Cardiac sarcoidosis defined by cardiovascular magnetic resonance: patient characteristics and outcomes

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Dedication

I dedicate this work to my family, my father, Omar, and my mother, Zaynab, with my all respect and love.

Acknowledgements

I want to thank my supervisor, Professor Ntobeko Ntusi, who always gave me his time so willingly and worked very hard and supportively with me during this project, I thank him greatly. I shall never forget his outstanding guidance and support. He embodies the standards I aspire to in thoughtfulness, leadership, and compassion. I am privileged to have him as a role model.

Above all, thanks be to God Almighty for giving me the strength and courage to undertake and complete this thesis.

Declaration

I, Mohamed Emhemed, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Plagiarism declaration

I confirm that this thesis is my own work and is not copied from any other person's work (published or unpublished).

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Abbreviations

ARVC	Arrhythmogenic right ventricular cardiomyopathy
AV	Atrioventricular
CAD	Coronary artery disease
CMR	Cardiovascular magnetic resonance
CS	Cardiac sarcoidosis
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
ECV	Extracellular space volume
EF	Ejection fraction
EMB	Endomyocardial biopsy
FDG-PET	^{18}-Fluorodeoxyglucose-Positron Emission Tomography
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HRS	Heart Rhythm Society
JMHW	Japanese Ministry of Health and Welfare
LA area	Left atrial area
LV	Left ventricle/ventricular
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
LVEDV	Left ventricular end diastolic volume
LVESV	Left ventricular end systolic volume
LVSV	Left ventricular stroke volume

LV mass	Left ventricular mass
LV mass	Left ventricular mass indexed to body surface area
MRI	Magnetic resonance imaging
RA area	Right atrial area
RV	Right ventricle/ventricular
RVEF	Right ventricular ejection fraction
RVEDV	Right ventricular end diastolic volume
RVESV	Right ventricular end systolic volume
RVSV	Right ventricular stroke volume
SA-CMR	South African Cardiovascular Magnetic Resonance Registry
SCD	Sudden cardiac death
SVT	Supraventricular tachycardia
VT	Ventricular tachycardia
WASOG	World Association of Sarcoidosis and Other Granulomatous Diseases

Abstract

Introduction: Sarcoidosis is an inflammatory disorder that affects multiple systems. On histologic examination, sarcoidosis is defined by the production of non-caseating granulomas. Cardiac sarcoidosis (CS) is common, occurring in 20% or more of patients with systemic sarcoidosis, but because many people with CS may have nonspecific clinical manifestations or subclinical disease, the real extent of the disease prevalence is uncertain and possibly underestimated.

Methods: Medical records of patients with CS diagnosed by cardiovascular magnetic resonance (CMR) were selected for inclusion into this study. We identified patients with a diagnosis of CS by CMR between March 2005 and January 2018 at Groote Schuur Hospital, Cape Town, South Africa and included into the South African Cardiovascular Magnetic Resonance (SA-CMR) registry. The demographics, clinical profile, and outcomes of patients diagnosed with CS via CMR were summarised utilising proportions, medians with interquartile ranges (IQRs), and means with standard deviations (SDs), as appropriate. Fisher's exact test was utilised to compare proportions, while T tests and Mann-Whitney U-tests were utilised to compare means and medians, respectively. Statistical Package for Social Sciences (version 26) program was used to analyse the data.

Results: Medical records of 35 patients with a confirmed diagnosis of CS using CMR during the study period were identified. There were 21 (60%) males, and a male: female ratio of 1.5:1. The mean age of study participants was 50.3 ± 11 years. Most patients (84%) were overweight and obese, and comorbidities included hypertension (9%) and diabetes mellitus (3%). Nearly a quarter (23%) of patients presented with complete heart block and a third (31%) had ventricular tachycardia (VT) as the initial presentation. Half (54%) of patients had a permanent pacemaker or

implantable cardioverter defibrillator implanted. A third (34%) of patients had evidence of acute myocardial oedema on T2-weighted imaging and T2 mapping, and 91% of subjects had evidence of focal fibrosis/infiltration on late gadolinium enhancement (LGE). Most patients (80%) had normal pericardial thickness and small pericardial effusions (< 1 cm) were noted in 49%. Extra-cardiac findings of sarcoidosis were characterised by hilar lymphadenopathy and pulmonary interstitial involvement (49%) and pleural effusions (11%). There were no deaths during the study period andmedian follow-up of 7 years.

Conclusions: Sarcoidosis is a granulomatous systemic multiorgan condition that is a challenge to diagnose and manage in many settings. The availability of CMR has made it possible to diagnose CS noninvasively. We show that in our setting CS is characterised by oedema in a third of patients and evidence of LGE in almost all patients. Heart block and VT are common presentations; however, the prognosis is good with modern device therapies once the diagnosis has been made.

