmatic.

As with most rare diseases, clinical guidance for CS relies not on randomized prospective data but on observational studies, limited clinical experiences, and expert opinion. Nonetheless, recent reports have helped to organize a rational approach to these patients and have provided key clinical insights.

Epidemiology

Demographic factors, including race, ethnicity, age, and gender, markedly influence the estimated prevalence of sarcoidosis. In the United States and Europe, there is a 10-40/100,000 persons lifetime prevalence, with a ten-fold increased prevalence in African-Americans compared to Caucasians [5]. The Scandinavian population has a higher prevalence of sarcoidosis than other Caucasian ethnicities [6].

Epidemiologic characterization of CS is problematic for a variety of reasons, including sampling bias and the absence of precise diagnostic methods. Population-based chest x-ray screening programs in Sweden and the United Kingdom have suggested that there are a sizeable number of sarcoidosis patients with subclinical disease [7, 8]. Many of these patients likely have asymptomatic cardiac involvement as well.

There is disparate data regarding the proportion of patients with systemic sarcoidosis who will ultimately have cardiac involvement. While diagnosed in only 5 % of living CS

This article is part of the Topical Collection on *Congestive Heart Failure*

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patients, an autopsy series found myocardial granulomas in 27 % of systemic sarcoidosis patients [9]. Cardiac involvement has been reported to be as high as 58 % and may be responsible for as many as 85 % of deaths of Japanese patients with sarcoidosis [10, 11]. The discrepancies in lifetime prevalence and autopsy data, and the apparent large proportion of cases going undiagnosed, likely reflects both the variable presentation of CS (i.e., many are unheralded or asymptomatic) and the possibility that the initial presentation can be sudden death.

Pathogenesis

Noncaseating granuloma is characteristic pathologic finding of sarcoidosis, and is the presumed final common pathway of antigenic exposure and acquired cellular immunity. Environmental, occupational, and infectious causes have been hypothesized as possible immunologic triggers in genetically predisposed individuals. One multicenter case–control study identified several exposures that were linked to sarcoidosis risk, including agricultural employment (HR 1.46, 95 % CI 1.13-1.89) and exposure to insecticides or microbial bioaerosols (HR 1.61, 95 % CI 1.13-2.28) [12]. Bacterial organisms, most commonly Mycobacteria (including tuberculosis) and Propionibacterium, and viruses, such as hepatitis C, Epstein-Barr, and retroviruses (e.g., HIV), have been linked as possible inciting agents for sarcoidosis. These may trigger cellular immunity and granuloma formation by a molecular mimicry mechanism [13, 14].

Several genetic polymorphisms in human leukocyte antigens (HLA) and various cytokines have been associated with sarcoidosis and may be responsible for providing the genetic predisposition [15]. There are reports of familial clustering, though linkage analysis of major histocompatibility genes in familial sarcoidosis suggests that inherited susceptibility likely involves many genes [16]. Ultimately, further studies are needed to better understand the role of genetics in both disease susceptibility and severity. Despite these associations, no specific factors have been identified to predispose patients with systemic sarcoidosis to the development of myocardial involvement.

Whatever the inciting event, the result is the formation of noncaseating epithelioid cell granulomas, which can then either resolve or progress to fibrosis. Early in the disease, activated T cells differentiate into type I helper T cells and produce interferon-γ, thereby activating macrophages and leading to inflammation. At a later stage in lesion evolution, which can be considered the fibroproliferative stage of the granuloma, regulatory type II helper T cells secreting inhibitory cytokines such as TGF-beta and IL-10 attenuate the inflammatory process and ultimately lead to the formation of scar [17]. With this evolution come three distinct histopathologic stages: inflammation and edema with the infiltration of leukocytes, granuloma formation, and fibrosis leading to post-inflammatory scarring.

This mechanism of pathogenesis has marked clinical implications. For instance, ventricular arrhythmias arising from the earlier inflammatory stage of granuloma formation may potentially be effectively managed with corticosteroids and immunosuppression, whereas these strategies will likely be ineffective after the formation of scar.

Clinical Manifestations

While patients with CS can present with a wide variety of signs and symptoms, many are asymptomatic. In fact, it is becoming more evident that asymptomatic CS is more common than previously thought. In several recent observational studies that screened patients with extracardiac sarcoidosis for myocardial enhancement by late gadolinium enhancement on cardiac magnetic resonance imaging (CMR), the percent of patients with asymptomatic CS ranged from 19 to 55 %.

Clinical manifestations of CS are largely a reflection of the location of granulomatous infiltration. Involvement of the ventricular myocardium can lead to LV and RV dysfunction, infiltration of the septum can lead to atrioventricular block, and atrial disease can lead to supraventricular arrhythmias, atrial fibrillation, and sinus node dysfunction. While autopsy studies show that granulomas are most frequently found in the left ventricular free wall and basal interventricular septum, the right ventricular free wall, papillary muscles, and left and right atria are also commonly involved [18]. Although myocardial involvement is most common, sarcoid granulomas can also in rare circumstances involve the pericardium [19] and lead to pericardial effusion and less commonly pericarditis.

Heart Failure

CS presenting as congestive heart failure with left ventricular systolic dysfunction is a sign that the disease has already progressed to an advanced stage. Prior to more widespread clinical awareness and screening programs with advanced imaging techniques, overt heart failure was a more common presentation of CS. In a 1976 study observational study, for example, 41 % of patients presented with congestive heart failure as the initial manifestation of CS. Other published reviews citing older literature estimate the proportion of CS patients with congestive heart failure to be between 25 and 75 % [20].

Today, however, at centers where patients with known extra-CS are referred for early screening for myocardial involvement, diagnosis is made at earlier stages of disease, and left ventricular dysfunction in these patients is far less common. Our local experience, where a multidisciplinary

approach with early screening is customary, showed that 18 % of patients followed with CS had evidence of left ventricular systolic dysfunction (LVEF<55 %) at the time of diagnosis, and a smaller proportion of these presented with clinical heart failure [21].

