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Diagnostic and therapeutic practices of cardiac sarcoidosis in the United States: A nationwide questionnaire based study

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Abstract. *Background and aim*: Cardiac sarcoidosis (CS) is the second most common cause of death in patients with sarcoidosis and data pertaining to its diagnosis and management is limited. We sought to describe diagnostic modalities and management of patients with CS in the United States, based on a national registry questionnaire. *Methods*: We conducted a retrospective study based on a national registry investigating 3,835 respondents to the Foundation for Sarcoidosis Research Questionnaire. The registry includes patient surveys completed between June 2014 and August 2019. Summary and univariate analyses were performed. *Results*: A total of 394 patients (10.3%) with CS were identified; 57% (n=223) were women and 81% (n=317) were white. The mean (±SD) age at diagnosis was 45 years (±13). CS was the initial presentation of sarcoidosis in 30%. Multiorgan involvement (≥3 organs) was present in 68%. Two thirds of patients were admitted at least once to the hospital. Cardiac magnetic resonance imaging (74.4%) was the most common diagnostic modality used followed by positron emission tomography (PET) scan (59.3%) and cardiac biopsy (n=52, 13%). Most patients received corticosteroids (86%) and steroid sparing medications (61%) including methotrexate (26%) and tumor necrosis factor (TNF) inhibitors (19%). A combined cardioverter defibrillator and pacemaker (39%) was the most common cardiac device implanted. *Conclusions*: The prevalence of CS in this cohort was higher than previously described. CS was a common initial presentation of sarcoidosis. The diagnosis was most likely made using cMRI. Steroids, methotrexate and infliximab are the most common medications used. Conduction abnormalities and arrhythmias often occurred.

Key words: cardiac sarcoidosis, registry, infiltrative cardiomyopathy, non-ischemic heart failure

Introduction

Sarcoidosis is a heterogenous, chronic, multisystem disorder of unknown etiology, characterized by the presence of noncaseating epithelioid granulomas in various organs (1,2). While sarcoidosis most often affects the lungs, it can involve virtually any organ (3). The prevalence of symptomatic cardiac sarcoidosis is estimated at 5% and varies globally (3). South Korea has a prevalence of 4.69 per 100,000, while Sweden has 160 per 100,000 (4-5). However, it is widely accepted that cardiac sarcoidosis is underdiagnosed. Imaging and autopsy studies of systemic sarcoidosis patients showed a prevalence ranging from 20-27% in the US to as high as 79% in Japan (3, 6-7). Moreover, a study showed that cardiac sarcoidosis was responsible for 25% of deaths from sarcoidosis in the United States and 85% in a Japanese cohort (8).

Cardiac sarcoidosis clinical presentation is variable. Between 16% and 35% of patients presenting with unexplained ventricular tachycardia (VT) or complete

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atrioventricular block (AVB) were cases of undiagnosed cardiac sarcoidosis (9-12). Heart failure can be the presenting symptom of cardiac sarcoidosis if myocardial involvement is extensive. Both right and left ventricles may be involved. Patients may present with either heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) (13). Another devastating presentation of cardiac sarcoidosis includes sudden cardiac death due to ventricular tachyarrhythmias or conduction block and it accounts for 30 to 65% of cardiac sarcoidosis deaths (14). Lastly, cardiac sarcoidosis is also rarely associated with valvulopathy, acute myocarditis, coronary vasculitis, pericarditis, and atrial arrhythmias (15).

Endomyocardial biopsy (EMBx) is considered the "gold standard" for diagnosis. However, due to the patchy nature of this disease, EMBx has a low diagnostic yield (16). Therefore, several criteria are proposed to diagnose CS, including the Japanese Ministry of Health and Welfare (JMHW) criteria and Heart Rhythm Society (HRS) criteria (17-18). Both utilize histological and clinical criteria, including imaging modalities, to diagnose cardiac sarcoidosis. While EMBx is recommended by HRS guidelines, it is not necessary to establish cardiac sarcoidosis diagnosis in the presence of histological evidence of extra-cardiac sarcoidosis and imaging findings suggestive of cardiac sarcoidosis. Imaging findings suggestive of cardiac sarcoidosis include late gadolinium enhancement (LGE) on cardiac MRI (cMRI), patchy uptake on dedicated cardiac positron emission tomography (PET), and positive gallium uptake (19). In recent years, both cMRI and 18F-FDG PET have been increasingly used to diagnose cardiac sarcoidosis (20-21). LGE in cMRI identifies myocardial injury in cardiac sarcoidosis that does not follow usual coronary distributions. However, this does not differentiate chronic scars from active disease (22).

