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Patient profile and comparison of three diagnostic criteria for cardiac sarcoidosis in a tuberculosis endemic population

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Abstract. Background: Cardiac sarcoidosis (CS) is an underdiagnosed and life-threatening condition. Histopathological diagnosis is difficult due to the risks and variable diagnostic yield of endomyocardial biopsy. **Objectives:** To study the clinical profile and compare the diagnostic criteria of CS in a cohort of sarcoidosis. **Methods:** A retrospective review of the Sarcoidosis database (375 patients) was performed to identify patients with CS. Demographic and clinical details were retrieved. We applied the available diagnostic criteria for the diagnosis of CS: The World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG), Heart Rhythm Society (HRS), and Japanese Ministry of Health and Welfare (JMHW) criteria. **Results:** Out of the 375 patients, 15 (4%) were identified with CS. The median age was 41 years, and 53% were female. The most common symptoms were breathlessness, palpitation, and fatigue in 80%, 53.3%, and 46.6% of patients, respectively. Tuberculin positivity (≥ 10mm induration) was seen in 26.6%. 80% and 53.3% of the patients had abnormal ECG and 2D echocardiography findings, respectively. Six patients had a history of Ventricular tachycardia (40%). LV Ejection fraction was reduced in 12 subjects (80%). Cardiac-MRI showed late gadolinium enhancement in 53.3%. A definitive histopathological diagnosis for sarcoidosis was established in 86.6% (13/15) patients. Of the 15, all satisfied JMHW criteria and WASOG criteria (12 (80%) at least probable category, 3 (20%) possible CS), and 13 (86.6%) met HRS criteria for a diagnosis of CS. **Conclusion:** In a cohort of 375 patients with sarcoidosis in a tuberculosis endemic setting, 4% were diagnosed with cardiac sarcoidosis. Histopathological diagnosis may be obtained by sampling from extracardiac sites. JMHW and WASOG criteria perform equally well in TB endemic settings.

Key words: Sarcoidosis; Cardiac Sarcoidosis; Granuloma; Inflammation; Imaging; MRI

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Introduction

Sarcoidosis is a multisystemic granulomatous disease of unknown aetiology. The condition occurs across the globe, affecting both sexes and all ethnicities and ages (1). It is characterized by the presence of non-necrotizing granulomas in the affected organs. Lungs are most commonly affected (2,3).

Cardiac involvement in Sarcoidosis is a serious and potentially life-threatening manifestation. Symptomatic cardiac sarcoidosis (CS) occurs in around 2-5% of all patients with Sarcoidosis (4). Data from tuberculosis endemic settings like India also report a similar prevalence (5-7% in tertiary hospital-based studies) (5,6). Approximately 20-25% of patients with systemic sarcoidosis are detected to have asymptomatic cardiac involvement (autopsy studies) (7). The important clinical features of CS are conduction abnormalities, ventricular arrhythmias, and heart failure. CS is the leading cause of death (up to 85%) in patients with sarcoidosis in Japan (8–10). Comprehensive descriptive studies on the clinical profile and diagnostic pathways of cardiac sarcoidosis from tuberculosis endemic areas are lacking (11).

The Heart Rhythm Society (HRS) criteria, Japanese Ministry of Health and Welfare (JMHW) criteria, and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) expert consensus statement are the most well established and accepted diagnostic guidelines for CS (7,12–15). However, these are based on expert consensus and are yet to be validated by prospective data or clinical trials. The HRS and JMHW histological group criteria require non-caseating granulomas on endomyocardial biopsy (EMB) to exclude alternate causes (16). However, EMB is challenging to obtain, may pose a risk to the patient, and has poor sensitivity (20–30%) (17). Hence, extracardiac tissue sampling remains vital to confirm the diagnosis of CS in many patients.

JMHW clinical diagnosis group needs to demonstrate epithelioid granulomas in other organs and features of cardiac involvement or features suggestive of pulmonary or ophthalmic sarcoidosis, along with characteristic laboratory findings of sarcoidosis and features of cardiac involvement. JMHW guidelines give objective criteria for cardiac involvement in terms of major and minor criteria and an accepted list of laboratory findings of sarcoidosis. WASOG consensus statement divides the diagnosis into three categories-highly probable category requires histological demonstration of granulomatous inflammation, while at least probable diagnosis can be made with clinical features alone.

One significant difference among various guidelines is the requirement for a positive biopsy in the clinical diagnosis pathway. The HRS guidelines require this, but the Japanese guidelines and WASOG do not. Another difference is the need for multiple clinical criteria to diagnose via the clinical pathway in the Japanese guidelines (two or more major criteria or one major and two or more minor criteria). At the same time, HRS and WASOG require only one. Reduced ejection fraction cut off is also different in the requirements. With WASOG mentioning no cutoff, HRS indicates evaluation for CS at EF <40%, while JMHW is more conservative with Ejection Fraction (EF) less than 50%.