Other recent studies have investigated CS patients and correlated LVEF to those who have displayed more malignant or benign clinical courses. In a 2001 Japanese study of 95 patients with CS, the initial mean left ventricular ejection fraction among those with CS at the time of diagnosis was 49 %±20 % (n=75), whereas the LVEF of autopsy subjects whose CS was diagnosed postmortem was 35 %±20 % (n=20) [4]. In the largest and most recent published study of CS patients with ICDs, the mean LVEF in patients receiving appropriate ICD shocks or antitachycardia pacing for ventricular arrhythmias was 38 %, compared to 49 % who had no history of VT/VF (p<0.0001) [22•]. These data suggest that in patients with CS, as has been shown in patients with other cardiomyopathies, left ventricular ejection fraction carries prognostic value.

Right ventricular granulomatous infiltration can lead to reduction in RV as well as left ventricular (LV) function. In fact, RV dysfunction may be just as common, if not more common, than LV dysfunction. In a multicenter study of 112 patients with CS and ICDs, RV dysfunction was present in 54 patients (48 %). As with LV dysfunction, the presence of RV dysfunction (as assessed by CMR) was significantly higher in patients who received appropriate ICD therapies than those who received no therapies (78 % vs. 36 %, p<0.01) [23•].

Ultimately, heart failure is a significant cause of morbidity and mortality in patients with CS. In a review of Japanese patients with CS, 26 % of patients were described as NYHA class III or IV, and multivariate analysis showed that left ventricular dimension and deterioration in NYHA functional class were independent predictors of mortality (HR 5.32, 95 % CI 1.15-5.84 and HR 7.72, 95 % CI 2.33-25.57)[4]. Chronic heart failure is a progressive syndrome related to ventricular dysfunction and pathologic remodeling; as with other cardiomyopathies, prognosis in CS appears to relate to the severity of heart failure symptoms and the extent of ventricular remodeling.

Conduction System Disease

Granuloma infiltration can cause injury to the various elements of the cardiac conduction system and result in a variety of conduction disturbances; specifically, involvement of the basal ventricular septum can lead to bundle branch block or atrioventricular block. Bundle branch block has been observed on surface electrocardiogram in 12-61 % of cases of CS, depending on study series [11, 18, 24, 25]. Conduction block itself can range from first-degree atrioventricular delay to complete atrioventricular block (CAVB), and the severity of block can progress with progression of inflammation and scar. CAVB is one of the most common findings in patients with clinically-evident CS, with a prevalence of 25 % in one retrospective analysis [1]. CAVB due to CS often occurs at a younger age than in individuals with complete heart block due to other etiologies. Furthermore, among patients with heart block without a prior diagnosis of sarcoidosis, a significant portion may ultimately have underlying CS. This was the case in a Japanese study of 89 consecutive patients with no known history of sarcoidosis with high-grade atrioventricular block requiring permanent dual chamber pacemaker implantation who prospectively evaluated for CS. Ten cases (11.2 %) of CS were diagnosed, most frequently in young women aged 40 to 69 (32 %) [26].

Extensive granulomatous lesions in the sinoatrial node subendocardium have been described in previous autopsy series [27, 28], and sinus node dysfunction may also be an under-recognized manifestation of CS [29].

Atrial Arrhythmias

Supraventricular arrhythmias—in particular, atrial tachycardia and atrial fibrillation—are common in CS, with a prevalence ranging from 23-36 % in three recent study series [30, 31•, 32]. In a retrospectively-investigated cohort of 100 patients with biopsy-proven systemic sarcoidosis and evidence of cardiac involvement by MRI, PET, or endomyocardial biopsy, a 32 % prevalence of supraventricular arrhythmias was observed over a mean follow-up period of 5.8 years. Arrhythmias were documented by ECG, device interrogation data, or ambulatory telemetry monitoring. Atrial fibrillation was the most common supraventricular arrhythmia reported, accounting for 56 % of those described. After multivariate analysis, left-atrial enlargement was the only parameter with a significant association with supraventricular arrhythmias (HR 6.12, 2.2-17.1, P<0.01) [31•].

A similar prevalence of atrial arrhythmias was described in a separate retrospective series, in which 16/44 (36 %) patients with evidence of CS by cardiac magnetic resonance imaging (CMR) had documented atrial arrhythmias, the most common of which was atrial tachycardia (18 %). In the 26 patients with ICDs in this cohort, 11.5 % received inappropriate ICD therapies for atrial arrhythmias [32]. This was similar to the 12 % incidence of inappropriate therapies in a separate study [23•].

The mechanism of atrial arrhythmias is diverse. In a third series [30], 15/65 patients (23 %) with CS experienced 28 distinct symptomatic supraventricular arrhythmias (nine Atrial Fibrillation; three Atrial Flutter; 16 Atrial Tachycardia); these patients went on to electrophysiologic testing to characterize the arrhythmias. The mechanism of atrial arrhythmias was determined to be triggered by activity in 11 %, abnormal automaticity in 47 %, and reentrant in 42 % of the non-AF atrial arrhythmias. Inflammation and edema with the initial

infiltrative stage and scar as the disease progresses to the fibrotic stage likely independently account for the differing mechanisms observed.

Ventricular Arrhythmias and Sudden Cardiac Death

Just as atrial inflammation and fibrosis can lead to atrial arrhythmias in CS, involvement of the ventricular myocardium can lead to ventricular arrhythmias by similar triggered, automatic, and reentrant mechanisms [33–37]. Prior to the use of the implanted cardiac defibrillators (ICD), sudden death caused by ventricular tachyarrhythmias accounted for approximately 25-65 % of deaths caused by CS [11, 18, 38]. Furthermore, ventricular arrhythmias have frequently been described as the initial presentation of CS [39]. Activated macrophages and the inflammatory response associated with granulomatous infiltration in the active phase of CS can play a significant role in the exacerbation of electrical storm in CS patients [23•]. Because corticosteroids can play an integral role in arrhythmia suppression, new presentations with ventricular tachycardia (VT) or ventricular fibrillation (VF) should begin with assessment for active sarcoid myocarditis and treatment with immunosuppression as indicated [4, 35, 40]. In other cases of VT in CS, the disease has already progressed to the fibrotic stage and generated scar. As in patients with other cardiomyopathies and VT, scar serves as substrate for reentry by creating both a zone of slow conduction and an anatomical barrier around which a circuit may propagate [37].

It has been speculated that ventricular arrhythmias in sarcoid patients, when present, can be more difficult to control (both with antiarrhythmic therapy and catheter ablation) than with patients with other cardiomyopathies because ventricular involvement may be more diffuse and heterogeneous. The pattern of scarring that occurs with CS can provide substrate for reentrant circuits involving the endocardium, epicardium, and mid-myocardium (Fig. 1).