Data regarding the management of cardiac sarcoidosis and how various therapies mitigate the increased risk associated is limited and highly variable. Although there is a lack of high-quality evidence on the optimum therapeutic intervention, the use of corticosteroids is widely accepted and recommended in clinical practice as it reduces the inflammatory burden which theoretically should prevent worsening of cardiac function and decreases the risk of arrythmias (23-24). Furthermore, the use of steroids before the onset of reduced ejection fraction is suggested and is associated with better outcomes (23). To limit the side effect profile of steroids, steroid sparing agents are frequently used either as an add on or replacement. Based on clinical experience and limited data, methotrexate is the most common steroid sparing agent utilized (25). However, the data supporting its benefit compared to other steroid sparing agents is limited. Given the high mortality rate associated with arrythmias and conduction abnormalities in CS, permanent pacemakers (PPM) and implantable cardiac defibrillators (ICD) are used when indicated and provide additional therapy to prevent sudden cardiac death or a life-threatening arrhythmia while being treated with anti-inflammatory therapy (18). Although in patients with conduction abnormalities the choice of PPM alone versus combined ICD-PPM remains a debate, recent guidelines give a class IIa recommendation supporting their conjugate use when a pacemaker is indicated (18).

Given the limited evidence discussing various clinical aspects of CS; in the present study, we aim to describe the demographics, clinical presentation, sarcoidosis organ involvement, choice of diagnostic modalities, impact on quality of life, and management strategies used in patients with cardiac sarcoidosis in the United States (US), based on a national self-reported registry questionnaire.

Methods

Study population

Our study population was extracted from a national registry investigating 3,835 adult respondents to the Foundation for Sarcoidosis Research (FSR)-Sarcoidosis Advanced Registry for Cures (SARC) questionnaire. The registry from FSR is open to patients self-identifying as having sarcoidosis and is administered via a web-based questionnaire that includes 72 questions. It provides an observational cohort platform to collect cross-sectional and longitudinal self-reported data on patients' demographics, diagnostics, organ involvement, treatment modalities, and the physical and psychosocial impact of sarcoidosis. The questionnaire is in English, and a glossary is provided in case participants encounter an unfamiliar term. Respondents are either directly recruited through their medical providers, by the Foundation for Sarcoidosis Research, or via national and international organizations. We included

subjects whose surveys were completed between June 01, 2014, and August 30, 2019. Respondents can update their surveys longitudinally with time. Data from the most current survey at that time from each respondent was used for our analysis. We excluded 13 subjects who were reported to be deceased or did not respond to whether the patient was living, bringing the final cohort to a total of 3822 respondents.

Data management

The responses "unsure" or "prefer not to answer" were labeled as missing information. Answers for organ involvement were only included if the participants answered: "diagnosed." Answers that included "suspected" were included with "not involved" as we believe "suspected" might cause confusion to the participants and result in an overestimation of the organ involvement. Multiorgan sarcoidosis was defined by the reported presence of three or more organs affected by sarcoidosis. As for questions in tick-box format, empty boxes were regarded as negative. Systemic medications used to treat sarcoidosis were divided into four categories: 1) corticosteroids (prednisone, methylprednisolone, dexamethasone), 2) steroid sparing agents (methotrexate, azathioprine, leflunomide, mycophenolate, cyclophosphamide), 3) tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, certolizumab, golimumab, etanercept) and 4) other systemic therapies (rituximab, pentoxifylline, intravenous immunoglobulin (IVIG), thalidomide, adrenocorticotropic hormone).

Data analysis

We compared the following data between the included subjects with and without cardiac sarcoidosis: demographics, clinical presentation, organ involvement, cardiac diagnostics, management and quality of life. The distribution of patient characteristics and outcomes were summarized as percentages for categorical variables and means ± standard deviation (SD) for continuous variables. To compare differences between groups, we used independent sample t-test for continuous variables and Chi-square test for categorical variables. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (released 2015, IBM Corp, Armonk, NY).

