Multimodality Diagnostic Approach in Cardiac Sarcoidosis: from ECG to Magnetic Resonance Imaging

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Abstract

Aim: To describe the non-invasive multi-imaging options in patients who develop ventricular, supraventricular arrhythmias and conduction defects as a manifestation of cardiac sarcoidosis (CS) with biopsy documented systemic sarcoidosis.

Method: We report four cases of patients with extra-cardiac sarcoidosis presented with different manifestations of CS.

Results: CS was presented by ventricular tachycardia, total AV block, paroxysmal atrial fibrillation, persistent atrial flutter, complete right bundle branch block and multifocal PVC’s. Moderate diastolic dysfunction (DD) was detected on echocardiography in one patient and mild DD in two patients. Systemic sarcoidosis was histologically and/or cytologically confirmed in all patients. No endomyocardial biopsy was performed. 18F-fluorodeoxyglucose positron emission tomography (FDG PET) was performed in three patients and cardiovascular magnetic resonance imaging (cMRI) was undertaken in 3. Merging of FDG PET with cMRI images revealed inflammatory activity at the sites of late gadolinium enhancement (LGE). All subjects were treated medically with a combination of prednisolone and methotrexate or azathioprine. A dual chamber implantable cardioverter-defibrillator (ICD) was implanted in three patients and the fourth received a dual chamber pacemaker. Transthoracic echocardiography findings of diastolic dysfunction were detected in one patient.

Conclusions: Non-invasive multi-imaging diagnostic approach is useful in patients with biopsy-proven extra-cardiac sarcoidosis who develop conduction disorder, supraventricular or ventricular tachyarrhythmias to confirm cardiac involvement and monitor treatment.

Keywords: Cardiac sarcoidosis, AV block, ventricular tachycardia, 18F-fluorodeoxyglucose positron emission tomography, magnetic resonance imaging.
Introduction
Sarcoidosis is a systemic inflammatory disorder with unknown etiology which is characterized by the formation of non-caseating giant-cell epitheloid granulomas affecting many organ systems. Most commonly, it localizes in the lungs, hilar lymph nodes and skin.1,2 Cardiac sarcoidosis (CS) is a challenging diagnosis due to the often focal nature of cardiac involvement. CS may be manifested by ventricular tachycardia (VT), high grade heart block, heart failure or sudden death.3,4 Cardiac manifestations are reported in 2.3% - 5% of the patients with systemic sarcoidosis,5,6 but a higher percentage of 8% of cardiac involvement has been seen in the World Trade Center survivals.7 The prevalence of CS in systemic sarcoidosis patients is estimated at 39% - 50%.4,8 In autopsy series of patients with systemic sarcoidosis, CS was found in 27% to 40% of patients.9,10

In this paper, we present 4 adult patients with non-invasively diagnosed cardiac sarcoidosis who presented with variable clinical manifestations. Diagnoses of CS was supported by extracardiac biopsy of lymph node and/or lung. The multimodality imaging techniques for diagnosis of cardiac sarcoidosis are briefly described.

Case presentations

Methods
We present 4 adult patients with non-invasively diagnosed cardiac sarcoidosis who presented with different clinical pictures. All clinical, diagnostic and therapeutic characteristics of the four patients (2 females; mean age 54.5, range 47-71 years) (Table 1) are described. The multimodality imaging techniques (Figures 1-4) for diagnosis of cardiac sarcoidosis are highlighted.