Chapter 1: Introduction, literature review and study rationale

Introduction

Sarcoidosis is an inflammatory disorder that affects all the body systems and is characterised by production of non-necrotising granulomas on histological examination.(1) Cardiac sarcoidosis (CS) is common, affecting up to 20% of individuals with systemic sarcoidosis, but the true prevalence and incidence are unclear and possibly underestimated as many people with CS have no definite symptoms or subclinical disease.(2) About 5% of those with sarcoidosis will develop clinically noticeable involvement of the heart, including manifestations as ventricular arrhythmias, conduction defects, and heart failure (HF).(2,3) Asymptomatic cardiac involvement affects around 20-25% of individuals with pulmonary/systemic sarcoidosis.(3) Around 25% of cases of CS are isolated and occur without extracardiac involvement. The absence of extracardiac sarcoidosis does not necessarily rule out the possibility of CS.(3) Despite the high specificity of endomyocardial biopsy (EMB) for detecting CS, this invasive test has a restricted sensitivity.(4) Further, there is limited understanding of the progression of the disease and a lack of consensus on the best procedures for disease diagnosis.

Pathophysiology of cardiac sarcoidosis

Sarcoidosis is defined as heterogeneous disease of uncertain aetiology whose hallmark lesion is a non-caseating granuloma. The disease can any part/portion of the heart. The papillary muscles, atria, valves, coronary arteries, and pericardium have all been implicated, but the ventricular myocardium is the most often affected part. In general, heart-related disease proceeds from regions of localised inflammation or scarring. Some individuals may only have a small area of inflammation or scarring and

will not experience any significant clinical sequelae. However, other patients may progress to develop a pattern of extensive inflammation and scarring. Given the limited data on how this disease progresses, it may be preferable to refer to different patterns of CS rather than stages, as use of staging implies a linear progression across the different stages.(5)

Clinical features of cardiac sarcoidosis

Atrioventricular (AV) block, HF, arrhythmia, and sudden cardiac death (SCD)are typical complications or clinical presentations of CS.(6, 7) Other manifestations of CS include syncope, presyncope, exhaustion, palpitations, and dyspnoea. Palpitations may happen due to either supraventricular or ventricular arrhythmias. Presyncope or syncope could be a result of AV block, ventricular tachycardia (VT), or supraventricular tachycardia (SVT).Fatigue, dyspnoea, and orthopnoea can all be symptoms of CS-related heart failure. However, tiredness and dyspnoea are nonspecific symptoms that can also happen in people with lung-related sarcoidosis or other non-sarcoid related chronic lung disease.(3) Angina is rarely associated with CS, hence angina symptoms are generally considered more suggestive of atherosclerotic coronary artery disease (CAD).(3) AV block is considered the commonest clinical manifestation in individuals with apparent CS.(7,8) Premature contractions of ventricles are also a common clinical presentation of CS.(7) The most common reasons for SCD in CS are VT and conduction block.(9)

Although HF is less prevalent in CS than arrhythmias, it is critical to properly assess individuals with established extracardiac sarcoidosis who present with cardiomyopathy or HF. CS can present either as dilated cardiomyopathy (DCM), HF with reduced ejection fraction (HFrEF) or a restrictive cardiomyopathy (RCM) that can result in HF with preserved EF (HFpEF). Right heart failure due to CS involving the right ventricle is quite hard to diagnose and should be distinguished from pulmonary hypertension (PH) following lung disease and arrhythmogenic right ventricular cardiomyopathy (ARVC).(10–12) The coronary arteries can be involved in sarcoidosis secondary to vasculitis, which can cause unstable angina or myocardial infarction.(13,14)

Diagnosis of cardiac sarcoidosis

Clinical suspicion, combined with pathologic data, and the results of advanced cardiovascular imaging are often required to reach a CS diagnosis.(15) In patients with the following clinical presentations, the diagnosis of CS should be considered:

i. Individuals who have extracardiac sarcoidosis, whether histologically or clinically diagnosed, with or without cardiac symptoms.
ii. Young adults with new onset conduction system disease or with unexplained syncope.
iii. Patients with fascicular VT and persistent VT that cannot be explained by normal outflow tract VT or VT caused by another structural cardiac disease, such as CAD.
iv. Patients with unexplained DCM, RCM or suspected ARVC.

The criteria for advanced cardiovascular imaging for selected patients with or without evidence of extracardiac sarcoidosis have previously been published.(16) These include:

A. CS with extra cardiac sarcoidosis

Criteria for histologic or clinical evidence of extra cardiac sarcoidosis are modified from those for individuals with histopathological evidence of extra cardiac sarcoidosis in the 2014 Heart Rhythm Society (HRS) Expert Consensus Statement. (16, 17) These are Patients with clinically confirmed or biopsy confirmed extra cardiac sarcoidosis and the following symptoms or indicators suggest, but not confirm, the presence of CS:

i. One or combination of these symptoms: Palpitations, presyncope, or syncope that persist more than two weeks.
ii. One or combination of the next ECG abnormalities: sustained AV block (first-, second-, or third-degree), continuous or non-sustained VT, complete right or left bundle branch block or existence of abnormal Q waves in two or more leads.
iii. One or combination of the next echocardiographic abnormalities: basal septal thinning, aberrant localised wall motion, ventricular aneurysm, or depressed left ventricular ejection fraction (LVEF).

