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ABSTRACT

INTRODUCTION: The course and prognosis of cardiac sarcoidosis (CS) are sparsely described. The purpose of this study was to assess the clinical presentation, treatment response and prognosis for patients with CS.

METHODS: This was a single-centre retrospective study of patients with CS from 2006 to 2016. A total of 197 patients with a sarcoidosis diagnosis were screened, and 17 patients (mean age 46.9 years, 59% men) were diagnosed with CS based on Japanese Ministry of Health and Welfare criteria; 53% were diagnosed by a positive MRI, 29% by endomyocardial biopsy. Of 17 patients, nine (53%) had a left ventricular ejection fraction (LVEF) < 45% at the time of diagnosis. The median follow-up was four years. In 13 patients, an implantable defibrillator was used and six of these (46%) received first appropriate shock therapy after a mean follow-up of two years. A total of 11 (65%) patients were treated with prednisolone and five (45%) of these 11 patients were also treated with another immunosuppressant.

RESULTS: The median LVEF did not change at the last follow-up (p = 0.68), but improved in 30% of patients on combination therapy with prednisolone and proliferation inhibitors, whereas 23% of patients with prednisolone monotherapy experienced further worsening of LVEF. Immunosuppression was not used in 35% of patients. During follow-up, one patient underwent a successful heart transplant, one had a left ventricular assist device implantation and one died from septic shock.

CONCLUSION: In CS patients, ventricular arrhythmias and impairment of LVEF were frequently seen, but the medium-term survival was excellent on heart failure therapy and immunosuppression.

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Sarcoidosis is a systemic granulomatous disease with a poorly understood aetiology. Non-caseating granulomas are the main pathological findings in patients with sarcoidosis. The role of Th1, a CD4+ T helper cell type 1 lymphocyte that activates phagocyte-dependent inflammation and the Th17 effector CD4+ T cell, which is a mediator of inflammation and granuloma development, is well documented in sarcoid formation [1, 2]. Sarcoidosis usually presents in the lung but may also involve lymph nodes, the skin, the eye, the central nervous system and the heart. Even though it is a systemic disease, the manifestations of sarcoidosis vary widely from patient to patient and especially in those with cardiac involvement [3]. Clinical manifestations of cardiac sarcoidosis (CS) include conduction disturbances, atrial and ventricular arrhythmias and ventricular dysfunction. CS is reported to be found in 5% of patients with extra-cardiac sarcoidosis and it is clinically silent in more than 20% of cases [3, 4], but autopsy and imaging reports of patients with extra-cardiac sarcoidosis have shown noncaseating granulomatous myocardial infiltration with a prevalence of 25-80%, varying by ethnicity [5].

Reports on diagnostic findings, treatment and outcome for CS are sparse and more knowledge is clearly needed [5, 6]. The main purpose of this investigation was to assess the clinical presentation, response to treatment and prognosis of patients with CS.

METHODS

This was a single-centre, retrospective study of patients diagnosed with CS from January 2006 to December 2016 at Rigshospitalet, Copenhagen, Denmark. During the study period, all patients admitted to the Department of Cardiology (including the Department for Lung Transplantation) with a diagnosis of sarcoidosis (International Classification of Diseases (ICD)-10 DD86), were identified using the hospital's electronic filing system. The medical records of the patients were reviewed systematically and examined in order to identify patients with cardiac involvement. Patients were selected for review if it was documented that they had cardiac findings or symptoms, i.e. dyspnoea, syncope, palpitations, chest pain, fatigue or dizziness, and were included if fully or partially fulfilling the diagnostic criteria for CS as presented by the Japanese Ministry of Health and Welfare (JMHW) from 1993 [6] or the modifications hereof [7]. We also included patients with ventricular tachycardia (VT), complete heart block or abnormal electrocardiography (ECG) with right-bundle brunch block, left-bundle brunch block, first-degree atrioventricular (AV) block and positive endomyocardial biopsy (EMB) or positive advanced imaging studies such as cardiac MRI, characterised by regional wall motion abnormalities, abnormal wall thickness, myocardial oedema and inflammation using late-