Results
The clinical presentations were dizziness (n =3), palpitation (n =2), dyspnea (n =2) and fatigue (n =2). Profuse sweating was present in 2 patients. Monomorphic ventricular tachycardia was found in one patient (patient 1), successfully terminated by electrical cardioversion; two patients (patients 1 and 3) (CHA2DS2-VASc score = 0) developed supraventricular arrhythmias (atrial fibrillation (AF), atrial flutter and atrial tachycardia). AF was treated with chemical conversion. Electrocardiographic (ECG) abnormalities were present in all. Twelve-lead ECG demonstrated sinus rhythm with first degree atrioventricular block (AV) in one patient (patient 1) and total AV block (TAVB) in another (patient 2). Prolonged QTc interval was present in one patient (patient 1) and complete right bundle branch block in another (patient 3). Two patients (patients 3 and 4) complained of unifocal and multifocal premature ventricular beats, respectively. A previous history of treated arterial hypertension and known systemic sarcoidosis (since 2008) was present in one patient (patient 2) and erythema nodosum was diagnosed in 2006 in another (patient 4). After discontinuation of beta blocker and on monitoring of patient 2, no signs of conduction recovery was observed, she remained in TAVB. Chest X-ray was abnormal in all four patients. Troponine T (normal range < 14 ng/l) was mildly elevated in three patients (patients 1, 2 and 3). Left ventricle systolic function and dimensions were normal in all patients. Mild diastolic dysfunction was detected in two patients (patient 1 and 4) and moderate in one (patient 2). Coronary angiography revealed normal coronary arteries in three and was not performed in one of the patients (patient 2). Myocardial

Figure 1A: Admission electrocardiogram showing broad-complex monomorphic ventricular tachycardia of 228 beats/min.
Figure 1B: ECG: depicting persistent atrial flutter with 4:1 AV block and sporadic premature ventricular contraction.
Figure 1C: Paratracheal (station 2R) lymph node biopsy, Hematoxylin & Eosin (H+E) staining demonstrating noncaseating, multinucleated giant cell granulomas without necrosis (double-headed arrow), magnification 200x.
Figure 1D: Whole body FDG-PET scan demonstrates showing the sarcoidosis activity, increased FDG uptake in the right ventricle and atrium with multiple mediastinal and abdominal lymphadhenopathy (arrows).
Figure 1E: increased FDG uptake in the right ventricle and atrium.
Figure 1F: FDG PET and MRI LGE fusion image localizes the cardiac FDG uptake in the right ventricular and atrial walls. Left panel: MRI LGE, right panel: fusion images of MRI LGE and FDG PET, demonstrating LGE producing the same zones of segmental wall thinning (arrows) with a mid-wall pattern in the right ventricle and right atrial wall.
<table>
<thead>
<tr>
<th>Case/age/sex (years)</th>
<th>Clin. present</th>
<th>Blood pressure (mmHg) on admission</th>
<th>ECG</th>
<th>Troponin T (N &lt; 14 ng/l)</th>
<th>Chest X-ray</th>
<th>TTE</th>
<th>CAG</th>
<th>Positive biopsy</th>
<th>18F-FDG-PET-CT uptake</th>
<th>Cardiac MRI (LGE)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- 52M</td>
<td>Dizziness Tachycardia</td>
<td>82/60</td>
<td>VT, AFl, transient 1e degree AV block and prolonged QTc</td>
<td>27</td>
<td>bilateral pleural effusion without signs of pulmonary venous congestion or hilar lymphadenopathy</td>
<td>DD-I, LVEF: 52.3%</td>
<td>N</td>
<td></td>
<td></td>
<td>Paratracheal lymph node (station 2R)</td>
<td>Increased activity RV and RA. Mediastinal and abdominal para-aortic lymphadenopathy</td>
</tr>
<tr>
<td>2- 71F</td>
<td>Dizziness Dyspnea</td>
<td>134/41</td>
<td>TAVB</td>
<td>17</td>
<td>Mediastinal and hilar lymphadenopathy</td>
<td>DD-II, Mild AR, MR and TR. LVEF: 62.6%</td>
<td>not performed</td>
<td>Lymph node EUS (station 7)</td>
<td>Extensive uptake in both lungs, mediastinal, supravacular and inguinal. Uptake in LV myocardium</td>
<td>not performed</td>
<td></td>
</tr>
<tr>
<td>3- 48M</td>
<td>Palpitation Dyspnea</td>
<td>120/68</td>
<td>SR, PVC’s, PAC’s, AT, PAF, RBBB</td>
<td>19</td>
<td>Mediastinal lymphadenopathy. Parenchymal nodular pattern of perilymphatic distribution in RUL</td>
<td>N, LVEF: 60.3%</td>
<td>N</td>
<td></td>
<td></td>
<td>Right upper lung lobe (RUL)</td>
<td>Not performed</td>
</tr>
<tr>
<td>4- 47F</td>
<td>Dizziness Palpitation Fatigue</td>
<td>140/80</td>
<td>SR, multifocal PVC’s</td>
<td>14</td>
<td>Hilar lymphadenopathy</td>
<td>DD-I, LVEF: 58.4%</td>
<td>N</td>
<td></td>
<td></td>
<td>Inguinal lymph node</td>
<td>Excessive FDG uptake infracavitular, mediastinal, abdominal and inguinal lymphadenopathy and myocardial uptake (septum and apex)</td>
</tr>
</tbody>
</table>