B. CS without extra cardiac sarcoidosis

Individuals who do not have a history of extra cardiac sarcoidosis and have one or combination of the following abnormalities are candidates for advanced cardiovascular imaging:

(i) Unexplained second-degree Mobitz type II or AV block from the third degree inpatients aged <60 years.

(ii) Monomorphic VT that persists without any identifiable cause. The majority of the 2014 HRS Expert Consensus Statement drafting group supported this criterion, but it was not considered as a formal recommendation. (16, 17)

C. Suspected CS without criteria for advanced cardiovascular imaging: Patients without any of the symptoms or signs described above that serve as criteria for advanced cardiovascular imaging are unlikely to benefit from additional assessment. The presence of at least one cardiac symptom, ECG abnormalities, Holter monitor findings, or echocardiographic findings was highly sensitive for CS in a study that included 62 individuals with extracardiac sarcoidosis.(17) Consequently, the possibility of CS is low in patients without any criteria for advanced imaging. Individuals with extracardiac sarcoidosis without current manifestations of CS should be followed prospectively with serial clinical examination and ECG to monitor for potential development of signs and symptoms of CS.

Imaging technologies that is more advanced, such as cardiovascular magnetic resonance (CMR) or 18F-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET), or both, are chosen for suspected patients with indications for advanced imaging based on test characteristics, patient characteristics, feasibility, availability, and available expertise. The pathologic confirmation on EMB provides the most definitive means of identifying CS. Efforts must performed to safely obtain a suitable tissue sample in patients with a probability to have CS who lack histologic confirmation. Extra cardiac biopsies may provide a higher yield (higher sensitivity) and have a less procedural risk than EMB, which has a sensitivity of about 20-30%.(16)

Identification of CS is frequently uncertain. The following categories (highly probable, probable, and possible CS) may be used in cases in which CS diagnosis is still a workin progress. The development of this classification system has been made based on the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) organ assessment instrument that has been utilised to evaluate the likelihood of sarcoidosis organ involvement.(18–20) The existence of non-necrotising granuloma on histologic study of cardiac tissue confirms the existence of CS when no other aetiology can be found. (16, 20, 21)

Cardiovascular magnetic resonance

CMR is the method we prefer to utilise in the examination of individuals with suspected CS because it permits noninvasive evaluation of subclinical or clinical CS, evaluation of RV and LV chamber measurements and function, viability, and LGE. Parametric mapping with CMR has particular benefit in the identification of myocardial tissue characteristics like oedema, fibrosis and infiltration, and is useful for tracking patients following antiinflammatory therapy such as corticosteroids.

The main CMR technique for diagnosing CS identifies regions of LGE that are usually present as multiple foci and include the midventricular wall or subepicardium or may resemble a myocardial infarction. CMR can also detect abnormal morphologic structures like the thinning of the wall or aneurysms. LGE most commonly represents scarring, although significant inflammation can also lead to expansion in extracellular space, resulting in hazy enhancement on LGE. It is worth noting that there is no particular pattern of LGE that is characteristic of CS, as a CS may mimic many pathologies.(22–24)

Typical LGE patterns in CS patients are as follows: multifocal LGE (as opposed to a single area); subepicardial and midmyocardial LGE (i.e., non-infarct pattern), though some patients may have sub-endocardial involvement in a pattern like that of myocardial infarction;(22–24) direct LGE extension from the LV, across the interventricular segment, and into RV.(25–27)

The existence of high level T2-weighted signal, an indicator of elevated content of water, can be utilised to identify regions with inflammation.(25) Generally, the areas where T2 signal is increased often represent inflammation, but the absence of such a signal does not reliably exclude inflammation when compared with ^{18}FDG-PET. Recently, some drawbacks of T2-weighted imaging of the myocardium could perhaps be overcome by T2 mapping techniques that provide a more reliable way for detecting and quantifying myocardial inflammation.(26)

The main advantage of CMR is its high negative predictive value for ruling out CS when no LGE is present. Because there is no gold standard to use as a guide, the diagnostic accuracy of LGE for detecting CS is unclear, but even though this test sensitivity likely exceeds 90% when compared to the Japanese Ministry of Health and Welfare (JMHW) criteria.(27) Furthermore, a study comparing the diagnostic accuracy of CMR to the Heart Rhythm Society (HRS) criteria found that CMR had a sensitivity of 97%.(28) Both the JMHW and HRS criteria for CS may be suboptimal reference standards against which to validate CMR and PET. Apparent false positives using JMHW or HRS criteria are more likely to reflect the limited sensitivity of these criteria (especially in patients without histologic diagnosis), rather than limited specificity of CMR and PET imaging.(16)

T1 mapping and cardiac extracellular volume (ECV) are increasingly essential in the evaluation of CS patients, both for diagnostic purposes and follow-up. CS lesions may be categorised pathologically into three phases: early phase which is mainly lymphocytic, like (lymphocytic myocarditis), intermediate phase (active granulomatous), and late phase (primarily scar). These pathogenic processes might alter the ECV in CS.(29)