Results

Demographics

A total of 394 patients (10%) subjects had CS, 57% (n=223) of whom were women, 81% (n=317) identified as white and 16% (n=62) as African American. The mean (±SD) age at diagnosis was 45 years (±13). Almost all (n=390, 99%) were diagnosed with sarcoidosis as adults. A family history of sarcoidosis was present in 64 (16%) patients. Patients with cardiac sarcoidosis were more likely to be male, more likely to self-report as Hispanic, and were significantly older compared to patients without cardiac sarcoidosis (Table 1).

Clinical presentation

Most patients were diagnosed with cardiac sarcoidosis after their initial sarcoidosis diagnosis, but cardiac sarcoidosis was the initial presentation of sarcoidosis in 101 (26%) patients. A total of 259 (66%) patients were admitted at least once to the hospital, with a mean (±SD) number of admissions 2 (±2).

Table 1. Difference in demographics between patients with and without cardiac sarcoidosis.

	Cardiac Sarcoidosis present 394 (10%)	**Cardiac Sarcoidosis absent 3428 (90%)**	**P value**
Male, n (%)	171/394 (43%)	531/2186 (24%)	<0.0001
Age, mean (+-SD)	46+-12	42+-12	<0.0001
Hispanic vs non-Hispanic, n (%)	Hispanics: 9/363 (2%) Non-Hispanics:354/363 (98%)	Hispanics: 123/1972 (6%) Non-Hispanics:1849/1972 (94%)	0.004
Race, n (%)	White: 317/386 (82%) Black: 62/386 (16%) Other: 7/386 (2%)	White: 1751/2157 (81%) Black: 362/2157 (17%) Other: 44/2157 (2%)	0.708
Family history, n (%)	64/323 (20%)	307/1778 (17%)	0.629

The most common clinical presentation of cardiac sarcoidosis was ventricular arrythmia (n=148, 38%), followed by cardiomyopathy (n=115, 29%), heart block (n=113, 29%), atrial arrhythmia (n=97, 25%), congestive heart failure (n=93, 24%), valvular pathology (n=48, 12%) and pericarditis (n=36, 9%).

Organ involvement

The most common organ involved in patients with cardiac sarcoidosis was the lungs (n=281, 77%). Patients with cardiac sarcoidosis had a median (IQR) number of organs involved with sarcoidosis of 4 (2-6) organs. Multiorgan involvement (≥3 organs) was present in 269 patients (68%). Patients with cardiac sarcoidosis were more likely to have multiorgan involvement compared to patients without cardiac sarcoidosis (OR:2.2, 95%CI:1.75-2.75, p<0.0001, Table 2). Apart from lung involvement, patients with cardiac sarcoidosis had increased odds of all organ involvement compared to patients without cardiac sarcoidosis.

Cardiac diagnostics

Most patients were evaluated by a cardiologist (n=361, 92%) and/or a cardiac electrophysiologist (n=269, 68%). Other physicians included a pulmonologist (n=181, 46%) and a rheumatologist (n=78, 20%). All patients had an echocardiogram (n=320, 100%) and an electrocardiogram (n=338, 100%). cMRI (n=293, 74%) was the most common diagnostic modality used to diagnose cardiac sarcoidosis followed by positron emission tomography (PET) scan (n=234, 59%) and lastly, cardiac biopsy (n=52, 13%). Other additional studies performed include cardiac catheterization (n=245, 62%) of which (n=21, 5.3%) patients received stents, Holter and/or event monitor (n=221, 56%), exercise stress test (n=193, 49%), nuclear stress test (n=156, 40%), invasive cardiac electrophysiology study (n=91, 23%) and gallium scan (n=59, 15%).

Management

Most patients received systemic corticosteroids (n=339, 86%) of which prednisone was most used (n=221, 56%) followed by methylprednisolone (n=15, 4%) and dexamethasone (n=1, 0.25%). Other medications administered include steroid sparing agents (n=240, 61%) of which methotrexate was most used (n=102, 26%), followed by mycophenolate (n=31, 8%), azathioprine (n=22, 6%), leflunomide (n=14, 4%) and cyclophosphamide (n=2, 0.5%). Tumor necrosis factor (TNF) inhibitors were used in (n=76, 19%) of which infliximab

Table 2. Difference in organ involvement comparing patients with and without cardiac sarcoidosis.