Table 1: Data of four patients with histologically/cytologicalley proven cardiac sarcoidosis.
perfusion imaging demonstrated normal perfusion without defects and no signs of ischemia (patient 2). 18F-fluorodeoxyglucose positron emission tomography (FDG PET) was performed in three patients (patients 1, 2 and 4) demonstrating increased activity in all and cardiovascular magnetic resonance imaging (cMRI) was undertaken in 3 revealing late gadolinium enhancement in all. Merging of FDG PET with cMRI images revealed inflammatory activity at the sites of late gadolinium enhancement (LGE). FDG PET showed increased activity in the right ventricle and right atrium as well as mediastinal and abdominal para-aortic lymphadenopathy (patient 1), augmented FDG uptake in the left ventricle (patient 2) and visible activity in cervical, mediastinal, hilar, para-aortic abdominal and inguinal lymph nodes with also myocardial septal and apical localization in the left ventricle (patient 4) (Figure 1-4). Systemic sarcoidosis was histologically and/or cytologically (paratracheal lymph node (patient 1), lymph node station 7 (patient 2), right upper lung lobe (patient 3) and inguinal lymph node (patient 4)) confirmed in all patients. No endomyocardial biopsy was performed.

Three patients (patients 1, 3 and 4) underwent dual chamber implantable cardioverter-defibrillator (ICD) placement and permanent dual chamber pacemaker was implanted in one patient (patient 2). Treatment with a combination of prednisolone and methotrexate was initiated in three patients and a combination of prednisolone and azathioprine in one (patient 1).

Discussion

History and incidence

Cardiac sarcoidosis (CS), is a highly lethal disorder due to heart failure, complex ventricular arrhythmias,3 or even sudden cardiac death.9 In 1929, cardiac involvement was first recognized in an autopsy case11 and in 1952, Longcope et al, described myocardial involvement in 20% of a large series of autopsied cases of sarcoidosis.12 Later autopsy studies have revealed that between 27% and 40% of patients with systemic sarcoidosis have myocardial involvement.9 10,13

Clinical presentations

CS may be asymptomatic in 3.7-54.9% of patients undergoing different imaging studies.14 15 Clinical presentations of CS, reported in decreasing order of frequency, are ventricular tachycardia (VT) 21%, syncope 17%, congestive heart failure 14% and palpitation in 6% of subjects. 16 Furthermore, in CS, sudden death due to ventricular arrhythmia accounts for 30-65% in this population. 17,18 It has been observed that the degree and severity of pulmonary involvement did not predict and is not correlated with cardiac sarcoidosis. 4,19 CS can be found prior, after or concurrently with involvement of the lungs or other systems and organs. In our female patients, CS took 5 to 7 years before it became manifest; one in association with pulmonary sarcoidosis and in the other following cutaneous sarcoidosis, respectively.