This study describes the clinical profile of patients with cardiac sarcoidosis in a tuberculosis endemic area. We retrospectively reviewed an existing cohort of sarcoidosis patients with intrathoracic involvement and compared the various diagnostic criteria for CS.

Methods

A retrospective review of an existing sarcoidosis database was performed to identify patients with cardiac sarcoidosis. This ongoing prospective database includes patients with sarcoidosis (predominantly with intrathoracic involvement) consecutively enrolled since 2014 and are prospectively followed up. In most patients with suspected sarcoidosis and intrathoracic involvement at our facility, Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) centred or a flexible bronchoscopic approach (with transbronchial and endobronchial biopsies) are employed for histopathological diagnosis. A definitive diagnosis of sarcoidosis was defined by the presence of non-necrotizing granulomas, along with consistent clinical and radiological findings. Although EMB may be considered the gold standard for cardiac sarcoidosis, it has a low and variable diagnostic yield with a 20-25% sensitivity. There are inherent issues with the performance of EMB in many patients. We, therefore, used extracardiac tissue sampling for confirmation of diagnosis. According to various guidelines, epithelioid granulomas found in extracardiac organs are also included in establishing the diagnosis of cardiac sarcoidosis.

Patients underwent investigations for the presence of cardiac involvement if there were any of the following: suggestive cardiac symptoms, abnormal echocardiography, abnormal ECG, or Holter. The abnormal ECG was defined as complete left or right bundle branch block or presence of unexplained pathological Q waves in 2 or more leads or sustained second or third-degree AV block or sustained or non-sustained VT. Abnormal echocardiogram defined as RWMA or wall aneurysm or basal septum thinning or LVEF < 40%. ECG was done in all patients. Previously published definitions of abnormal ECG, echocardiography, and Holter were used (14,18). The rest of the investigations were performed in the presence of suggestive cardiac symptoms. Pulmonary hypertension and impaired ejection fraction were calculated on echocardiography. Right heart catheterization was not performed.

All the suspected CS patients underwent cardiac magnetic resonance imaging (Cardiac MRI) unless there was a contraindication like an implanted pacemaker. Cardiac MRI diagnosis of CS was ascertained using the established criteria by identifying regions of LGE (late gadolinium enhancement), which are most commonly multifocal and involve the mid-ventricular wall or sub-epicardium. (13). The CMR provides anatomical and functional information as well as tissue characterization with high spatial and contrast resolution. MRI was performed on a 1.5 Tesla scanner. The imaging module used in cardiac sarcoidosis was as follows: The anatomical and morphological information was obtained from T1 and T2 weighted turbo spin sequences (TSE). The ventricular function and wall motion was assessed by Cine SSFP (steady-state free precession) sequences. Cine SSPF was done in short axis, 2-chamber, and 4-chamber views. Tissue characterization was performed by T2 weighted images (myocardial oedema), early gadolinium-enhanced MRI (1 to 3 minutes after gadolinium injection), and late gadolinium-enhanced images (10 minutes after gadolinium contrast injection).

Gallium-68 or FDG-PET-CT were also performed and analyzed wherever available. (19). Patients were kept fasting for four h before the injection of 18F-FDG. FDG–PET–CT scans were performed on the dedicated scanners (Siemens, Washington, USA, [Biograph 64]). The blood glucose level was checked to ensure that it was less than 150 mg/dL before the injection of 18F-FDG. 18F-FDG was administered in a dose of 5.2 MBq (0.14 mCi)/kg through a peripheral vein one h before imaging. Initial CT acquisition was performed without oral or intravenous contrast injection, followed by a PET scan. During the uptake phase, patients sat quietly in a dimly lit room. They were asked to refrain from talking, walking, and any other muscular activity to prevent non-specific FDG uptake in the skeletal muscles. Sequential overlapping emission scans of the heart were acquired 60 min after the injection of the radiotracer.

Patients with sarcoidosis without intrathoracic involvement were diagnosed by sampling either an extra-thoracic site or a bronchoscopic lung biopsy. In many patients with suspected sarcoidosis without any apparent lung parenchymal involvement, endobronchial mucosal biopsy and transbronchial lung biopsy may also demonstrate granulomas.

Patients' follow-up, including response to steroids or immune-suppressants, was recorded. All the patients received treatment with corticosteroids. Among therapeutic interventions, two patients underwent pacemaker insertion, and one underwent radiofrequency ablation. Ethical approval for the study was obtained from the Institute Ethics Committee.