	Cardiac Sarcoidosis present 394 (10%)	**Cardiac Sarcoidosis absent 3428 (90%)**	**P value**
Multiorgan sarcoidosis, n (%)	269/394 (68%)	1083/2186 (50%)	<0.0001
Arthritis, n (%)	104/291 (36%)	510/2085 (24%)	<0.0001
Bone and/or vertebrae, n (%)	39/268 (15%)	180/1993 (9%)	0.006
Muscle, n (%)	45/274 (16%)	150/2011 (7%)	<0.0001
Brain and/or cranial nerves, n (%)	51/273 (19%)	191/1982 (10%)	<0.0001
Peripheral neuropathy, n (%)	91/288 (32%)	411/2055 (20%)	<0.0001
Eyes, n (%)	113/307 (37%)	437/2080 (21%)	<0.0001
Parotid, salivary and lacrimal glands, n (%)	23/257 (9%)	106/1996 (5%)	0.018
Lymphadenopathy, n (%)	200/324 (62%)	1166/2101 (55%)	0.035
Lungs, n (%)	281/365 (77%)	1591/2148 (74%)	0.237
Liver, n (%)	57/275 (21%)	230/2036 (11%)	<0.0001
Kidneys, n (%)	37/267 (14%)	116/2018 (6%)	<0.0001
Spleen, n (%)	57/269 (21%)	207/2008 (10%)	<0.0001
Stomach and/or intestines, n (%)	37/266 (14%)	109/2027 (5%)	<0.0001

was the most used (n=43, 11%) followed by adalimumab (n=8, 2%), certolizumab (n=2, 0.5%), golimumab (n=2, 0.5%) and etanercept (n=1, 0.25%). Patients stated they were actively on corticosteroids alone (n=120, 30%), methotrexate with corticosteroids (n=45, 11%), methotrexate alone (n=23, 6%), mycophenolate with corticosteroids (n=16, 4%), methotrexate along with corticosteroids and infliximab (n=11, 3%), infliximab alone (n=11, 3%), corticosteroids and infliximab (n=10, 3%), methotrexate and infliximab (n=8, 2%), leflunomide and corticosteroids (n=7, 2%), mycophenolate alone (n=7, 2%), infliximab alone (n=5, 1%), azathioprine alone (n=5, 1%), rituximab alone (n=4, 1%), corticosteroids along with methotrexate and rituximab (n=4, 1%), adalimumab alone (n=4, 1%), infliximab with mycophenolate and corticosteroids (n=3, 1%) or rituximab with corticosteroids (n=3, 1%). Other medications used include hydroxychloroquine (n=25, 6%), rituximab (n=8, 2%), IVIG (n=8, 2%), thalidomide (n=1, 0.25%) and chloroquine (n=1, 0.25%). In comparison to patients without cardiac sarcoidosis, patients with cardiac sarcoidosis were more likely to receive steroids (86% vs 74%; OR:2.2, 95%CI:1.62-2.98, p<0.0001), steroid sparing medication (83% vs 61%; OR:3.1, 95%CI:2.26-4.30, p<0.0001) and TNF inhibitors (33% vs 21%; OR:1.88, 95%CI:1.39-2.55, p<0.0001).

A combined implantable cardioverter defibrillator (ICD) and pacemaker (n=154, 39%) was most likely to be placed followed by ICD alone (n=26, 7%) and pacemaker alone (n=23, 6%). ICD appropriately shocked 67 (17%) patients and inappropriately shocked 14 (4%). Sixty-three patients (16%) had a cardiac ablation. Eight patients (2%) received a heart transplant, four patients (1%) required a valve replacement and coronary arterial bypass graft was performed in three patients (1%). Few patients were involved in clinical trials (n=16, 4%).