When there is no biopsy-confirmed extracardiac sarcoidosis or the evidence is equivocal, combining data from CMR imaging may be helpful in assessing thelikelihood of CS.(3) Despite the difficulties in identifying the diagnostic accuracy of CMR, the prognosticvalue of CMR in CS has been previously demonstrated.(3)

Although there is evidence that LGE imaging may have a benefit in assessing the effectiveness of glucocorticoid therapy, repeated imaging is difficult because patientswith CS frequently require the insertion of an ICD or a pacemaker.(30, 31) These implanted cardiac devices may cause imaging artefacts, which may interfere with interpretation, and some devices, including most current ICDs, are not always magnetic resonance imaging (MRI) conditional. LGE signal quality varies and may be difficult to evaluate, as it often represents concomitant scar and inflammation. CMR is also less useful in assessing for extracardiac sarcoidosis than computed tomography(CT) or ^{18}FDG-PET imaging. Contraindications to CMR (e.g., estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2, implanted devices that are not MRI conditional, severe claustrophobia with inability to sedate the patient) limit the utility of the technique.

Positron emission tomography

FDG-PET can identify active cardiac inflammation that may be utilised to assess the possibility of CS in the right clinical context. Although efforts have been made by numerous studies to examine the diagnostic accuracy of FDG-PET,(32,33) these have always been restricted to using the JMHW criteria as a reference standard, likely resulting in a lower accuracy than ^{18}FDG-PET. The specificity and sensitivity of ^{18}FDG-PET were found to be 78% and 89%, respectively, in a meta-analysis of seven trials (with 164 patients) comparing it to the 1993 JMHW guidelines.(33) ^{18}FDG-PET has more sensitivity than single-photon emission computed tomography with gallium-67, thallium-201, or technicium-99m (SPECT).(32, 34, 35)

A comprehensive FDG-PET imaging exam for CS involves 3 components:

i. Rest myocardial perfusion imaging can be obtained with either a SPECT or PET camera. Perfusion defects may represent either fibrosis or inflammation.

ii. Cardiac FDG-PET images need special PET camera. Myocardial inflammation is shown by areas of localised FDG absorption by the myocardium. To inhibit FDG absorption from the normal myocardium, this method requires sufficient patient preparation. It is worth noting that FDG absorption by the heart is not specific to sarcoidosis; it may also be found in other inflammatory myocardial disorders and hibernating myocardium. So, in the appropriate clinical context, existence of a resting perfusion deficit with increased FDG uptake may necessitate excluding obstructive CAD.

iii. Limited whole-body images are recommended strongly when there are no previous data regarding the existence of or disease activity of extracardiac sarcoidosis. The scan range is typically performed from the orbits to the upper thigh, and at least should include the chest, liver, and spleen, as these are the

most frequently affected organs.

Comparison of CMR with FDG-PET

The imaging with the highest sensitivity techniques for detecting CS appear to be CMR and FDG-PET. (28,32) Furthermore, both CMR and FDG-PET could be used to make death and other adverse events predictions. There are no well-powered studies that test the accuracy of diagnosis using CMR compared to PET. Because CMR has a high negative predictive value for excluding prognostically relevant disease and is less prone to provide nonspecific data (as can occur in 10 to 30% of FDG-PET studies, for individuals with suspected CS who have no contraindications to CMR, CMR is the recommended initial diagnostic test.

FDG-PET is very helpful for diagnosis of myocardial inflammation and follow-up imaging for evaluating the response to anti-inflammatory therapy. The combination of CMR and PET provides additional information for many patients with suspected CS, because the existence and extent of scarring are more likely to be shown by CMR, whereas the existence, extent, and severity of myocardial inflammation is more likely to be detected by PET. Therefore, when any one test provides inconclusive results, the standard practice is to combine data from both exams in order to determine the likelihood of CS.(28)

Endomyocardial biopsy (EMB)

The "gold standard" for diagnosing CS is the detection of non-caseating granulomas, which has a high specificity for sarcoidosis. If there is no histologic confirmation of non-caseating granulomas from another source, an EMB is recommended. The procedure, however, has a low sensitivity, approaching only 20% in one series of 26 patients.(36) The use of EMB is limited by the possibility of false negative results owing to sampling

error caused by the disease's patchy distribution. EMB is mainly performed starting from the RV at the midmyocardial level. Although disease involvement in the basal septum and lateral LV wall is more common, these areas are more difficult to biopsy. Given the restricted area of RV midmyocardium that is safely accessible to traditional transvenous cardiac biopsy, there is a limited role for using CMR or PET findings to guide biopsy. However, when there is a suspicion of CS during an electrophysiology study, electroanatomic mapping can be utilised to detect the low voltage areas that could be a granuloma and could be targeted for biopsy, improving the diagnostic yield.