Statistical analysis

The representative data are shown as means ± standard deviation or median (interquartile range) for quantitative data. For categorical data, numbers (percentages) is described. Specific analysis related to Inter-Rater Reliability (IRR) was performed using R-package. An inter-rater reliability (IRR) analysis was performed to estimate the degree of agreement in diagnosing Cardiac Sarcoidosis based on the three established criteria- HRS, JMHW and WASOG. As the experimental design was fully crossed with three coders (criteria), Cohen's kappa was calculated for all pairs of criteria. Then the average was calculated (20,21) in 30 suspected Cardiac Sarcoidosis patients. Cohen's kappa values can be interpreted as follows: < 0.00: poor agreement, 0.00 to 0.20: slight agreement,

0.21 to 0.40: fair agreement, 0.41 to 0.60: moderate agreement, 0.61 to 0.80: substantial agreement, 0.81 to 0.99: almost perfect, and 1.00: complete. Bootstrap confidence intervals (CI) was calculated based on 1000 bootstrap replicates.

Results

The database comprising 375 clinico-radiologically or histologically confirmed patients with sarcoidosis were screened. Of the 375, 30 (8%) patients had either cardiac symptoms, abnormal ECG, or abnormal echocardiography examination. After a final review of the records, 15 (4% in total 375 patients) patients were identified with CS based on the inclusion criteria (Figure 1) (Table 1).

The baseline characteristics of 15 patients with CS are presented in Table 2.

The mean age was 42.87 (11.46) years (median 41 years), and 7 (46.6%) were males. Shortness of breath (80%), palpitations (53.3%), fatigue (46.6%), chest pain (15%), and syncope (6.6%) were the common symptoms. Among comorbidities, diabetes was the

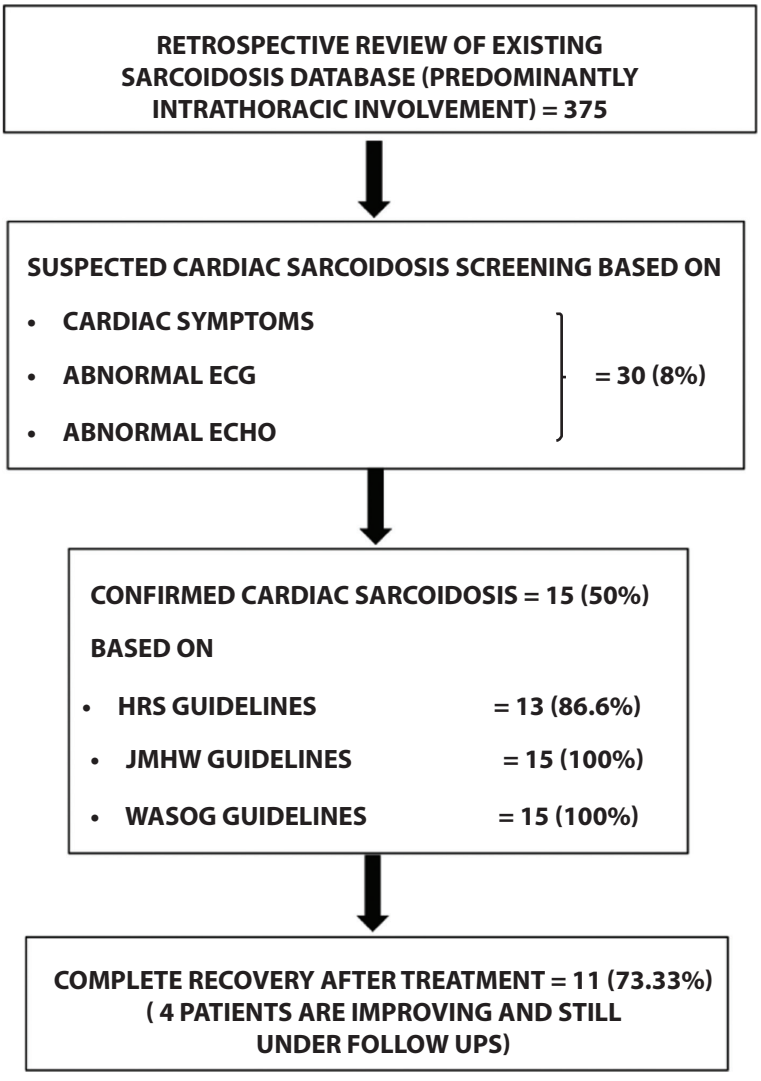

Figure 1. Diagnostic algorithm for the evaluation of patients with Cardiac Sarcoidosis.