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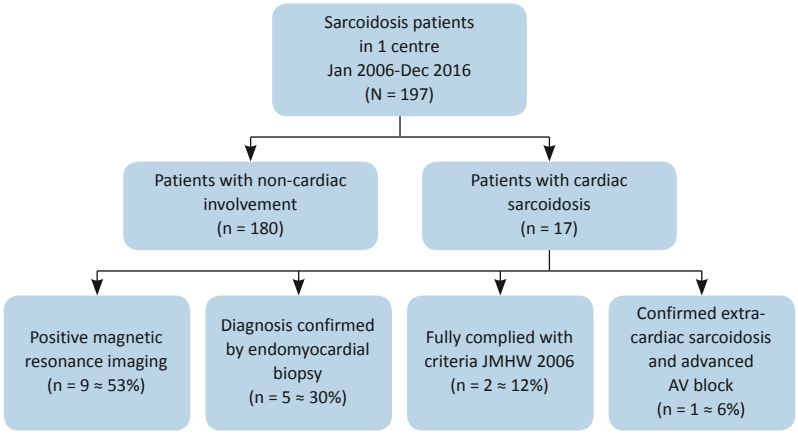
FIGURE 1

Flow chart for the study of patients with sarcoidosis.



AV = atrioventricular block; JMHW = Japanese Ministry of Health and Welfare.

TABLE 1

Positive magnetic resonance imaging (MRI) of patients based on sarcoid localisation in the myocardium.

Localisation	Positive MRI, % (n = 9)
Right ventricle	29
Left ventricle	41
Septum	35

gadolinium-enhanced (LGE) images and T2-weighted imaging.

For patients identified with CS, the following additional parameters were recorded: age at diagnosis, gender, cardiac symptoms, organ involvement in extra-cardiac sarcoidosis, echocardiographic data including left ventricular ejection fraction (LVEF), ECG readings, cardiovascular drug therapy, treatment with corticosteroids and other immunosuppressive medications, implantation of defibrillators like implantable cardioverter-defibrillator (ICD), cardiac resynchronisation therapy-defibrillator (CRT-D) or pacemakers and ICD therapies.

Follow-up was maintained until 31 December 2016 with an average follow-up period of 55.4 months. The study was approved by the Danish Data Protection Agency (File no. RH-2016-301, I-Suite no: 04965). Patients were not asked for informed consent for this chart review.

Trial registration: Danish Data Protection Agency: (File no. RH-2016-301, I-Suite no. 04965).

RESULTS

During the ten-year period, a total of 197 subjects with sarcoidosis were identified. By far, the lungs were the most commonly affected organ (91%). Subjects with a history of sarcoidosis without cardiac involvement (n = 180) were excluded from the analysis. However, we cannot exclude that some of the 180 patients not entered into the current study did, indeed, have CS as they were not prospectively investigated for this. A total of 17 patients with cardiac involvement were identified during the study period and included in this study. Given the retrospective nature of the study, we only included patients with a diagnosis of CS (**Figure 1**). The median age at diagnosis was 46.9 years and 59% were males. The initial symptoms were dyspnoea in 70% of patients, palpitation in 35% of the patients and fatigue in 23% of the patients. Cardiac arrest was the initial presentation in two patients (12%), two patients (12%) complained of chest pain, two patients (12%) complained of dizziness and one (6%) presented with bradycardia.