Study rationale

There is a paucity of data on CS in Africa. Several gaps remain in our understanding of the concepts of disease epidemiology, phenotypes, and outcomes, particularly in South Africa. The South African Cardiovascular Magnetic Resonance (SA-CMR) Registry is a multi-centre registry that consists of both retrospective and prospective CMR data, from urban areas, primarily in Cape Town. SA-CMR was founded in January 2016. The retrospective arm consists of all patients that underwent CMR at Groote Schuur Hospital (GSH) from the introduction of CMR in 2005. SA-CMR was founded with a view to gaining insight into CMR in the South African setting, specifically,to establish the clinical use and indications for CMR, to assess the quality of CMR imaging, to assess the country's baseline demographics and clinical features of CS patients, in addition to the assessment of CMR's impact on patient management.

In the SA-CMR registry retrospective arm, we decided to review our experience with diagnosis, management, and outcomes of CS at GSH between the years 2005 and 2018.

Aims and objectives

This study had three objectives:

1. In the SA-CMR, describe the demographic profile of patients with CS at GSH.
2. To describe outcomes of patients with CS in the SA-CMR.
3. To determine CMR biomarkers that predict outcome in CS in the SA-CMR.

References

1. Loke WSJ, Herbert C, Thomas PS. Sarcoidosis: Immunopathogenesis and ImmunologicalMarkers. International Journal of Chronic Diseases. 2013; 2013:1–13.
2. Blankstein R, Stewart GC. Clinical Manifestation and Diagnosis of Cardiac Sarcoidosis.UpToDate [Internet]. 2018.
3. Birnie DH, Kandolin R, Nery PB, Kupari M. Cardiac manifestations of sarcoidosis:diagnosis and management. Eur Heart J. 2017 Sep 14;38(35):2663–70.
4. Yoshida A, Ishibashi-Ueda H, Yamada N, Kanzaki H, Hasegawa T, Takahama H, et al.Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure. European journal of heart failure.2013;15(2):166–75.
5. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiacsarcoidosis-state of the art review. Cardiovasc Diagn Ther. 2016 Feb;6(1):50–63.
6. Yatsynovich Y, Dittoe N, Petrov M, Maroz N. Cardiac Sarcoidosis: A Review ofContemporary Challenges in Diagnosis and Treatment. Am J Med Sci. 2018 Feb;355(2):113–25.
7. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, et al. Cardiacsarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. Circulation. 2015 Feb 17;131(7):624–32.
8. Zipse MM, Sauer WH. Cardiac sarcoidosis. Curr Cardiol Rep. 2014 Aug;16(8):514.
9. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, McArdle BA, et al. Atrioventricularblock as the initial manifestation of cardiac sarcoidosis in middle-aged adults. J Cardiovasc Electrophysiol. 2014 Aug;25(8):875–81.
10. Joyce E, Kamperidis V, Ninaber MK, Katsanos S, Debonnaire P, Schalij MJ, et al. Prevalence and Correlates of Early Right Ventricular Dysfunction in Sarcoidosis and Its Association with Outcome. J Am Soc Echocardiogr. 2016 Sep;29(9):871–8.
11. Patel MB, Mor-Avi V, Murtagh G, Bonham CA, Laffin LJ, Hogarth DK, et al. Right Heart Involvement in Patients with Sarcoidosis. Echocardiography. 2016 May;33(5):734–41.

12. Lønborg J, Ward M, Gill A, Grieve SM, Figtree GA. Utility of cardiac magnetic resonance in assessing right-sided heart failure in sarcoidosis. BMC Med Imaging. 2013Jan 11;13:2.
13. Lam CSP, Tolep KA, Metke MP, Glockner J, Cooper LT. Coronary sarcoidosispresenting as acute coronary syndrome. Clin Cardiol. 2009 Jun;32(6):E68-71.
14. Butany J, Bahl NE, Morales K, Thangaroopan M, Ross H, Rao V, et al. The intricacies ofcardiac sarcoidosis: a case report involving the coronary arteries and a review of the literature. Cardiovasc Pathol. 2006 Aug;15(4):222–7.
15. Soejima K, Yada H. The work-up and management of patients with apparent orsubclinical cardiac sarcoidosis: with emphasis on the associated heart rhythm abnormalities. J Cardiovasc Electrophysiol. 2009 May;20(5):578–83.
16. Chareonthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, et al. Joint SNMMI-ASNC Expert Consensus Document on the Role of 18F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring. J Nucl Med. 2017 Aug;58(8):1341–53.
17. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associatedwith cardiac sarcoidosis. Heart Rhythm. 2014 Jul;11(7):1305–23.
18. Mehta D, Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, Goldman M, et al. Cardiacinvolvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. Chest. 2008 Jun;133(6):1426–35.
19. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and OtherGranulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999 Aug;160(2):736–55.
20. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, et al. The WASOGSarcoidosis Organ Assessment Instrument: An update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis. 2014 Apr 18;31(1):19–27.