Table 1. Diagnostic criteria for cardiac sarcoidosis

I: Heart Rhythm Society expert consensus statements on criteria for the diagnosis of cardiac Sarcoidosis (2014)	
Histological Diagnosis	**Clinical Diagnosis**
Non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified	Probable CS if: a) Histological diagnosis of extracardiac sarcoidosis and b) One or more of following is present; • Steroid +/- immunosuppressant responsive cardiomyopathy or heart block • Unexplained reduced LVEF (<40%) • Unexplained sustained (spontaneous or induced) VT • Mobitz type II 2nd degree heart block or 3rd degree heart block • Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS) • Late Gadolinium Enhancement on CMR (in a pattern consistent with CS) • Positive gallium uptake (in a pattern consistent with CS) • and c) Other causes for the cardiac manifestation(s) have been reasonably excluded
II: Japanese Ministry of Health and Welfare criteria for the diagnosis of cardiac Sarcoidosis (2019)	
Histological Diagnosis	**Clinical Diagnosis**
Endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas	1) Epithelioid granulomas are found in organs other than the heart, and clinical findings strongly suggestive of the cardiac involvement are present; or 2) Patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least two of the five characteristic laboratory findings of sarcoidosis with clinical findings strongly suggest cardiac involvement.
Clinical findings defining cardiac involvement should be assessed based on the major criteria and the minor criteria.1) Two or more of the five major criteria, 2) One of the five major criteria and two or more of the three minor criteria	
Major Criteria	**Minor Criteria**
• High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e. g., sustained ventricular tachycardia and ventricular fibrillation) • Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening) • Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50%) • Ga citrate scintigraphy or 18F-FDG PET reveals abnormally high tracer accumulation in the heart • Gadolinium-enhanced CMR reveals delayed contrast enhancement of the myocardium	• Abnormal ECG findings: Ventricular arrhythmias (non-sustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves. • Perfusion defects on myocardial perfusion scintigraphy (SPECT). • Endomyocardial biopsy: Monocyte infiltration and moderate or severe myocardial interstitial fibrosis

(*continued*)

Table 1. Diagnostic criteria for cardiac sarcoidosis (*Continued*)

III: World Association for Sarcoidosis and Other Granulomatous Disorders criteria for the diagnosis of cardiac Sarcoidosis (2019)			
Highly Probable	**At Least Probable**	**Possible**	**No consensus**
Biopsy with granulomatous inflammation of no alternate cause	• Treatment-responsive cardiomyopathy or AV block • Reduced LVEF in the absence of other clinical risk factors • Spontaneous or induced sustained VT with no other risk factors • Mobitz type II or 3rd degree AV block • Patchy uptake on dedicated cardiac PET • Delayed enhancement on CMR • Positive gallium uptake • Defect on perfusion scintigraphy or SPECT scan • T2 prolongation on CMR	• Reduced LVEF in the presence of other clinical risk factors (e.g., HTN and DM) • Atrial dysrhythmias	• Frequent ectopy (> 5% QRS) • Bundle branch block • Impaired RV function with a normal PVR • Fragmented QRS or pathologic Q waves in two or more anatomically contiguous leads • At least one abnormal SAECG domain • Interstitial fibrosis or monocyte inflammation

AV, atrioventricular; LVEF, left ventricle ejection fraction; VT, ventricular tachycardia; PET, positron emission tomography; CMR, cardiac MRI; SPECT, single-photon emissioncomputerized tomography; HTN, hypertension; DM, diabetes; RV, right ventricle; PVR, pulmonary vascular resistance; SAECG, signal-averaged ECG.

Table 2. Demographic characteristics of patients with Cardiac Sarcoidosis

Parameter	**Mean ± SD, n (%)**
Total number of patients	15
Age (years); Median (Range)	41 (16-63)
Males; n (%)	7 (46.6%)
BMI; (kg/m2)	26.18 ± 4.48
Days since symptom onset; Mean ± SD	259.2 ± 183.84
Symptoms; n (%) • Shortness of breath • Palpitations • Fatigue • Chest pain • Syncope	 12 (80%) 8 (53.3%) 7 (46.6%) 3 (15%) 3 (15%)
Elevated serum ACE levels (> 65 IU/L)	4 (26.6%)
Positive Mantoux test (induration >10 mm); n (%)	4 (26.6%)
Radiographic stage; n (%) O I II III	 4 (26.6%) 9 (60%) 1 (6%) 1 (6%)
Lung parenchymal involvement (CT Thorax); n (%)	10 (66.6%)
Non-necrotizing Granuloma on any biopsy; n (%)	13 (86.6%)

Table 2 (*continued*)