Half of the patients (n = 9; 53%) were diagnosed by positive MRI (**Table 1**). An EMB was done in eight (47%) patients, of whom five (29%) were diagnostic of sarcoidosis (**Table 2**). Subjects without a diagnostic biopsy and no documentation of extra-cardiac involvement (n = 2; 12%) were diagnosed clinically by fulfilling the JMHW criteria which included; advanced AV block, LVEF below 50% and an abnormal electrocardiogram with ventricular tachycardia or ventricular fibrillation. The last patient (n = 1; 6%) was diagnosed by positive extra-cardiac biopsy of one isolated organ and advanced AV block. At the follow-up, 16 (94%) of the patients were alive. One female patient aged 37 died from septic shock after 48 months of follow-up.

During a median follow-up of four years, 65% of patients complained of dizziness, 59% of dyspnoea, 53% had palpitation and only 6% had chest pain. However, 47% of the patients who were treated with prednisolone monotherapy or a combination therapy with other immunosuppressants experienced dizziness, tiredness, nausea, mood changes, insomnia and Cushingoid features.

In our study, AV conduction delay was frequently seen (n = 8; 47%), advanced AV block being present in six (35%). The second-most common abnormality in four (23%) patients with CS was sinus rhythm with complete right bundle branch block. Two patients with CS presented with ventricular tachycardia and the remaining two (12%) had a normal ECG.

Treatment is presented in **Table 3**. Anti-congestive medications were used in 13 patients (76%), anti-arrythmics in 15 (88%), a defibrillator (ICD) was implanted in 11 (65%), a CRT-D was used in two (12%) and two (12%) had a pacemaker implant. Of the 13 (77%) patients in whom an ICD or CRT-D was implanted, six (46%) received first appropriate shock therapy after a mean fol-

TABLE 2

Symptoms, diagnostic features and extra-cardiac sarcoid involvement.

Patient no.	EMB/MRI	Initial symptoms	Extra-cardiac sarcoidosis	LVEF, %	ECG	Japanese criteria
1	ND/ND	Palpitation, dyspnoea	Renal	60	3rd-degree AV block	+
2	Pos./pos.	Dyspnoea	-	40	SR + 1st-degree AV block	+
3	Neg./pos.	Palpitation, dyspnoea, dizziness	-	60	SR + 1st-degree AV block	+
4	ND/pos.	Dyspnoea	Pulmonary Cutaneous	30	VT	+
5	Pos./ND	Dyspnoea	Pulmonary	60	SR	+
6	Neg./pos.	Palpitation, dyspnoea	Pulmonary	35	VT	+
7	Neg./pos.	Cardiac arrest	Pulmonary	60	SR	
8	ND/ND	Chest pain	-	30	VT ⇒ multiple PVC + SVES with Q-wave ⇒ 3rd-degree AV block	+
9	Pos./ND	Palpitation, dyspnoea, tiredness	-	30	SR + LBBB	+
10	ND/pos.	Dyspnoea	Pulmonary	60	SR + 3rd-degree AV block	+
11	ND/pos.	Chest pain, dyspnoea	Mediastinal lymph node	60	SR + CRBBB	+
12	ND/pos.	Palpitation, dyspnoea, tiredness	Pulmonary	45	SR + 3rd-degree AV block	+
13	Pos./ND	Dyspnoea, tiredness	-	15	SR + CRBBB	+
14	Pos./ND	Chest pain, tiredness, dyspnoea	-	20	SR + CRBBB	+
15	ND/pos.	Syncope palpitation, dyspnoea	Pulmonary	60	SR + 3rd-degree AV block	+
16	ND/ND	Cardiac arrest, dyspnoea	-	30	VF ⇒ SR + 3rd-degree AV block	+
17	ND/ND	Bradycardia	Mediastinal lymph node	60	SR + multiple PVC	+

AV = atrioventricular; CRBBB = complete right bundle branch block; EMB = endomyocardial biopsy; ECG = electrocardiography; LBBB = left bundle branch block; LVEF = left ventricle ejection fraction; MRI = magnetic resonance imaging; ND = not done; neg. = normal answer; pos. = positive answer; PVC = premature ventricular complexes; SR = sinus rhythm; SVES = supraventricular extrasystoles; VF = ventricle defibrillation; VT = ventricle tachycardia.

low-up of two years and four (31%) received first anti-tachycardia pacing therapy after a mean follow-up of 1.9 years. One patient underwent a heart transplantation and one required a left ventricular assist device implantation.