21. Zhou Y, Lower EE, Li H-P, Costea A, Attari M, Baughman RP. Cardiac Sarcoidosis: TheImpact of Age and Implanted Devices on Survival. Chest. 2017 Jan;151(1):139–48.
22. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA, et al. Detection of myocardial damage in patients with sarcoidosis. Circulation. 2009 Nov 17;120(20):1969–77.
23. Sharma S. Cardiac imaging in myocardial sarcoidosis and other cardiomyopathies. CurrOpin Pulm Med. 2009 Sep;15(5):507–12.
24. Greulich S, Deluigi CC, Gloekler S, Wahl A, Zürn C, Kramer U, et al. CMR imagingpredicts death and other adverse events in suspected cardiac sarcoidosis. JACC Cardiovasc Imaging. 2013 Apr;6(4):501–11.
25. Cain MA, Metzl MD, Patel AR, Addetia K, Spencer KT, Sweiss NJ, et al. Cardiacsarcoidosis detected by late gadolinium enhancement and prevalence of atrial arrhythmias. Am J Cardiol. 2014 May 1;113(9):1556–60.
26. Patel AR, Klein MR, Chandra S, Spencer KT, Decara JM, Lang RM, et al. Myocardialdamage in patients with sarcoidosis and preserved left ventricular systolic function: an observational study. Eur J Heart Fail. 2011 Nov;13(11):1231–7.
27. Smedema J-P, Snoep G, van Kroonenburgh MPG, van Geuns R-J, Dassen WRM, Gorgels APM, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol. 2005 May17;45(10):1683–90.
28. Vita T, Okada DR, Veillet-Chowdhury M, Bravo PE, Mullins E, Hulten E, et al. Complementary Value of Cardiac Magnetic Resonance Imaging and Positron EmissionTomography/Computed Tomography in the Assessment of Cardiac Sarcoidosis. Circ Cardiovasc Imaging. 2018 Jan;11(1):e007030.
29. Yang Y, Zavodni A, Roifman I, Zia MI, Balter M, Dick A, et al. Myocardial extracellularspace volume in patients with systemic sarcoidosis: quantitative measurement using a T1mapping technique. Journal of Cardiovascular Magnetic Resonance. 2014 Jan 16;16(1):P279.
30. Komada T, Suzuki K, Ishiguchi H, Kawai H, Okumura T, Hirashiki A, et al. Magneticresonance imaging of cardiac sarcoidosis: an evaluation of the cardiac segments and layers that exhibit late gadolinium enhancement.

Nagoya J Med Sci. 2016 Dec;78(4):437–46.
31. Murtagh G, Laffin LJ, Patel KV, Patel AV, Bonham CA, Yu Z, et al. Improved detectionof myocardial damage in sarcoidosis using longitudinal strain in patients with preserved left ventricular ejection fraction. Echocardiography. 2016 Sep;33(9):1344–52.
32. Ishimaru S, Tsujino I, Sakaue S, Oyama N, Takei T, Tsukamoto E, et al. Combination of18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in assessing cardiac sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005 Oct;22(3):234–5.
33. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, et al. The use of18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. Journal of nuclear medicine. 2012;53(2):241–8.
34. Langah R, Spicer K, Gebregziabher M, Gordon L. Effectiveness of prolonged fasting18f-FDG PET-CT in the detection of cardiac sarcoidosis. J Nucl Cardiol. 2009 Oct;16(5):801–10.
35. Okumura W, Iwasaki T, Toyama T, Iso T, Arai M, Oriuchi N, et al. Usefulness of fasting18F-FDG PET in identification of cardiac sarcoidosis. J Nucl Med. 2004 Dec;45(12):1989–98.

Chapter 2: Methods

Study design

The study was a retrospective descriptive study of patients diagnosed with CS by CMR at GSH between 2005 and 2017.

Study population

All participants were obtained from the retrospective arm of the SA-CMR registry which enrolled participants from 2005 to 2018. All patients with a diagnosis of CS were included. Patient records were accessed from the GSH Cardiac Clinic records. CMR images of the participants were reviewed by, at least, 3 trained CMR readers, each with a minimum of 5 years' experience.

Data collection

Variables captured included patient demographic profiles, comorbid status, CMR parameters, cardiovascular symptoms at presentation, complications, and viability status. Data were entered onto a Microsoft Excel spreadsheet.

Ethical considerations

In 2015, the Human Research Ethics Committee at the University of Cape Town approved the SA-CMR registry. (HREC Reference: R055/2015). This MMed project was approved as a sub study of the SA-CMR registry.

Because this was a retrospective analysis of existing information with no participant contact, we were able to get a waiver of informed consent. This was considered a low ethical risk study because the study only included patient records. Patient confidentiality was always respected, and all data were analysed in an anonymised fashion. It is not possible to identify individual participants, as the results are presented in aggregate. Only members of the research team who were involved actively in the study had access to patient records. The study was conducted in keeping with the principles of the 2013 Helsinki Declaration.

Risks and benefits

When properly supervised, CMR is a completely risk-free and non-invasive technology. It does not include the use of ionizing radiation. Participants who have ferromagnetic objects or implanted devices in their bodies that could be damaged by the CMR magnet should have been evaluated individually prior to MRI. Gadolinium contrast is a safe and widely used contrast agent in CMR for clinical indications. Gadolinium clearance is within hours and adverse events are uncommon, and include mild headache, nausea, itching and severe allergic reaction in less than 1 in 1000.