Quality of life

Most patients (n=312, 79%) endorsed limited physical activity with mobility device use in 74 (19%) patients. Cardiac sarcoidosis resulted in disability in 116 (29%) patients and 128 (32%) ended their job because of sarcoidosis. Patients with cardiac sarcoidosis were more likely to end their job due to health effects from sarcoidosis (42% vs 36%; OR: 1.29, 95%CI: 1.00-1.66, p=0.044). Family finances were affected in 192 (49%) patients.

Discussion

With over 3,800 patients with sarcoidosis, this is the largest US study to report prevalence and characteristics of patients with cardiac sarcoidosis. The most conspicuous findings in our study were the differences in demographics noted, including the high prevalence of cardiac sarcoidosis among patients with sarcoidosis and the higher proportion of males diagnosed with cardiac sarcoidosis. Cardiac MRI was the most common diagnostic modality utilized in 75% of cardiac sarcoidosis diagnoses and steroids, methotrexate and infliximab were the most common immunosuppressive agents used to treat CS.

The prevalence of cardiac sarcoidosis in our patient cohort was high at 10.3%, in contrast to previous studies that estimated the prevalence of cardiac sarcoidosis to range from 2.3% to 5% (26-27). However, Judson et al. and Baughman et al. required a histopathological diagnosis of cardiac sarcoidosis when estimating their prevalence (26-27). Also, these studies were conducted from 1997 to 2010 when the use and/or availability of cMRI and FDG-PET were likely limited. Furthermore, we were unable to differentiate symptomatic disease from silent cardiac sarcoidosis with our data. A higher proportion of clinically manifest disease may possibly explain the observed prevalence. Lastly, with the recent increased awareness of cardiac sarcoidosis, more patients with systemic sarcoidosis are actively screened for cardiac involvement; thus, more cases of cardiac sarcoidosis are being identified. However, is it noteworthy that our data presents self-reported cardiac sarcoidosis cases and data representing the exact number of screened individuals was not available.

Patients with cardiac sarcoidosis were almost twice as likely to be male. This is in line with a study of 1774 patients with sarcoidosis, cardiac involvement was seen in 6.7% of male patients compared to 3.3% in female patients (26). Hispanics were less likely to be diagnosed with cardiac sarcoidosis compared to non-Hispanics. In a study by Innabi et al., cardiac sarcoidosis was uncommon among US Hispanics (28). We found that 1 out of 5 patients had a family history of sarcoidosis. A study by Rybicki et al. found an increased risk of sarcoidosis amongst

first- and second-degree relatives of patients with sarcoidosis (29).

In our study, we note that patients with cardiac sarcoidosis were significantly older and were more likely to have multiorgan involvement. This age difference could explain why 68% of patients with cardiac sarcoidosis have multiorgan involvement (≥3 organs). Previous reports have shown that the number of organs involved in patients with sarcoidosis increase over time. In a study of 1774 patients with sarcoidosis, the number of organ involvement increased from 2.19 organs per patient at the beginning of the study to 2.99 organs per patient in those who were followed for more than 6 years (26).

There is growing evidence that cardiac sarcoidosis can be the first manifestation of sarcoidosis. Herein, cardiac sarcoidosis diagnosis was the initial presentation in one out of four patients with cardiac sarcoidosis. In a study of 72 patients with unexplained AVB, cardiac sarcoidosis was found to be the responsible etiology in 19% of the patients (9). In another study of patients presenting with unexplained monomorphic VT, cardiac sarcoidosis was found to be the underlying etiology in 28% of the patients (12).The most common clinical presentation of cardiac sarcoidosis in our study was ventricular arrythmia (n=148, 38%). This is an intriguing finding as most of the prior studies report AVB as the most common presenting finding in patients with cardiac sarcoidosis (10, 13). One possible explanation for the increased risk of ventricular arrythmias in our patient population is that most of our patients had abnormal cMRI (74.4%). A retrospective study of 135 patients with cardiac sarcoidosis found that patients with LGE on cMRI had significantly higher rates of ventricular arrythmias compared to those with no LGE on cMRI (27% vs 2.2%, P = 0.0008) (30).