The median (range) LVEF at baseline was 45 (15-60%). Overall, LVEF did not change at the last follow-up 45 (10-60%), regardless of treatment with prednisolone. In six (35%) patients with no symptoms or very mild symptoms, neither corticosteroids nor other immunosuppressants were used. In one of these patients, LVEF decreased significantly during follow-up.

DISCUSSION

In patients with CS, ventricular arrhythmias and impairment of LVEF were frequent, which is in line with previous research [8]. The clinical presentation of the patients in our study was comparable to findings in other studies, i.e. symptoms of serious cardiac arrhythmias, heart failure, sudden cardiac death or diffuse mild symptoms of dizziness, tiredness and palpitation [9-13]. In addition, CS is often clinically silent and may present with sudden cardiac death [10, 14]. ECG and echocardiography may be normal in the initial phase of the disease [15]. While the heterogeneous presentation of CS makes the diagnosis challenging, it is essential to identify and treat CS at an early stage to avoid malignant arrhythmia and development of heart failure.

This single-centre study shows that more than half of patients with CS were middle-aged men (59%). This is in contrast to the study by Kandolin et al [11], which reported that CS was more frequently found in young or middle-aged women.

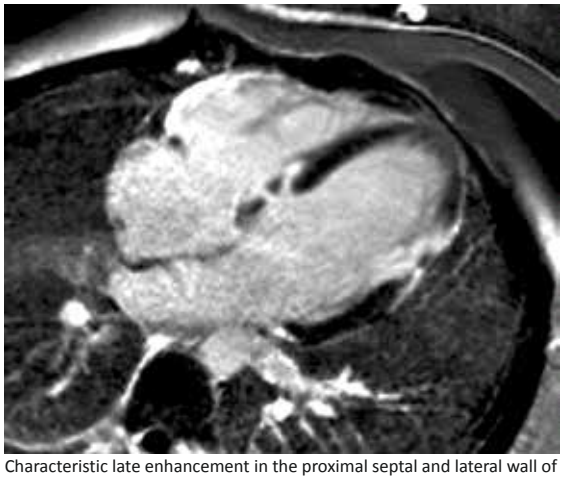
LGE has demonstrated an improved sensitivity for the diagnosing of CS. Smedema et al [12] have compared the JMHW criteria with CMR sensitivity for CS and found that all 12 patients who fulfilled the JMHW criteria had a positive CMR. Patel et al [13] examined the prognostic value of LGE in CMR and demonstrated that patients with LGE had a nine-fold higher occurrence of adverse events with arrhythmias and cardiac death than non-LGE patients. A study by Greulich et al [16] explored a large population of 155 patients with systemic sarcoidosis who were examined by CMR for possible CS. After a follow-up of 2.6 years, they concluded that the presence of positive LGE by CMR was the best independent predictor for potential future lethal events like cardiac death, aborted sudden cardiac death, appropriate ICD therapy or ventricular tachycardia. In our study, 53% of patients were retrospectively diagnosed by positive

TABLE 3

Treatment.

	Treated patients, n (%) (N = 17)
Anti-congestive drugs/anti-arrhythmics	
ACE-I/ARB	13 (76)
Beta blocker	13 (76)
Furosemide	5 (29)
Spironolactone	5 (29)
Amiodarone	1 (6)
Eplerenone	2 (12)
Ca^{2+} antagonist	1 (6)
Devices	
PM	2 (12)
CRT-D	2 (12)
ICD	11 (65)
Heart transplant	1 (6)
LVAD	1 (6)
Immunosuppression	
Corticosteroid	11 (65)
Azathioprine	3 (18)
Mycophenolate	2 (12)
Everolimus	1 (6)
Infliximab	1 (6)
None	6 (35)

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CRT-D = cardiac resynchronisation therapy-defibrillator; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; PM = pacemaker.