Parameter	Mean ± SD, n (%)
Co-morbidities; n (%) • Diabetes • Hypothyroidism • Hypertension	 7 (46.6%) 2 (13.3%) 3 (20%)
Pulmonary hypertension; n (%)	3 (20%)
Abnormal ECG; n (%)	14 (93.3%)
Abnormal ECHO; n (%)	8 (53.3%)
Left ventricular dysfunction (LVEF < 40%); n (%)	10 (66.6%)
Permanent Pacemaker Implantation; n (%)	2 (13.3%)
Late gadolinium enhancement on Cardiac MRI; n (%)	10 (66.6%)
68- Ga DOTANOC or FDG-PET abnormal uptake; n (%)	4 (26.6%)

BMI: Body mass index, Serum ACE: Serum Angiotensin-converting enzyme, CT Thorax: Computed Tomography-Thorax, LVEF: Left ventricular ejection fraction, Cardiac MRI: Cardiovascular Magnetic Resonance Imaging, 68- Ga DOTANOC: [^{68}Ga-DOTA, 1-Nal^{3}]-octreotide, FDG-PET: Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose.

most common (7 patients, 46.6%). The mean duration from symptom onset to evaluation was 259.2 (183.84) days. A majority (9 patients, 60%) belonged to Scadding stage 1 on chest radiography. Lung parenchymal involvement was present on high resolution computed tomography (HRCT) of the thorax in 10 (66.6%) patients. The mean serum angiotensin-converting enzyme (ACE) level was 57.73 (36.03) U/L. Serum ACE levels were elevated in 26.6% of patients at a cut off of 65 IU/L. Tuberculin skin test was reactive (induration> 10 mm) in 4 (26.6%) patients.

Out of the 15 recruited patients, 12 (80%) patients had abnormal ECG, and 8 (53.3%) had abnormal echocardiography findings. Six patients had a history of monomorphic ventricular tachycardia (40%). Atrial fibrillation was uncommon (one patient). Second or third-degree atrioventricular block was seen in 3 patients. Ejection fraction was impaired in 10 subjects (66.6%) (According to JMHW criteria), with echocardiography demonstrating dilated cardiomyopathy (DCMP) in 5 (33%), restrictive cardiomyopathy (RCMP) in 2 (13.3%), and pulmonary hypertension in 3 (20%) patients. Cardiac MRI revealed late gadolinium enhancement in basal or mid ventricular or apical, Subendocardial or mid-wall or subepicardial in 10/15 (66.6%) patients. However, 4 (28.57%) patients also had T2 hyperintensity on Cardiac MRI indicative of active inflammation. Four patients were having regional wall motion abnormalities (RWMA) found in MRI. One patient had a normal Cardiac MRI, but an abnormal Ga-68 PET scan reveals a focal area of abnormal Ga-68 DOTANOC uptake in the mid and proximal lateral wall. Three cases had normal Cardiac MRI, but further imaging studies were not done.

A definitive cytological/histopathological diagnosis of sarcoidosis was established in 13 of the 15 patients (86.6%). Eleven patients underwent EBUS-TBNA along with endobronchial biopsy (EBB) and transbronchial lung biopsy (TBLB). One patient underwent EBUS alone and one only flexible bronchoscopy with EBB and TBLB. EBUS-TBNA had the highest yield with diagnostic samples in 9/12 patients (75%). Clot core obtained during EBUS-TBNA revealed granuloma in 5 patients and was the sole diagnostic sample in one case. Hence, EBUS-TBNA was diagnostic in 77% (10/13). TBLB revealed non necrotizing granuloma in 1/12 (8%), EBB in 2/12 (16%). One patient had lacrimal gland enlargement, the biopsy of which demonstrated non-necrotizing granuloma. Endomyocardial biopsies were not performed on any patient (Table 3). Tuberculosis was ruled out in all cases by a negative acid-fast bacillus staining, CBNAAT (cartridge-based nucleic acid amplification test), and MGIT (Mycobacterium growth indicator tube) culture on EBUS-TBNA aspirate samples.

Table 3. Demographic and diagnostic characteristics of patients with Cardiac Sarcoidosis