Patients undergoing CMR will have done so for investigation of suspected underlying heart disease. The CS diagnosis will have already been reported to the physician or the cardiologist. If an abnormality of obvious clinical significance is discovered by chance, the treating doctor or cardiologist would have been notified and would have discussed the consequences with the patient and, if necessary, arranged for more investigations.

The participants whose images will have been analysed as part of this research will not have any direct benefits

Statistics analysis

The data were analysed with SPSS (version 26). The demographic profile and the outcomes of the individuals who were diagnosed with CS by CMR were proportionally summarised as necessary: medians (with interquartile ranges), and means (with standard deviations). Fisher's exact test was utilised to make a comparisons between proportions, while T-test and Mann-Whitney U-test were utilised to make comparison between the means and medians, respectively.

Chapter 3: Submissible manuscript

Abstract

Introduction: Sarcoidosis is an inflammatory disorder that affects multiple systems. On histologic examination, sarcoidosis is defined by the production of non-caseating granulomas. Cardiac sarcoidosis (CS) is common, occurring in 20% or more of patients with systemic sarcoidosis, but because many people with CS may have nonspecific clinical manifestations or subclinical disease, the real extent of the disease prevalence is uncertain and possibly underestimated.

Methods: Medical records of patients with CS diagnosed by cardiovascular magnetic resonance (CMR) were selected for inclusion into this study. We identified patients with a diagnosis of CS by CMR between March 2005 and January 2018 at Groote Schuur Hospital, Cape Town, South Africa and included into the South African Cardiovascular Magnetic Resonance (SA-CMR) registry. The demographics, clinical profile, and outcomes of patients diagnosed with CS via CMR were summarised utilising proportions, medians with interquartile ranges (IQRs), and means with standard deviations (SDs), as appropriate. Fisher's exact test was utilised to compare proportions, while T tests and Mann-Whitney U-tests were utilised to compare means and medians, respectively. Statistical Package for Social Sciences (version 26) program was used to analyse the data.

Results: Medical records of 35 patients with a confirmed diagnosis of CS using CMR during the study period were identified. There were 21 (60%) males, and a male: female ratio of 1.5:1. The mean age of study participants was 50.3 ± 11 years. Most patients (84%) were overweight and obese, and comorbidities included hypertension (9%) and diabetes mellitus (3%). Nearly a quarter (23%) of patients presented with complete heart block and a third (31%) had ventricular tachycardia (VT) as the initial

presentation. Half (54%) of patients had a permanent pacemaker or implantable cardioverter defibrillator implanted. A third (34%) of patients had evidence of acute myocardial oedema on T2-weighted imaging and T2 mapping, and 91% of subjects had evidence of focal fibrosis/infiltration on late gadolinium enhancement (LGE). Most patients (80%) had normal pericardial thickness and small pericardial effusions (< 1 cm) were noted in 49%. Extra-cardiac findings of sarcoidosiswere characterised by hilar lymphadenopathy and pulmonary interstitial involvement (49%) and pleural effusions (11%). There were no deaths during the study period andmedian follow-up of 7 years.

Conclusions: Sarcoidosis is a granulomatous systemic multiorgan condition that is a challenge to diagnose and manage in many settings. The availability of CMR has made it possible to diagnose CS noninvasively. We show that in our setting CS is characterised by oedema in a third of patients and evidence of LGE in almost all patients. Heart block and VT are common presentations; however, the prognosis is good with modern device therapies once the diagnosis has been made.

Keywords

Sarcoidosis, cardiac sarcoidosis, cardiovascular magnetic resonance, late gadolinium enhancement, South Africa

Introduction

Sarcoidosis is an inflammatory disease with multiple organ involvement and histologically characterised by the existence of non-necrotising granulomas.(1) Cardiac sarcoidosis (CS) is common, occurring in 20% or more of individuals with systemic sarcoidosis, but the true prevalence remains unknown. Many people with CS have nonspecific symptoms or subclinical disease, therefore prevalence is likely underestimated.(2) About 5% of individuals with sarcoidosis will develop clinically noticeable involvement of the heart, including manifestations such as: ventricular arrhythmias, conduction defects, and heart failure (HF). (3) A quarter of cases of CS are isolated (occur without extracardiac involvement).(4) As a result, the absence of extracardiac sarcoidosis does exclude the probability of CS.

CMR (cardiovascular magnetic resonance) has become a popular method for non-invasive diagnosis of CS.(5-6) CMR has several advantages, including lack of ionising radiation, a high level of spatial and temporal resolution, and its capacity to characterise tissues (for evaluation of inflammation, infiltration and fibrosis).(5–6)CMR enables the non-invasive diagnosis of subclinical or clinical CS, and is the imaging technique of choice. While morphologic abnormalities, like aneurysm or thinning in the wall, can be detectedwith CMR, identification of late gadolinium enhancement (LGE) and use of parametric mapping is helpful. CS lesions are usually multifocal and affect the midventricular wall, the subepicardium or may resemble transmural infarction.(5–8) LGE most commonly represents scarring, although significant inflammation can also lead to hazy LGE appearance. There is no single LGE pattern that is pathognomonic for CS.(5–10) CS is the great mimicker, as any pattern of LGE may be evident on CMR.