Diagnosis

The diagnosis of CS should be considered in two clinical scenarios: (1) in patients with extracardiac biopsy-proven sarcoidosis, with or without cardiac symptoms, and (2) in patients with no previous histologic diagnosis of sarcoidosis but with unexplained cardiomyopathy, atrioventricular block, or ventricular tachycardia.

Cardiac involvement in sarcoidosis is particularly difficult to diagnose because the manifestations are nonspecific, and the sensitivity and specificity of diagnostic modalities are limited. There is no gold standard, and unfortunately, as reflected by an array of disease definitions and guidelines for diagnosis [2, 41–48], there is not yet consensus on the best diagnostic approach. The Japanese Ministry of Health and Welfare 2006 revised guidelines are in need of an update to expand on the role of advanced imaging in the diagnosis of CS (Table 1).

Clinicians must have a high level of suspicion and low threshold to screen patients with sarcoidosis for cardiac involvement, particularly since the initial clinical presentation can be sudden death [11, 49]. In patients with biopsy-proved extracardiac sarcoidosis, further evaluation should be prompted by any abnormality on (1) screening ECG (i.e., atrial or ventricular ectopy, bundle branch block, or any level of atrioventricular block), (2) screening echocardiogram (i.e., wall-motion abnormality, depressed left- or right-ventricular function, and/or wall aneurysm or basal septum thinning), or (3) the presence of cardiac symptoms such as palpitations, presyncope, or syncope. Even so, because clinically-isolated CS can occur, consideration of the diagnosis of CS only in patients with previously-diagnosed extracardiac sarcoidosis is insufficient and will miss cases. CS must also be considered in young patients with unexplained atrioventricular block, as well as patients with VT and an otherwise unexplained cardiomyopathy. Nery et al. reported on 32 patients with unexplained AV block, and found 11 of them to have CS [50•]. In a separate series, Nery et al. also reported that in the six abnormal PET scans out of 14 total performed on patients with unexplained monomorphic VT, four patients ultimately were diagnosed with CS [51].

Ultimately, CS can masquerade as a number of diseases, including coronary artery vasculitis [52], giant cell myocarditis [53, 54], and arrhythmogenic right ventricular cardiomyopathy [55–57], which can make the diagnosis of CS all the more challenging.

Clinical History, Electrocardiography, and Echocardiography

Patients with biopsy-proven extra cardiac sarcoidosis should undergo a comprehensive cardiac history and physical exam, with special attention to a history of palpitations, presyncope, syncope, or symptoms of heart failure. A 12-lead electrocardiogram is useful in the screening of asymptomatic patients as well, given the higher incidence of bundle branch block and QRS complex fragmentation seen in patients with cardiac involvement [25]. Other ECG findings that should prompt further evaluation include frequent atrial or ventricular ectopy, any level of atrioventricular block, and pseudo-infarct patterns that may indicate localized myocardial infiltration. Patients should undergo screening echocardiography to assess biventricular function and wall motion [58], and consideration of additional testing with signal-averaged electrocardiography [21] and ambulatory telemetric monitoring may also be warranted [59] as part of the initial panel of diagnostic tests. Serum biomarkers, such as cardiac troponin and serum angiotensin-converting enzyme

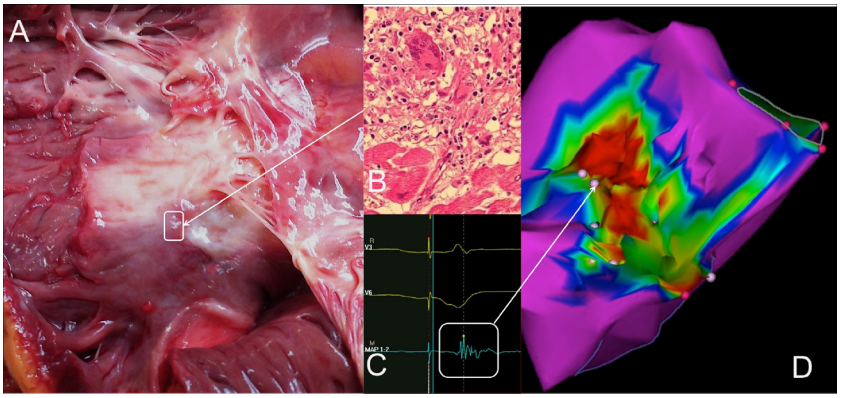

Fig. 1 Gross examination of an explanted heart at autopsy in a patient with cardiac sarcoidosis, revealing granulomatous myocardial scarring of the RV septum (panel A). Panel B shows the characteristic noncaseating granuloma infiltrating the myocardium at the borderzone with hematoxylin-eosin stained tissue at 400X power. Panel C shows an intracardiac electrogram recorded at a similar borderzone site. Panel D is the electroanatomical map of the right ventricular septum of this same patient recorded 2 years prior to autopsy. This area of reduced voltage with heterogeneous distribution of low amplitude electrograms corresponds to the myocardial scar caused by sarcoidosis related granuloma seen in the pathological examination

(ACE) levels, have little utility in screening for cardiac involvement of sarcoidosis owing to poor sensitivity [60].

Table 1 2006 Revised guidelines for diagnosing cardiac sarcoidosis (Japan Society of Sarcoidosis and Other Granulomatous Disorders)*. CS diagnosis is made based on satisfying either the histologic diagnostic criteria or the clinical diagnostic criteria, as outlined below

1. Histologic diagnosis group. Cardiac sarcoidosis is confirmed when myocardial biopsy specimens demonstrate noncaseating epithelioid cell granuloma with histological or clinical diagnosis of extracardiac sarcoidosis.
2. Clinical diagnosis group. Although myocardial biopsy specimens do not demonstrate noncaseating epithelioid cell granuloma, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one in six basic diagnostic criteria.

(1) More than 2 of 4 major criteria are satisfied.

(2) One in 4 major criteria and more than 2 in 5 minor criteria are satisfied.

Major criteria

(a) Advanced AV block.

(b) Basal thinning of the interventricular septum.

(b) Positive cardiac ^{67}Ga uptake.

(d) Depressed ejection fraction of the left ventricle (LVEF<50 %).