S. No	Age/Sex	Symptoms	Past Medical History	ECG and/or ECHO (LVEF %)	Cardiac Imaging	Serum ACE Level (IU/L)	Lung Imaging	Non-necrotizing Granuloma	Guidelines for Diagnosis
1	38/M	SOB, Palpitation	No	RBBB, Ventricular tachycardia (40%)	CMR: LGE + ve & T2 Hyperintensity, PET: Increased FDG-PET uptake	48	Mediastinal nodes	EBUS-TBNA, Clot Core, EBB	HRS, WASOG, JMHW
2	44/F	Visual, Syncope	No	AV Block (60%)	CMR: Normal T2 WI and Gadolinium enhanced images PET: Increased 68- Ga DOTANOC PET uptake	88.4	Mediastinal nodes, Lung nodules	Lacrimal gland biopsy	HRS, WASOG, JMHW
3	55/F	SOB, Cough, Fatigue, LoW, Palpitation, Syncope	Diabetes	Ventricular tachycar-dia (40%)	CMR: Normal T2 WI and Gadolinium enhanced images	145	Mediastinal nodes, Lung Nodules	No	WASOG, JMHW
4	40/M	SOB, Cough, Palpitation	No	RCMP, Ventricular tachycardia (30%)	CMR: LGE + ve	28	Mediastinal nodes, Lung nodules	EBUS-TBNA	HRS, WASOG, JMHW
5	39/F	SOB, Palpitation	No	Ventricular tachycar-dia (34%)	CMR: LGE + ve	34.6	Mediastinal nodes, Lung nodules	EBUS-TBNA	HRS, WASOG, JMHW
6	40/M	SOB, Fatigue, Syncope	No	AF, RCMP (45%)	CMR: LGE + ve & T2 Hyperintensity	49	Mediastinal nodes	EBUS-TBNA	HRS, WASOG, JMHW
7	52/F	SOB, Chest Pain, Fa-tigue, LoW, Palpitation	Hypertension	LBBB, DCMP (35%)	CMR: LGE + ve	44	Mediastinal nodes, Lung nodules	EBB	HRS, WASOG, JMHW
8	41/M	SOB, Fever, Fatigue, LoW	Diabetes	DCMP (15%)	CMR: Global hypokinesia	34	Mediastinal nodes, Lung nodules	EBUS-TBNA	HRS, WASOG (Possible), JMHW
9	16/F	SOB, Chest pain	No	DCMP (27%)	CMR: LGE + ve	67.6	Mediastinal nodes	No	WASOG, JMHW

S. No	Age/Sex	Symptoms	Past Medical History	ECG and/or ECHO (LVEF %)	Cardiac Imaging	Serum ACE Level (IU/L)	Lung Imaging	Non-necrotizing Granuloma	Guidelines for Diagnosis
10	49/M	SOB, Fatigue	Diabetes	AV Block, LBBB (45%)	CMR: LGE + ve	116	Mediastinal nodes, Lung nodules	TBLB	HRS, WASOG, JMHW
11	30/F	SOB, Cough, Chest Pain, Fever, Fatigue, LoW,	Hypothyroidism	ST-T wave changes (60%)	PET: Increased 68-Ga DOTANOC PET uptake	22	Mediastinal and subcarinal nodes	EBUS-TBNA, Clot Core	HRS, WASOG, JMHW
12	46/M	Palpitation	Diabetes	Ventricular tachycardia, AV Block (40%)	CMR: LGE + ve & T2 Hyperintensity, PET: Increased FDG-PET uptake	28.4	Mediastinal nodes, Lung nodules	EBUS-TBNA, Clot Core	HRS, WASOG, JMHW
13	35/F	SOB, Palpitation	No	LBBB, DCMP (25%)	CMR: LGE + ve	17	Mediastinal nodes, Lung nodules	EBUS-TBNA, Clot Core	HRS, WASOG, JMHW
14	55/M	Palpitation, LoW	Diabetes, Hypothyroidism, Hypertension	RBBB, Ventricular tachycardia (60%)	CMR: LGE + ve & T2 Hyperintensity	52	Mediastinal nodes	EBUS-TBNA	HRS, WASOG, JMHW
15	63/F	SOB, Cough, Fatigue	Diabetes, Hypertension	DCMP (40%)	CMR: Normal T2 WI and Gadolinium enhanced images	62	Mediastinal nodes, Lung nodules	Clot Core	HRS, WASOG (Possible), JMHW

SOB: Shortness of Breath, LoW: Loss of Weight, RBBB: right bundle branch block, AV Block: Atrioventricular block, RCMP: Restrictive cardiomyopathy, AF: Atrial fibrillation, LBBB: left bundle branch block, DCMP: Dilated cardiomyopathy, ST-T wave changes: ST-segment and T-wave changes, CMR-LGE: late gadolinium enhancement-cardiac magnetic resonance, EBUS-TBNA: Endobronchial ultrasound-transbronchial needle aspiration, EBB: endobronchial biopsy, TBLB: Transbronchial lung biopsy.