Characteristic late enhancement in the proximal septal and lateral wall of the left ventricle and there probably is also some late gad enhancement in the right ventricular free wall.

CMR. Three of the patients in our cohort underwent fluorodeoxyglucose (FDG)-PET and had positive scans. FDG-PET technique may supplement and in some instances replace MRI and will likely play a greater role in the future [17]. It is possible that a proportion of the 180 patients without a CS diagnosis did, in fact, have cardiac involvement. Further studies are required to investigate early or "silent" CS in patients with extra-cardiac sarcoidosis [3, 4] and possibly the new non-invasive techniques will help provide this information

Immunosuppressive therapies, specifically corticosteroids, have been shown to be effective in the prevention of further granulomatous affection of the myocardium and subsequent organ dysfunction, although large studies are not available [7]. Some studies suggest that administering steroids in CS patients may prevent development of LV dysfunction if LVEF is initially normal [15, 18] and may even improve moderately depressed LV function (LVEF 35-55%). However , beneficial effects of steroid on severely depressed LVEF have not been reported [15, 19]. In our study, 11 patients (65%) were treated with prednisolone, and other immunosuppressants were added in five patients who had improved LVEF. Four patients out of eleven were treated only with prednisolone and had reduced LVEF at follow-up and two of them had no changes in LVEF regardless of prednisolone treatment. In the remaining six (35%) patients with no symptoms or very mild symptoms, neither corticosteroids nor other immunosuppressants were used. In one of these patients, LVEF decreased significantly during follow-up. Interestingly, patients treated with combination therapy with prednisolone and proliferation inhibitors exhibited improved LVEF; still, overall, LVEF did not change with a median (range) at baseline of 45% (15-60) or at the last follow-up (45% (10-60)) with a p-value of 0.68.

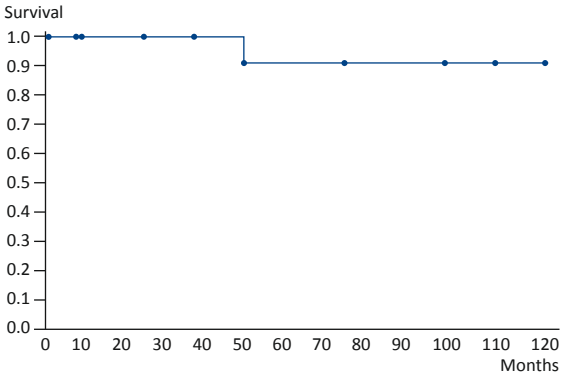
Given the observational nature of the study, it is not possible to determine if this difference in outcome was related to treatment. Also, caution in interpreting any differences between outcomes should be exerted given the low number of patients. As such, the results are merely hypothesis-generating. Clearly, randomised trials of different immunosuppressive CS treatment regimens are needed. Given the prevalence of the disease, this would require collaborative efforts between dedicated centres. More than half of the patients in whom an ICD or CRT-D was implanted experienced appropriate shocks. Although ICD shocks are not exact surrogates of haemodynamically significant VT episodes or sudden cardiac death, the finding supports the guidelines recommending ICD implantation at a low threshold in CS [7, 20]. The medium-term survival in patients with CS was excellent with a median follow-up of four years, an average period of 55.4 months with the range of 0-120 months. However, despite prednisolone treatment, VT and reduced LVEF were frequent, which is consistent with findings from Finland [9].

CONCLUSION

The survival in this cohort of patients with CS was excellent (**Figure 2**), but a substantial proportion of patients experienced ventricular arrhythmias or worsening heart

FIGURE 2

Kaplan-Meier survival curve of the 17 patients.



failure. Patients treated with a combination of prednisolone and other immunosuppressants appeared to fare better, which should be explored in further studies.

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