Minor criteria

(a) Abnormal ECG findings: Ventricular arrhythmias (VT, multifocal or frequent PVCs), RBBB, axis deviation or abnormal Q-wave.

(b) Abnormal echocardiography: Regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening).

(c) Nuclear medicine: Perfusion defect detected by ^{201}Tl myocardial scintigraphy or ^{99}Tc myocardial scintigraphy.

(d) Gd-enhanced MRI: Delayed enhancement of myocardium.

(f) Endomyocardial biopsy: Interstitial fibrosis or monocyte infiltration over moderate grade.

*These outdated guidelines under-emphasize advanced-imaging techniques, listing CMR only as a minor criterion. Diagnosis of CS by current practice relies much more heavily on CMR, and in some cases PET (which is not mentioned in this document). Gallium uptake studies, listed here as a major criterion, are no longer used in clinical practice.

Histologic Diagnosis

Abnormalities on initial noninvasive testing should prompt further investigations. The only absolute test for organ involvement in sarcoidosis is histologic examination of tissue for the presence of noncaseating granulomas (Fig. 1), after excluding other known causes of granuloma formation such as tuberculosis [61]. Myocardial involvement can, however, be diagnosed by clinical features and noninvasive testing, even in the absence of an endomyocardial biopsy if sarcoidosis has already been demonstrated histologically in another organ, and other causes for the cardiac manifestations have been reasonably excluded.

In patients with known extracardiac sarcoidosis, myocardial involvement is commonly demonstrated with advanced imaging techniques and not by endomyocardial biopsy, given the small procedural risk and the characteristically low sensitivity of histologic examination (<25 %) as a result of the focal and patchy nature of CS [62, 63].

However, in situations where young adults present with unexplained atrioventricular block, tachyarrhythmias, or cardiomyopathy without a prior histologic diagnosis of extra CS, obtaining pathology ultimately becomes important for diagnostic confirmation. Biopsies should be performed on the most accessible lesion that appears to be affected. If no cutaneous lesions or palpable lymph nodes can be identified, then lung or intrathoracic lymph nodes are typically targeted if radiographic and CT abnormalities are detected, due to higher diagnostic yield and lower procedural risk. In cases of isolated CS or negative extra-cardiac biopsy, endomyocardial biopsy may be required to confirm the diagnosis, and yield may be improved with electroanatomical guidance (to identify areas of reduced voltage, i.e., abnormal tissue) in the electrophysiology lab [64•, 65] or with imaging guidance by PET or CMR [3]. In Fig. 1, we demonstrate the corresponding histological

and intracardiac electrocardiographic findings in a patient with CS.

Advanced Cardiac Imaging

Cardiac magnetic resonance (CMR) and positron emission tomography (PET) appear to be the imaging modalities with the highest sensitivity and specificity in the detection of CS [2, 42, 44, 66, 67]. CMR, in particular, has emerged as the test of choice at many centers in the evaluation of CS, owing in part to a lower false positive rate [67]. CMR uses T-2 weighted signal and early gadolinium images to detect acute inflammation and late gadolinium enhancement (LGE, also known as delayed contrast enhancement) to assess for fibrosis or scar. Accordingly, CMR findings vary depending on the stage of the pathological process, and preliminary observations suggest that surveillance with CMR can assess the efficacy of steroid therapy [68, 69].

CMR also provides important prognostic information. In a recent study of 155 consecutive patients with systemic sarcoidosis who underwent CMR for workup of suspected CS, LGE was present in 39 patients (25.5 %), and its presence was associated with a Cox hazard ratio of 31.6 for death, aborted sudden cardiac death, or appropriate ICD discharge [70] over a median 2.6 year follow-up period. Of the 12 patients who with sudden cardiac death or appropriate ICD discharge in this study, all had LGE present on CMR. Sarcoid patients without LGE, even those with LV dilatation and severely impaired LVEF, did not experience SCD, suggesting CMR may provide prognostic data beyond that conferred by ejection fraction alone.

While CMR may have a higher specificity, ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) appears to detect active inflammation in CS with a slightly higher sensitivity [71, 72]. However, as the uptake of ^{18}F-FDG is seen in other inflammatory myocardial diseases, PET is non-specific for CS and must be interpreted in the appropriate clinical context. Like CMR, PET carries prognostic value—in a study of 118 patients with suspected CS, 60 % had abnormal cardiac PET findings. Over a median follow-up of 1.5 years, abnormal PET findings were associated with a hazard ratio of 3.9 for death or VT, and an abnormal PET remained a significant predictor of death or VT even after multivariate analysis to adjust for ejection fraction and other clinical variables [66], indicating PET offers prognostic value beyond EF alone.

Historically, radionuclide imaging has also been used in the evaluation of patients in whom CS is suspected. However, these studies have been replaced by CMR and PET, due to the inferior spatial resolution, nonspecific results, prevalence of imaging artifacts, and associated radiation dose [73].

Electrophysiologic Testing

In some instances electrophysiologic study can add useful diagnostic information, particularly if CMR or PET is inconclusive. Electroanatomical mapping, or "voltage-mapping," of the right ventricle can help identify areas of scar, which can suggest the presence of myocardial involvement in patients with biopsy-proven extracardiac sarcoidosis and no other clear explanation for cardiomyopathy.

More studies, however, have investigated the role for programmed electrical stimulation (PES) for the inducibility of sustained monomorphic ventricular tachycardia as a means of risk stratification of sudden cardiac death in patients with CS. One study of 76 patients with CS undergoing PES showed that six of eight patients (75 %) with inducible VT went on to have ventricular arrhythmias and ICD therapies, compared to one patient with sudden cardiac death amongst the 68 patients (1.5 %) who had been noninducible by PES [74]. In another study of 32 patients with CS, four of six patients (67 %) with inducible VT went on to have appropriate ICD therapies while two of 20 patients (10 %) who were noninducible went on to have ventricular arrhythmias or sudden cardiac death [75]. While these studies suggest a potential role for electrophysiologic testing for risk stratification, these data need to be replicated in larger cohorts. Furthermore, these studies are limited by mean follow-up periods of 5 years and 2.6 years, respectively; and, in light of CS as a progressive disease, the long-term prognostic value of a single negative EP study is unclear.