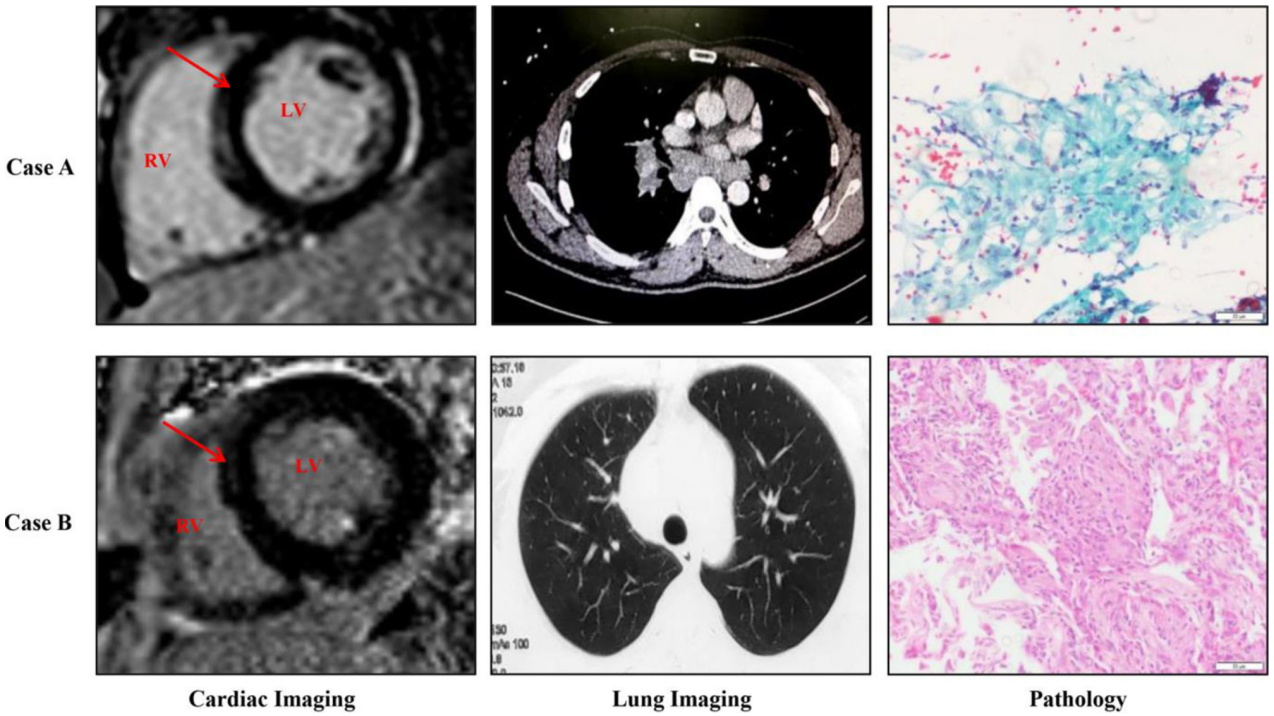

Figure 2. Case A was a 38-year male having shortness of breath, palpitations with VT. The cardiac MRI showed LGE. Chest CT showed mediastinal lymphadenopathy but no parenchymal involvement. Non-necrotizing Granulomas were demonstrated in the EBUS-TBNA sample. Case B was a 49 years old male having shortness of breath and fatigue, with an ejection fraction of 45% on echocardiography. The cardiac MRI showed LGE. Chest CT showed bilateral lung nodules. Non -necrotizing granuloma was demonstrated in the TBLB sample. (MRI Magnetic resonance imaging, LGE Late gadolinium enhancement, VT Ventricular tachycardia, CT Computed tomography, EBUS Endobronchial ultrasound, TBLB Transbronchial lung biopsy).

Table 4. Inter-rater agreement statistics in suspected Cardiac Sarcoidosis patients.

	Evaluation		
Criteria	**0**	**1**	**Total**
HRS Criteria	17	13	30
JMHW Criteria	15	15	30
WASOG Criteria	15	15	30

0 = No, 1 = Yes

Out of the 15 patients, all satisfied JMHW clinical criteria and WASOG criteria (12 (80%) at least probable, 3 (20%) possible CS), 13 (86.6%) met HRS criteria for clinical diagnosis of CS (Table 3). Figure 2 demonstrates cardiac and lung images and pathological images of two representative cases of a definitive diagnosis of Cardiac Sarcoidosis. Two patients did not have any histopathological diagnosis of sarcoidosis and hence did not fulfil HRS criteria.

A kappa value of 0.911 (95% CI: 0.78, 1.0; p = 0.0001) was obtained from IRR analysis, indicating an excellent agreement among the criteria in diagnosing Cardiac Sarcoidosis out of 30 suspected patients. The lack of a perfect agreement could be explained by the fact that the HRS criteria require histological diagnosis (Table 4).

All 15 patients received treatment with corticosteroids with clinical response to therapy. A standardized dose was not used. The initial dose of prednisolone ranged between 0.75mg/kg to 1mg/kg body weight. Other immunomodulator drugs were not used as initial treatment. All the patients were assessed after three months, six months, nine months, 12 months, and 24 months after initiation of therapy. All the recruited patients were under telephonic follow up and were asked to contact in case of any emergency.