Cardiac sarcoidosis is associated with worse outcomes including substantial morbidity and mortality (31). In the current study, 79% of patients with cardiac sarcoidosis endorsed limited physical activity and disability was reported in 116 patients (29%). This is the first study to report this extremely high rate of limitation in physical activity and disability due to cardiac sarcoidosis. The limitation in physical activity is most likely attributable to the increase rate of cardiomyopathy (29%) and CHF (24%) in our study population. Roughly two thirds of patients with cardiac sarcoidosis reported at least one hospital admission with an average of two hospitalizations during their lifespan. Cardiomyopathy related complications (CHF exacerbation, arrhythmias, syncope, etc.) and immunosuppressive therapy related complications (infections, osteoporosis and bone fractures) are likely contributors to the increased risk of hospitalization .

Although the diagnosis of cardiac sarcoidosis remains challenging, recent advancements in imaging modalities has been valuable. It is of no surprise that only 13% of our patients had EMBx. Presence of non-caseating granuloma is not mandatory for establishing cardiac sarcoidosis diagnosis under the updated Japanese Circulation Society guidelines (17). The most common diagnostic modality used to diagnose cardiac sarcoidosis was cMRI (74.4% of patients), followed by PET scan (59.3%). In a study of 107 patients who underwent cMRI and PET scan for evaluation of cardiac sarcoidosis (32), the combination of these diagnostic modalities provided a synergistic value in the diagnosis and management of patients with cardiac sarcoidosis. Specifically, ~ 45% of patients with abnormal cMRI were reclassified as having more or less likely cardiac sarcoidosis diagnoses once the FDG PET result was added to cMRI result interpretation.

Treatment of cardiac inflammation and its clinical sequelae is the mainstay treatment in patients with cardiac sarcoidosis. Among the anti-inflammatory agents, glucocorticoids is the most used agent. However, this is based on modest data from small retrospective observational studies. This includes small studies that have shown corticosteroid therapy can improve AV conduction in 47% to 67% of patients with cardiac sarcoidosis and AV conduction disease (23-24). Currently, there are no guidelines to guide steroid dosing or treatment duration. In our study, steroids were the most common medication administered for patients with cardiac sarcoidosis. In a Japanese study of 95 patients with cardiac sarcoidosis, the 5-year survival rate in patients who received corticosteroids was 75% compared with only 10% in patient who didn't receive corticosteroids (33). Other medications used to treat cardiac sarcoidosis patients in this study include steroid sparing agents such as methotrexate and mycophenolate in addition to TNF inhibitors. Patients with cardiac sarcoidosis often require chronic immunosuppressive therapy. Steroid-sparing agents should be utilized to minimize complications due to chronic steroid use. In a study by Ballul et al., adding steroid-sparing agents

to glucocorticoids reduced cardiac sarcoidosis relapse rate from 46% to 17% (p=0.048) (34). In another study of 17 patients with cardiac sarcoidosis, combining methotrexate with low-dose prednisolone resulted in stable LVEF and NT-proBNP after three years of follow-up compared to patients treated with prednisolone alone (35). Hamzeh et al. evaluated the efficacy of mycophenolate mofetil (MMF) in 37 patients with pulmonary sarcoidosis, 10 of whom had cardiac sarcoidosis (36). Only 6 out of 10 had pretreatment 18F-FDG PET. Improvement or resolution in myocardial hypermetabolic activity was seen in all 6 patients after six months of treatment with MMF. This finding supports the use of other steroid sparing agents aside from methotrexate in the management of cardiac sarcoidosis.