Management

Immunosuppression

If active CS is revealed by diagnostic work-up, corticosteroids should be initiated. It should be noted that no randomized controlled studies have confirmed their efficacy. Prednisone is generally initiated at 30–40 mg/day for 8–12 weeks, with gradual tapering over a period of months until establishing a minimum effective maintenance dose. Steroid-sparing immunosuppressive therapies, such as infliximab, methotrexate, azathioprine, and others are frequently utilized as well with reports of success [76–78].

In the past, steroids have been reserved for patients with CS and left ventricular dysfunction, atrioventricular block, or ventricular arrhythmias [42]; however, this approach is associated with a high mortality risk, and many believe that steroid therapy should be initiated early, before advanced clinical manifestations develop [79]. Chiu et al. found that the benefit of steroids was limited to those whose EF had not already declined <30 % [80]. Yazaki et al. found that 75 CS patients

treated with steroids had a significantly better 5-year survival compared to untreated patients (75 % vs. 10 %) [4]. In addition to improving survival, other observational studies have suggested that steroid therapy may decrease arrhythmic burden [4, 35, 40, 81] and even reverse high-grade atrioventricular block [36, 82–84].

Antiarrhythmic Drugs

Corticosteroids alone can be ineffective at preventing monomorphic VT [33, 35, 36] and some atrial arrhythmias, as disease progression through the inflammatory stage has already led to scar, which serves as arrhythmic substrate and may not be reversed with immunosuppression. Antiarrhythmic drug use varies widely and can include beta blockers, class IA, IB, IC, and III agents—used both in isolation or in combination, each with variable outcome [35, 37, 85, 86].

Catheter Ablation

Early inflammatory and late scar phases of CS both can be pro-arrhythmic and result in both ventricular and atrial arrhythmias. Medical therapy alone is commonly ineffective at complete arrhythmia suppression [33], in which case catheter ablation may be indicated. While further studies are needed to determine the efficacy of catheter ablation in CS, particularly in the acute inflammatory phase in active CS, there have been a few published descriptions of experience with catheter ablation for VT in CS. Jefic et al. have reported on nine patients with CS and VT who underwent radiofrequency ablation, resulting in elimination of 31 of 44 (70 %) of inducible VTs, and a subsequent decrease (n=4) or complete elimination (n=5) of VT over a mean follow-up period of 20 months. Koplan et al. reported their experience of VT ablation in CS patients, after which four of eight patients remained free of VT over a follow-up period ranging from 6 months to 7 years [34]. Ultimately, a combination of immunosuppression, antiarrhythmic therapy, and catheter ablation may be required for arrhythmia control in CS.

Indications for and Outcomes of Implantable Cardiac Defibrillator Therapy

The ACC/AHA/HRS 2008 guidelines have a class IIA recommendation (level of evidence C) for ICD therapy in sarcoidosis patients with evidence of myocardial involvement, regardless of symptoms or presentation [87]. The specific role for the primary prevention ICD in patients with CS does remain controversial, with some centers implanting all patients with CS, while others only offer ICDs to those with a LVEF≤35 %. Practice patterns also vary regarding whether patients with atrioventricular block are treated with pacemakers alone or offered ICDs [43].

Three observational studies were published in 2012–13 that reported on ICD therapies in patients with CS. Betensky et al. reviewed 45 patients (64 % primary prevention, 2.6 year mean follow-up period), and found a high annualized appropriate therapy (shock and/or ATP) rate of 14.5 %. Predictors of appropriate therapies included lower LVEF and complete heart block, signifying more advanced disease. Schuller et al. reported on 112 patients (74 % primary prevention, 2.8 year mean follow-up period) and found a similarly high annualized therapy rate of 13.2 %. Interestingly, in this cohort, no primary prevention patient with normal right and left ventricular function received an appropriate therapy, though there were many patients with only mild systolic dysfunction who received shocks and ATP [23•]. Kron et al. published a multicenter retrospective review of 235 patients (99 of which were included in the aforementioned studies), and found male gender, syncope, lower LVEF, and high proportion of ventricular pacing each to be independent risk factors for appropriate therapies (with an annualized incidence of 8.6 % in this study) [22•]. Altogether, the rates of appropriate therapies in these three studies are notably higher than that observed in large primary prevention ICD trials such as Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), where the incidence was approximately 5 % per year [88].

Sudden cardiac death risk may be stratified in CS, though limited data exist directing strategies for doing so. Ultimately, risk stratification may be guided by a combination of CMR and PET findings, electrophysiologic testing with programmed electrical stimulation, or by other high risk clinical features such as atrioventricular block, systolic dysfunction, or a history of syncope. Current guidelines recognize the paucity of randomized, prospective data, and cite the limitations of retrospectively analyzed series; ultimately, further research is needed to better advise practice.

Heart Failure Management and Advanced Heart Failure Therapies

The treatment of CS is aimed at controlling inflammation in hopes of preventing extensive fibrosis, which can lead to AV block, ventricular arrhythmias, and advanced heart failure. When systolic function and heart failure do occur, management is similar to other forms of dilated cardiomyopathy. Angiotensin-converting-enzyme (ACE) inhibitors, aldosterone antagonists, diuretics, and beta-blockers are mainstays of therapy, in addition to a background of immunosuppression. Cardiac resynchronization therapy may also be indicated in cases of high-grade atrioventricular block or in patients with a LBBB and a wide QRS complex.

Ultimately, despite optimal medical therapy, heart failure may progress or intractable ventricular arrhythmias may persist despite best efforts, and advanced therapies, such as ventricular assist devices or cardiac transplantation, may be

required. In these cases of end-stage disease, the diagnosis of sarcoidosis should not necessarily preclude consideration of potential transplantation by itself. While there are reports of sarcoidosis recurring in a cardiac allograft [89, 90], this is rare [91], and one-year post-transplant survival has been reported to be similar for sarcoid patients (n=65) as patients receiving transplantation for all other diagnoses (87.7 % vs. 84.5 %). Furthermore, estimated post-transplant survival at five years was a favorable 80 % for patients with CS [92].