Among therapeutic interventions, two patients underwent pacemaker insertion, and one underwent

radiofrequency ablation. None had a recurrence of arrhythmias after the start of immunosuppression. Out of 15 patients, 11 (73.3%) patients showed complete resolution based on clinical and radiological features after six months of treatment. Steroids were tapered and stopped in these patients. Four patients are in remission but continuing on low-dose steroids. There were no steroid-sparing drugs given to any patient.

Other 15 suspected cardiac Sarcoidosis patients were found to have ischemic heart disease in 3 subjects, 1 had valvular heart disease, 2 had heart failure with preserved ejection fraction, and 9 had concentric left ventricular hypertrophy attributed to hypertensive heart disease.

Discussion

In our cohort of patients with sarcoidosis with predominant intrathoracic involvement, we observed a prevalence of 4% of symptomatic cardiac sarcoidosis, consistent with previous reports (5,22). The high yield of EBUS-TBNA in confirming a definite histopathological diagnosis of sarcoidosis and ruling out tuberculosis indicates the importance of looking for mediastinal lymphadenopathy in all suspected CS patients. This approach may potentially avoid an endomyocardial biopsy.

Mediastinal lymphadenopathy was present in all patients with CS, and a majority had associated lung parenchymal involvement on CT. More patients had an elevated ACE level in our cohort than previously described cardiac sarcoidosis series from the Indian population (23). One reason for this may be the higher proportion of pulmonary involvement in our cohort. As the predominant presenting symptoms are often cardiac, extracardiac involvement may go unnoticed. For screening for pulmonary sarcoidosis in suspected CS, chest radiograph has a reported sensitivity of 30% and specificity of 85% with an AUC of 0.54 (22). Thorax CT demonstrated a better sensitivity of 90% and specificity of 86% with AUC of 0.82, and thorax MRI showed a sensitivity of 100% and specificity of 50% with AUC of 0.77 (22). TB is an uncommonly described cause of monomorphic VT with mediastinal adenopathy in tuberculosis endemic areas, with a previous series reporting 36% out of 14 subjects demonstrating evidence of tuberculosis on the evaluation of mediastinal lymph nodes and 2/14 with active tuberculosis (24). In assessing suspected granulomatous mediastinal lymphadenopathy, EBUS-TBNA has excellent diagnostic yield exceeding 80% for both sarcoidosis and tuberculosis, even in tuberculosis endemic areas (25,26). Pursuing extracardiac involvement is vital as endomyocardial biopsy is associated with a higher complication rate (up to 6%), and diagnostic yield is low and variable (20-30%) (27).

There is limited data supporting evaluation for asymptomatic cardiac involvement in a patient diagnosed with sarcoidosis. Expert guidelines do not recommend routine screening. In a study describing a cohort of 62 patients with sarcoidosis, screening for CS was performed with history, echocardiography, Holter monitoring, and ECG, followed by Cardiac MRI or PET scan if any of these were positive. A sensitivity of 100% for the diagnosis of CS was observed (17). We followed a similar protocol for the diagnosis of CS.

In our cohort, all the expert diagnostic criteria for CS performed well. A recent study of 69 patients showed a comparatively higher proportion of patients with CS that were unclassifiable using all these criteria (28). This study had a greater proportion of patients with isolated cardiac sarcoidosis (26%) and a lower percentage of histologically confirmed cases (42%). The diagnostic criteria of CS, though sufficiently sensitive for the diagnosis of CS, require that other cardiac diagnoses be excluded. A CS registry of 212 patients revealed eight patients who satisfied all the criteria for the diagnosis of CS but were subsequently found to have alternate diagnoses, including amyloidosis, Non-Hodgkin's lymphoma, and mycobacterium avium infection, among others (29). In our cohort, the large proportion of histologically confirmed sarcoidosis helped improve the diagnostic performance of the various criteria.

Disease-specific treatment with steroids resulted in clinical response with remission induction in the majority of patients. Despite tuberculin positivity in 26%, active tuberculosis was ruled out with CBNAAT from the TBNA sample in all four, and anti-tubercular therapy (ATT) was not given along with steroids as

is the usual practice. In a series of 14 granulomatous monomorphic VT patients, ATT was given to 9/14 cases based on tuberculin positivity and TB PCR on the lymph node sample (24). Adequate treatment of underlying inflammation with steroids or anti-tuberculosis therapy is necessary for preventing further arrhythmic episodes despite therapeutic interventions (30).

Conclusion

Establishing a diagnosis of cardiac sarcoidosis in an endemic tuberculosis area requires histological confirmation to rule out tuberculosis. There is good agreement on diagnosing CS by the three well-established diagnostic criteria in this cohort.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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