Diagnosis

Revised Japanese Ministry of Health Welfare (JMHW) criteria and biopsy results were used to confirm the diagnosis of CS. Systemic sarcoidosis is a clinical diagnosis supported by laboratory, radiologic and nuclear imaging studies and histopathologic or cytologic examinations. Furthermore, Heart Rhythm Society expert consensus recommendations on criteria for the diagnosis of CS provides 2 pathways to a diagnosis of CS: First, histological diagnosis from myocardial tissue and second, clinical non-invasive and invasive imaging studies for establishing the diagnosis of CS.19

When CS is suspected, several diagnostic modalities have been recommended. Assessment by TTE, ambulatory ECG monitoring, myocardial perfusion imaging, cardiac MRI or 18F-FDG PET-CT are recommended.

Electrocardiography: ECG findings of CS are fractionation of QRS complex (75%), RBBB (19-23.1%) and LBBB (3.8%-6%). 16,20 The ECG of the first patient showed an episode of sustained monomorphic VT. Recently, it has been reported that isolated cardiac sarcoidosis may be highly suspected in subjects with sustained ventricular tachycardia. 21 In a prospective study, four of 14 (28%) patients presenting with monomorphic VT had CS as the causing etiology. 22 Persistent atrial flutter occurred also in the first patient and paroxysmal atrial fibrillation was documented in the third patient. Multifocal ventricular premature contractions were found on the ECG of the fourth patient. Commonly, atrial arrhythmias occur less frequently in CS. 23 Various degrees of AV block occurs in 26-67% and complete heart block in 23-30% of CS cases. 16,17,18 Recently, in a prospective study of patients with unexplained total AV block, previously undiagnosed CS was found in 34% of the patients. 24 Resting ECG has low sensitivity (8%) for detecting CS. 4

In patients with proven systemic sarcoidosis ECG alterations...
can be used as a marker of cardiac involvement. Presence of fragmented QRS or a bundle branch block or a Q wave increase the likelihood of cardiac sarcoidosis. Right bundle branch block was found in one or our patients. Corrected QT interval was within the normal limits in three subjects ranging from 405 to 426 and in one male patient it was slightly increased to 468 msec.

Echocardiography is readily available and provides valuable information of myocardial, valvular, pericardial, and congenital heart defects associated with ventricular arrhythmias. It is recommended in subjects with ventricular arrhythmias who are suspected of having structural heart disease. In our series, the echocardiography images were optimal for judgment which excluded cardiomyopathy and pericardial effusion with slightly abnormal dilatation of the RV with septal D-sign in one patient (patient 1) suggesting echocardiographic pulmonary hypertension (PHT). In three patients, various degrees (grade I and II) of diastolic dysfunction were detected. Recently, Joyce et al, have shown that RV dysfunction detected using right ventricular global longitudinal peak systolic strain (RVGLS) is commonly found in sarcoidosis in the absence of manifest cardiac involvement or pulmonary hypertension.

LV dysfunction, WMAs and abnormal septal thickness are most frequently reported. 26 27 As early as 1996, Fahy et al., reported LV diastolic dysfunction in 14% (7/50) of patients (6/7= 86% had normal systolic function) with biopsy-proved pulmonary sarcoidosis.26 Chiu et al., reported echocardiographic manifestations in 52 patients with CS, they found WMAs in 77% (40/52), impaired LV function in 54% (28/52), thinning of basal IVS in 52% (27/52), thinning of LV free wall in 35% (18/52) and apical aneurysm in 23% (12/52).27 Smedema et al., found that WMAs, MR, LV dimensions and diastolic and systolic function correlated with the degree of myocardial involvement detected by cardiac MRI.14

Coronary angiography (CAG) is pivotal in patients with life threatening ventricular tachyarrhythmias in establishing the presence of significant atherosclerotic coronary heart disease (CHD). CAG is commonly performed as part of the diagnostic evaluation, to rule out coronary vessel anomalies or malformations. CHD was ruled out in our presented patients by absence of anginal complaints and normal findings on CAG and normal myocardial perfusion imaging.