Conclusion

CS can present in the setting of advanced systemic disease or in clinical isolation. The manifestations of CS are highly variable; myocardial involvement can be subclinical, or it may lead to atrioventricular block, heart failure, atrial and ventricular arrhythmias, or sudden cardiac death. While no universally-accepted diagnostic algorithm exists, the diagnosis is determined by extracardiac histopathologic demonstration of noncaseating granulomas, the exclusion of other diseases known to cause granuloma formation, and a combination of abnormal findings by noninvasive cardiac testing, such as a 12-lead ECG, echocardiogram, and cardiac PET or MR. Adequate immunosuppression is the mainstay of therapy, and an ICD may be indicated for the prevention of sudden death. Ultimately, a multidisciplinary approach to the patient with CS is necessary, with open communication between the pulmonologist, heart failure specialist, and cardiac electrophysiologist for the successful management of these complex patients.

Compliance with Ethics Guidelines

Conflict of Interest Matthew M. Zipse and William H. Sauer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Chapelon-Abric C, de Zuttere D, Duhaut P, Veyssier P, Wechsler B, Huong DLT, et al. Cardiac sarcoidosis: a retrospective study of 41 cases. Medicine. 2004;83:315–34.
2. Kim JS, Judson MA, Donnino R, Gold M, Cooper LT, Prystowsky EN, et al. Cardiac sarcoidosis. Am Heart J. 2009;157:9–21.
3. Kandolin R, Lehtonen J, Graner M, Schildt J, Salmenkivi K, Kivistö SM, et al. Diagnosing isolated cardiac sarcoidosis. J Intern Med. 2011;270:461–8.
4. Yazaki Y, Isobe M, Hiroe M, Morimoto S-I, Hiramitsu S, Nakano T, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol Elsevier. 2001;88:1006–10.
5. Rybicki BA, Major M, Popovich J, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 1997;145:234–41.
6. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med. 1997;336:1224–34.
7. Hosoda Y, Yamaguchi M, Hiraga Y. Global epidemiology of sarcoidosis. What story do prevalence and incidence tell us? Clin Chest Med. 1997;18:681–94.
8. Hillerdal G, Nöu E, Osterman K, Schmekel B. Sarcoidosis: epidemiology and prognosis. A 15-year European study. Am Rev Respir Dis. 1984;130:29–32.
9. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation. 1978;58:1204–11.
10. Tachibana T, Iwai K, Takemura T. Study on cause of death in the patients with sarcoidosis in Japan. Sarcoidosis Sigilim SRL. 1992;9:307–7.
11. Matsui Y, Iwai K, Tachibana T, Fruie T, Shigematsu N, Izumi T, et al. Clinicopathological study of fatal myocardial sarcoidosis. Ann N Y Acad Sci. 1976;278:455–69.
12. Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med. 2004;170:1324–30.
13. Eishi Y. Etiologic aspect of sarcoidosis as an allergic endogenous infection caused by propionibacterium acnes. BioMed Res Int. 2013;2013:1–18.
14. Tchernev G, Ananiev J, Cardoso JC, Wollina U, Verma SB, Patterson JW, et al. Sarcoidosis and molecular mimicry—important etiopathogenetic aspects: current state and future directions. Wien Klin Wochenschr Springer. 2012;124:227–38.
15. Baughman RP, Lower EE, Bois du RM. Sarcoidosis. Lancet. 2003;361:1111–8.
16. Schürmann M, Lympany PA, Reichel P, Müller-Myhsok B, Wurm K, Schlaak M, et al. Familial sarcoidosis is linked to the major histocompatibility complex region. Am J Respir Crit Care Med. 2000;162:861–4.
17. Doughan AR. Cardiac sarcoidosis. Heart. 2006;92:282–8.
18. Roberts WC, McAllister HA, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). Am J Med. 1977;63:86–108.
19. Navaneethan SD, Venkatesh S, Shrivastava R, Mehta J, Israel R. Recurrent pleural and pericardial effusions due to sarcoidosis. PLoS Med. 2005;2:e63.
20. Sekhri V, Sanal S, DeLorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. Arch Med Sci. 2011;4:546–54.
21. Schuller JL, Lowery CM, Zipse M, Aleong RG, Varosy PD, Weinberger HD, et al. Diagnostic utility of signal-averaged electrocardiography for detection of cardiac sarcoidosis. Ann Noninvasive Electrocardiol. 2011;16:70–6.
22.• Kron J, Sauer W, Schuller J, Bogun F, Crawford T, Sarsam S, et al. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. Europace. 2013;15:347–54. *A multicenter retrospective review which represents the largest published cohort of cardiac sarcoidosis patients with ICDs.*