TNF-α plays a pivotal role in the development of granulomatous inflammation in sarcoidosis (37). TNF-α inhibitors are currently considered third-line agents in treating cardiac sarcoidosis. Infliximab, a monoclonal anti-TNF-α IgG antibody, has shown promising results in patients with cardiac sarcoidosis. In a study of 36 patients with refractory cardiac sarcoidosis, treatment with infliximab for 12 months resulted in a decrease in the steroid dose from 20mg at baseline to 5mg (p<0.001) and a non statistically significant decrease in the rate of VT from 32% at baseline to 19% (p = 0.07) (38). Importantly, there was no worsening in LV function. In another study of 22 patients with cardiac sarcoidosis, treatment with Infliximab (5mg/kg) resulted in reduction in inflammation on FDG-PET and an improvement in LV function (median LVEF increased from 45.0% to 55.0%, p = 0.02) (39). In a study of 77 patients with cardiac sarcoidosis, 20 were treated with anti-TNF-α inhibitor (10 infliximab, 10 adalimumab) (40). All 20 patients were on methotrexate at the time of TNF-α inhibitor initiation. Anti TNF-α inhibitor was initiated due to progressive heart failure, tachyarrhythmia, or worsening imaging findings. Treatment with anti-TNF-α inhibitor resulted in the resolution of disease activity on imaging in all 20 patients within 12 months of treatment initiation. In another study of 28 patients with cardiac sarcoidosis, 25 patients received prednisone (>30mg/day initially and were later tapered down to <10mg/day) plus methotrexate (41). Patients intolerant to methotrexate or with persistently active cardiac sarcoidosis were started on Adalimumab (n=19). Prednisone and methotrexate reduced or eliminated FDG uptake in 88% and 60% of patients, respectively. Treatment with Adalimumab improved or resolved 18F-FDG uptake in 84% and 63% of patients, respectively. Nine patients discontinued immunosuppressive therapy; repeat FDG PET showed cardiac sarcoidosis recurrence in 8/9 patients (88.9%) compared to 15.8% of patients with uninterrupted immunosuppression. A higher rate of VT was seen in patients who discontinued immunosuppressive therapy (33.3%) compared to 15.8% in those who continued immunosuppressive therapy. These findings support the use of other anti-TNF inhibitors aside from infliximab.

Management of VT in patients with cardiac sarcoidosis can follow a stepwise approach. First, in patients with active inflammation on FDG-PET, immunosuppressive therapy can be tried first. If VT persists, then adding anti arrhythmic medication is suggested. If these two interventions fail, patients should be referred for catheter ablation. In a study of 42 patients with cardiac sarcoidosis and VT, corticosteroids with/without anti arrhythmic medications effectively suppressed VT in 33/42 patients (42). In the remaining 9 patients, catheter ablation was effective in eliminating VT or markedly reducing the VT burden. Amiodarone and Sotalol are used to treat VT in patients with cardiac sarcoidosis (43).

The most common cardiac device implanted in our study population was a combined implantable cardioverter defibrillator (ICD) and pacemaker (n=154, 39%) followed by ICD alone (n=26, 7%) and pacemaker alone (n=23, 6%). ICD implantation is a class I recommendation in patients with cardiac sarcoidosis and LVEF ≤ 35% despite optimal medical therapy and a period of immunosuppression, history of cardiac arrest and/or spontaneous sustained ventricular arrythmias (18). ICD implantation is a Class IIa indication in patients with cardiac sarcoidosis and unexplained syncope/pre-syncope that is felt to be arrhythmic in etiology and inducible sustained ventricular arrhythmias. HRS guidelines recommend that primary prevention ICDs be considered for all cardiac sarcoidosis patients with an indication for permanent pacing [class IIa recommendation] (18). This recommendation is supported by a study of 53 patients with cardiac sarcoidosis (43); patients with high grade AV block (22 patients) and those with VT and/or HF (31 patients), had a similar rate of ventricular fibrillation and sustained VT after a follow up period of 34 months.

We acknowledge the limitations of our study that are related to the self-reported nature of this registry leading to recall bias and non-differential misclassification of our variables, most importantly the diagnosis of cardiac sarcoidosis. It may have caused the higher prevalence of cardiac sarcoidosis in our cohort when compared to previous studies. Unfortunately, this bias is commonly noted in self-reported registry studies; however, the relatively large participant number in our study as compared to previously published literature might alleviate this bias. The electronic recruitment process of this registry may have led to a referral bias which may explain over-representation of white women in this registry; this might limit the generalizability of our data. Furthermore, patients with more severe sarcoidosis and chronic forms of sarcoidosis are more likely to be included in this registry but not self-remitting sarcoidosis. This could lead to a selection bias since such patients may be at more risk for developing cardiac sarcoidosis.

In conclusion, cardiac sarcoidosis is more prevalent than previously described. It can be the initial presentation in one-third of cardiac sarcoidosis patients. Cardiac sarcoidosis is associated with high morbidity and mortality and thus should be managed by providers with experience in this evolving field. Immunosuppressive therapy should be started as early as possible. Clinical response and serial imaging should guide the treatment plan.

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