Cardiac MRI is a useful diagnostic utility when echocardiography is unable to provide accurate assessment of LV or RV function. In addition to echocardiography, CMRI can characterize tissue revealing inflammation and fibrosis. Diagnostic MRI findings in cardiac sarcoidosis are midwall rather than subendocardial or transmural LGE not corresponding to any particular coronary artery distribution. 13 LGE has a high sensitivity (100%) and moderate specificity (78%) for diagnosing cardiac sarcoidosis suggesting that myocardial scars indicated by LGE were an independent predictor of sudden cardiac death in patients with suspected CS. 28 The new Japanese guidelines consider LGE as a major criterion of CS. In our current case series, MRI revealed several features of cardiac involvement such as delayed enhancement in RV and RA (patient 1), RV midmyocardial late enhancement, edema and fibrosis of RV (patient 3) and edema of basal anteroseptal region of LV, apical infereoseptal area of both ventricles and moderator band (patient 4). With cardiac MRI both scar and myocardial edema can be demonstrated. It has been reported that LGE may be localized in the basal portion of the septal wall with nodular involvement which are suggestive of cardiac sarcoidosis.

FDG PET can detect sarcoïd lesions of the whole body and might be more sensitive as a diagnostic tool in detecting CS (Fig. 1E, Fig. 2B and Fig. 4B). PET-CT has been recommended for patients with cutaneous lesions, as was the case in (patient 4) who had a past history of erythema nodosum.

In 2013, abnormal 18F-FDG-PET/82Rubidium scans were found in 60% of patients following a high fat/low carbohydrate diet. 16 In 29% of patients, cardiac PET findings were predictors of adverse events with the presence of both a perfusion defect (82Rubidium/ perfusion) and abnormal 18F-FDG uptake (metabolism/ inflammation activity).

In patients with cutaneous sarcoidosis, 18F-FDG-PET or gallium scintigraphy detected cardiac involvement in 4 out of 12 patients (33%). 31 In another study by Youssef et al., found that pooled estimates for 18F-FDG PET yielded higher sensitivity (89%) and specificity (78%) for establishing CS in comparison with the Ontario registry which yielded sensitivity of 79% and specificity of 70%. 8

Biopsy

The most common histological features of sarcoidosis are non-casating sarcoïd granulomas with limited lymphocyte infiltration and patchy fibrosis. 32 (Fig. 1D, Fig. 3C and Fig. 4D). Endomyocardial biopsy (EMB) is not indicated as long as systemic sarcoidosis has been confirmed by lymph node biopsy or extracardiac biopsy. 33 EMB has a low sensitivity of 30% with a poor yield due to the focal nature of CS. 34 Systemic sarcoidosis was confirmed by biopsy of the paratracheal (station 2R) lymph node (patient 1), lymph node endoscopic ultrasound fine-needle biopsy (EUS) of station 7 (patient 2) and right upper lung lobe (patient 3) and inguinal lymph node (patient 4) revealing granulomatous inflammation without specific features or signs of Mycobacterium tuberculosis infection. In none of our current patients EMB was performed. EMB has proven useful for histologic diagnosis of CS. EMB has several limitations (invasive procedure and insensitivity due to focal involvement of the myocardium).

Differential diagnosis

CS should be differentiated from arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/C), ischemic heart disease, Lyme disease, giant cell myocarditis and dilated cardiomyopathy. Patients with CS have lower left ventricular ejection fraction.
(LVEF) than ARVD/C, and LV septal involvement is seen exclusively in CS patients. In MRI comparison study, Steckman et al., found greater late gadolinium enhancement in CS patients compared with ARVD/C patients. In CS, the LV involvement is more common, CS should also be differentiated from conditions associated with the development of inverted precordial T-waves.