23.• Schuller JL, Zipse M, Crawford T, Bogun F, Beshai J, Patel AR, et al. Implantable cardioverter defibrillator therapy in patients with cardiac sarcoidosis. J Cardiovasc Electrophysiol. 2012;23:925–9. *One of three 2012 studies of CS patients with ICDs. No primary prevention patients with normal LV and RV function received an appropriate therapy for VT.*
24. Chapelon-Abric C, de Zuttere D, Duhaut P, Veyssier P, Wechsler B, Huong DLT, et al. Cardiac sarcoidosis. Medicine. 2004;83:315–34.
25. Schuller JL, Olson MD, Zipse MM, Schneider PM, Aleong RG, Wienberger HD, et al. Electrocardiographic characteristics in patients with pulmonary sarcoidosis indicating cardiac involvement. J Cardiovasc Electrophysiol. 2011;22:1243–8.
26. Yoshida Y, Morimoto S, Hiramitsu S, Tsuboi N, Hirayama H, Itoh T. Incidence of cardiac sarcoidosis in Japanese patients with high-degree atrioventricular block. Am Heart J. 1997;134:382–6.
27. Gozo EG, Cosnow I, Cohen HC, Okun L. The heart in sarcoidosis. Chest Am Coll Chest Phys. 1971;60:379–88.
28. Abeler V. Sarcoidosis of the cardiac conducting system. Am Heart J. 1979;97:701–7.
29. Ton K, Schulman S, Lima J, Tandri H. Cardiac Sarcoidosis Presenting as Sick Sinus Syndrome and Recurrent Ventricular Tachycardia. HRS 2014. 2014. pp. 1–1.
30. Zipse MM, Schuller JL, Katz DF, Steckman DA, Gonzalez JE, Sung RK, et al. Atrial Arrhythmias are Common and Arise from Diverse Mechanisms in Patients with Cardiac Sarcoidosis. Heart Rhythm 2013. 2013. pp. 1–2.
31.• Viles-Gonzalez JF, Pastori L, Fischer A, Wisnivesky JP, Goldman MG, Mehta D. Supraventricular arrhythmias in patients with cardiac sarcoidosis prevalence, predictors, and clinical implications. Chest. 2013;143:1085–90. *The first retrospective study of atrial arrhythmias in CS.*
32. Cain MA, Metzl MD, Patel AR, Addetia K. Cardiac sarcoidosis detected by late gadolinium enhancement and prevalence of atrial arrhythmias. Am J Cardiol. 2014;113(9):1556–60.
33. Winters SL, Cohen M, Greenberg S, Stein B, Curwin J, Pe E, et al. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. JAC. 1991;18:937–43.
34. Koplan BA, Soejima K, Baughman K, Epstein LM, Stevenson WG. Refractory ventricular tachycardia secondary to cardiac sarcoid: electrophysiologic characteristics, mapping, and ablation. HRTHM. 2006;3:924–9.
35. Jefic D, Joel B, Good E, Morady F, Rosman H, Knight B, et al. Role of radiofrequency catheter ablation of ventricular tachycardia in cardiac sarcoidosis: report from a multicenter registry. Heart Rhythm. 2009;6:189–95.
36. Banba K, Kusano KF, Nakamura K, Morita H, Ogawa A, Ohtsuka F, et al. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. HRTHM. 2007;4:1292–9.
37. Furushima H, Chinushi M, Sugiura H, Kasai H, Washizuka T, Aizawa Y. Ventricular tachyarrhythmia associated with cardiac sarcoidosis: its mechanisms and outcome. Clin Cardiol. 2004;27:217–22.
38. Fleming HA, Bailey SM. Sarcoid heart disease. J R Coll Physicians Lond. 1981;15:245.
39. Uusimaa P, Ylitalo K, Anttonen O, Kerola T, Virtanen V, Pääkkö E, et al. Ventricular tachyarrhythmia as a primary presentation of sarcoidosis. Europace. 2008;10:760–6.
40. Stees CS, Khoo MSC, Lowery CM, Sauer WH. Ventricular tachycardia storm successfully treated with immunosuppression and catheter ablation in a patient with cardiac sarcoidosis. J Cardiovasc Electrophysiol. 2011;22:210–3.
41. Schulte W, Kirsten D, Drent M, Costabel U. Cardiac involvement in sarcoidosis. Eur Respir Monogr Eur Respir Soc. 2005;32:130.
42. Soejima K, Yada H. The work-up and management of patients with apparent or subclinical cardiac sarcoidosis: with emphasis on the associated heart rhythm abnormalities. J Cardiovasc Electrophysiol. 2009;20:578–83. *Wiley Online Library.*
43. Hamzeh NY. Management of cardiac sarcoidosis in the United States. Chest. 2012;141:154.
44. Youssef G, Beanlands RSB, Birnie DH, Nery PB. Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. Heart. 2011;97:2078–87.
45. Yeboah J, Lee C, Sharma OP. Cardiac sarcoidosis. Curr Opin Pulm Med. 2011;17:308–15.
46. Nery PB, Leung E, Birnie DH. Arrhythmias in cardiac sarcoidosis. Curr Opin Cardiol. 2012;27:181–9.
47. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999. pp. 736–55.
48. Judson MA, Baughman RP, Teirstein AS, Terrin ML, Yeager H. Defining organ involvement in sarcoidosis: the ACCESS proposed instrument. ACCESS Research Group. A case control etiologic study of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 1999;16:75–86.
49. Lubitz SA, Goldbarg SH, Mehta D. Sudden cardiac death in infiltrative cardiomyopathies: sarcoidosis, scleroderma, amyloidosis, hemachromatosis. Prog Cardiovasc Dis. 2008;51:58–73.
50.• Nery PB, Beanlands RS, Nair GM, Green M, Yang J, Mc Ardle BA, et al. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. J Cardiovasc Electrophysiol. 2014. doi:10.1111/jce.12401. *This study reports a high incidence of cardiac sarcoidosis in young patients with initially-unexplained AV block.*
51. Nery PB, Mc Ardle BA, Redpath CJ, Leung E, Lemery R, Dekemp R, et al. Prevalence of Cardiac Sarcoidosis in Patients Presenting with Monomorphic Ventricular Tachycardia. Pacing and Clinical Electrophysiology. 2013.:n/a–n/a.
52. Ward EV, Nazari J, Edelman RR. Coronary artery vasculitis as a presentation of cardiac sarcoidosis. Circulation. 2012;125:e344–6.
53. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circ Arrhythmia Electrophysiol. 2011;4:303–9.
54. Blauwet LA, Cooper LT. Idiopathic giant cell myocarditis and cardiac sarcoidosis. Heart Fail Rev. 2012;18:733–46.
55. Chia P-L, Subbiah RN, Kuchar D, Walker B. Cardiac sarcoidosis masquerading as arrhythmogenic right ventricular cardiomyopathy. Heart Lung Circ. 2012;21:42–5.
56. Vasaiwala SC, Finn C, Delpriore J, Leya F, Gagermeier J, Akar JG, et al. Prospective study of cardiac sarcoid mimicking arrhythmogenic right ventricular dysplasia. J Cardiovasc Electrophysiol. 2009;20:473–6.
57. Mohsen A, Panday M, Wetherold S, Jimenez A. Cardiac sarcoidosis mimicking arrhythmogenic right ventricular dysplasia with high defibrillation threshold requiring subcutaneous shocking coil implantation. Heart Lung Circ. 2012;21:46–9.
58. Aggeli C, Felekos I, Tousoulis D, Gialafos E, Rapti A, Stefanadis C. Myocardial mechanics for the early detection of cardiac sarcoidosis. Int J Cardiol Elsevier Irel Ltd. 2013;168:4820–1.
59. Suzuki T, Kanda T, Kubota S, Imai S, Murata K. Holter monitoring as a noninvasive indicator of cardiac involvement in sarcoidosis. Chest. 1994;106:1021–4.
60. Adamson P, Melton I, O'Donnell J, MacDonald S, Crozier I. Cardiac sarcoidosis: the Christchurch experience. Int Med J. 2014;44:70–6.
61. Judson MA, Thompson BW, Rabin DL, Steimel J, Knattereud GL, Lackland DT, et al. The diagnostic pathway to sarcoidosis. Chest. 2003;123:406–12.