Lyme carditis may be excluded by negative serology. Lyme carditis occurs in 0.3-8% of Borrelia Burgdorferi infection and it is usually self-limiting when appropriately treated with antibiotics. With regard to ischemic heart disease, the first patient had a normal coronary arterial tree on his CAG. The slight troponin elevation and inverted T-wave in the precordial leads may be attributed to the tachyarrhythmia and considered as “cardiac memory” subsequent to the tachyarrhythmias. Furthermore, in our series, ischemic heart disease was excluded because of absence of anginal complaints associated with normal myocardial perfusion imaging in the other patients. In the current series, myocarditis was less likely because cardiac MRI findings were specific for sarcoidosis. Cardiac MRI findings that show patchy focal edema in the subepicardium and/or subepicardially distributed late gadolinium enhancement are indicative of myocarditis. Furthermore, in the current series, combining the images of cardiac MRI with FDG PET-CT demonstrated that the late gadolinium enhancement corresponded well to the increased FDG uptake. In our patients, the diagnosis of cardiac sarcoidosis was established based on the combination of clinical presentation, findings on ECG (sustained monomorphic ventricular tachycardia, persistent atrial flutter, paroxysmal atrial fibrillation and AV conduction abnormalities), 18F-FDG-PET-CT and cardiac MRI images.

Pharmacologic (corticosteroids and immune-suppression) and non-pharmacologic (device therapy of implantable cardioverter-defibrillator (ICD) and pacemaker) treatment was initiated.

Management

CS is associated with high rate of mortality due to heart failure, complex ventricular arrhythmias, or even sudden cardiac death. ICD implantation is a class IIA indication in patients with cardiac sarcoidosis for primary prevention and class I for secondary prevention. Studies describing randomized controlled trials of therapy are lacking in cardiac sarcoidosis. The cornerstone of therapy for sarcoidosis is immune-suppression (corticosteroids) either alone or combined with other immune modulators (methotrexate, azathioprine). It has been postulated that pharmacologic treatment can promote fibrosis which in turn can facilitate more VT substrate. Corticosteroids improve survival, and pacemaker implantation for advanced heart block and ICD treatment should be considered to decrease the incidence of sudden cardiac death. In an electrophysiology study by Kumar et al., catheter ablation was found to be able to terminate VT storm resulting in reduction in the burden of defibrillator shocks in the majority of patients with CS. Our first patient had initially an episode of sustained VT necessitating electrical cardioversion in the acute phase and the placement of an implantable cardioverter-defibrillator for secondary prevention. The second patient suffered an attack of a total heart block requiring dual chamber pacemaker implantation. The other two patients were managed with medical treatment including prednisone and methotrexate accompanied with prophylactic ICD implantation.

Patients at higher risk of ventricular arrhythmias, conduction abnormalities should be considered for early corticosteroid/immunosuppressive treatment, ICD therapy or permanent pacemaker implantation. Normal LV function is the most significant predictor of high survival 5-year rate (89% vs 27%).

Patients are considered at higher risk when there is a poor New York Heart Association functional class, increased left ventricular end diastolic diameter, reduced ejection fraction and sustained VT. Furthermore, LGE positive patients had higher rate of adverse events and sudden cardiac death.

Conclusion

In conclusion, cardiac involvement of systemic sarcoidosis is increasingly detected. The spectrum of ventricular, supraventricular arrhythmias and AV block may serve as the initial sign of presence of CS. Besides MRI, FDG PET is pivotal, not only for diagnosis, but also, as noted in this study, for monitoring of therapeutic response. Diagnosis requires high index of suspicion and multidisciplinary teamwork. The diagnosis of CS can often be established with non-invasive modalities when consistent clinical and/or histological/cytological findings are consequent with systemic sarcoidosis. Identifying early cardiac dysfunction with non-invasive modalities among subjects with systemic sarcoidosis is a critical step in providing opportunities for risk stratification and early intervention to decrease the associated risk of long term cardiovascular disease in this high-risk group of patients.

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Reference