62. Ardehali H, Howard DL, Hariri A, Qasim A, Hare JM, Baughman KL, et al. A positive endomyocardial biopsy result for sarcoid is associated with poor prognosis in patients with initially unexplained cardiomyopathy. Am Heart J Elsevier. 2005;150:459–63.
63. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. Am Heart J. 1999;138:299–302.
64.• Nery PB, Keren A, Healey J, Leug E, Beanlands RS, Birnie DH. Isolated cardiac sarcoidosis: establishing the diagnosis with electroanatomic mapping-guided endomyocardial biopsy. Can J Cardiol. 2013;29(1015):e1–3. *Describes the by which electroanatomical mapping can guide endomyocardial biopsy to improve diagnostic yield*.
65. Pieroni M, Russo Dello A, Marzo F, Pelargonio G, Casella M, Bellocci F, et al. High prevalence of myocarditis mimicking arrhythmogenic right ventricular cardiomyopathy. JAC Am Coll Cardiol Found. 2009;53:681–9.
66. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol. 2014;63:329–36.
67. Ohira H, Tsujino I, Ishimaru S, Oyama N, Takei T, Tsukamoto E, et al. Myocardial imaging with 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. Eur J Nucl Med Mol Imaging Springer. 2008;35:933–41.
68. Vignaux O, Dhote R, Duboc D, Blanche P, Dusser D, Weber S, et al. Clinical significance of myocardial magnetic resonance abnormalities in patients with sarcoidosis: a 1-year follow-up study. Chest. 2002;122:1895–901.
69. Sekiguchi M, Yazaki Y, Isobe M, Hiroe M. Cardiac sarcoidosis: diagnostic, prognostic, and therapeutic considerations. Cardiovasc Drugs Ther. 1996;10:495–510.
70. Greulich S, Deluigi CC, Gloekler S, Wahl A, Zürn C, Kramer U, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. JCMG Elsevier Inc. 2013;6:501–11.
71. Ishimaru S, Tsujino I, Sakaue S, Oyama N, Takei T, Tsukamoto E, et al. Combination of 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in assessing cardiac sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22:234–5.
72. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. J Nucl Med. 2012;53:241–8.
73. Pandya C, Brunken RC, Tchou P, Schoenhagen P, Culver DA. Detecting cardiac involvement in sarcoidosis: a call for prospective studies of newer imaging techniques. Eur Respir J. 2007;29:418–22.
74. Mehta D, Mori N, Goldbarg SH, Lubitz S, Wisnivesky JP, Teirstein A. Primary prevention of sudden cardiac death in silent cardiac sarcoidosis: role of programmed ventricular stimulation. Circ Arrhythmia Electrophysiol. 2011;4:43–8.
75. Aizer A, Stern EH, Gomes JA, Teirstein AS, Eckart RE, Mehta D. Usefulness of programmed ventricular stimulation in predicting future arrhythmic events in patients with cardiac sarcoidosis. Am J Cardiol. 2005;96:276–82.
76. Baughman RP, Ohmichi M, Lower EE. Combination therapy for sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2001;18:133–7.
77. Baughman RP, Costabel U, du RM B. Treatment of sarcoidosis. Clin Chest Med. 2008;29:533–48. *x–x*.
78. Baughman RP, Drent M, Kavuru M, JUDSON MA, Costabel U, du Bois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006;174:795–802.
79. Mantini N, Williams Jr B, Stewart J, Rubinsztain L, Kacharava A. Cardiac sarcoid: a clinician's review on how to approach the patient with cardiac sarcoid. Clin Cardiol. 2012;35:410–5.
80. Chiu C-Z, Nakatani S, Zhang G, Tachibana T, Ohmori F, Yamagishi M, et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. Am J Cardiol. 2005;95:143–6.
81. Yodogawa K, Seino Y, Ohara T, Takayama H, Katoh T, Mizuno K. Effect of corticosteroid therapy on ventricular arrhythmias in patients with cardiac sarcoidosis. Ann Noninvasive Electrocardiol. 2011;16:140–7.
82. Yodogawa K, Seino Y, Shiomura R, Takahashi K, Tsuboi I, Uetake S, et al. Recovery of atrioventricular block following steroid therapy in patients with cardiac sarcoidosis. J Cardiol. 2013;62:320–5.
83. Sadek MM, Yung D, Birnie DH, BEANLANDS RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. Can J Cardiol. 2013;29:1034–41.
84. Kato Y, Morimoto S-I, Uemura A, Hiramitsu S, Ito T, Hishida H. Efficacy of corticosteroids in sarcoidosis presenting with atrioventricular block. Sarcoidosis Vasc Diffuse Lung Dis. 2003;20:133–7.
85. Mohsen A, Jimenez A, Hood RE, Dickfeld T, Saliaris A, Shorofsky S, et al. Cardiac sarcoidosis: electrophysiological outcomes on long-term follow-up and the role of the implantable cardioverter-defibrillator. J Cardiovasc Electrophysiol. 2013.
86. Zipse MM, Sauer WH. Electrophysiologic manifestations of cardiac sarcoidosis. Curr Opin Pulm Med. 2013;19:485–92.
87. Writing Committee Members, Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM, Freedman RA, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary: a report of the American college of cardiology/american heart association task force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices): developed in collaboration with the American association for thoracic surgery and society of thoracic surgeons. Circulation. 2008;117:2820–40.
88. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37.
89. Oni AA, Hershberger RE, Norman DJ, Ray J, Hovaguimian H, Cobanoglu AM, et al. Recurrence of sarcoidosis in a cardiac allograft: control with augmented corticosteroids. J Heart Lung Transplant. 1992;11:367–9.
90. Yager JEE, Hernandez AF, Steenbergen C, Persing B, Russell SD, Milano C, et al. Recurrence of cardiac sarcoidosis in a heart transplant recipient. J Heart Lung Transplant. 2005;24:1988–90.
91. Milman N, Andersen CB, Mortensen SA, Sander K. Cardiac sarcoidosis and heart transplantation: a report of four consecutive patients. Sarcoidosis Vasc Diffuse Lung Dis. 2008;25:51–9.
92. Zaidi AR, Zaidi A, Vaitkus PT. Outcome of heart transplantation in patients with sarcoid cardiomyopathy. J Heart Lung Transpl Elsevier. 2007;26:714–7.