Existence of elevated T2-weighted signal which indicates myocardial oedema can be utilised to identify areas of inflammation.(8) Absence of elevated T2 signal does not reliably exclude inflammation when compared with T2 mapping or ^{18}FDG-PET imaging.(8,9) The main advantage of CMR is its high negative predictive value for excluding CS when no LGE is detected.(10) Accuracy of LGE for detecting CS is unknown, as there is no trustworthy reference standard. LGE has been demonstrated to have a sensitivity >90% when compared with Japanese Ministry of Health and Welfare (JMHW) criteria.(10)

The South African Cardiovascular Magnetic Resonance (SA-CMR) registry is a multi-centre registry that consists of both retrospective and prospective CMR data, from South African centres, mostly in Cape Town. SA-CMR was established in January 2016. The retrospective arm consists of all patients who underwent CMR at Groote Schuur Hospital (GSH) since the introduction of CMR in 2005. SA-CMR was founded with a view to gain insight into CMR in the South African setting, specifically, to define the clinical usage and indications for CMR, evaluate the quality of CMR imaging, identify the demographic and clinical parameters of patients undergoing CMR across the country, and to analyse the value of CMR on patient management.

In Africa, there is a scarcity of publications on CS. Several gaps in our knowledge of disease epidemiology, phenotypes, natural history, and outcomes of CS in South Africa exist. Therefore, the objective of this study was to discover CMR biomarkers that predict CS outcomein the SA-CMR and to analyse the demographic profile of patients with CS.

Methods

Study design: The study was a retrospective descriptive study of patients diagnosed with CS by CMR at GSH between 2005 and 2017.

Study population: All participants were obtained from the retrospective arm of the SA-CMR registry which enrolled participants from 2005 to 2018. All patients with a diagnosis of CS were included. Patient records were accessed from the GSH Cardiac Clinic records. CMR images of the participants were reviewed by, at least, 3 trained CMR readers, each with a minimum of 5 years' experience.

Data collection: Variables captured included patient demographic profiles, comorbid status, CMR parameters, cardiovascular symptoms at presentation, complications, and viability status. Data were entered onto a Microsoft Excel spreadsheet.

Ethical considerations: In 2015, the Human Research Ethics Committee at the University of Cape Town approved the SA-CMR registry. (HREC Reference: R055/2015). This MMed project was approved as a sub-study of the SA-CMR registry. Because this was a retrospective analysis of existing information with no participant contact, we were able to get a waiver of informed consent. This was considered a low ethical risk study because the study only included patient records. Patient confidentiality was always respected, and all data were analysed in an anonymised fashion. It is not possible to identify individual participants, as the results are presented in aggregate. Only members of the research team who were involved actively in the study had access to patient records. The study was conducted in keeping with the principles of the 2013 Helsinki Declaration.

Risks and benefits: When properly supervised, CMR is a completely risk-free and non-invasive technology. It does not include the use of ionizing radiation. Participants who have ferromagnetic objects or implanted devices in their bodies that could be damaged by the CMR magnet should have been evaluated individually prior to MRI. Gadolinium contrast is a safe and widely used contrast agent in CMR for clinical indications. Gadolinium clearance is within hours and adverse events are uncommon, and includemild headache, nausea, itching and severe allergic reaction in less than 1 in 1000.

Statistical analysis: The data were analysed with SPSS (version 26). The demographic profile and the outcomes of the individuals who were diagnosed with CS by CMR were proportionally summarised as necessary: medians (with interquartile ranges), and means (with standard deviations). Fisher's exact test was utilised to make a comparisons between proportions, while T-test and Mann-Whitney U-test were utilised to make comparison between the means and medians, respectively.

Results

a. Baseline demographics

Through a search of the SA-CMR registry, 35 individuals with a CS diagnosis were identified, with a mean age of 53 ± 11 years, and were 60% male. Other clinical features are reported in Table 1.

Table 1. Baseline clinical characteristics of the study population (N=35)

Characteristic	Descriptive statistics
Age in years, mean (±SD)	50.3 ± 11
Sex, n (%)	
Female	14 (40)
Male	21 (60)
Height, mean (±SD)	170.5 ± 13
Weight, median (IQR)	84 (70-96)
BMI, median (IQR)	30.7 (10.8)
BMI categories, n (%)	
Normal	5/31 (16.1)
Overweight	14/31 (45.2)
Obese	12/31 (38.7)
BSA, mean (±SD)	2.0 ± 0.2
Heart Rate, mean (±SD)	69.9 ± 18.7

BMI, body mass index; BSA, body surface area; IQR, interquartile range; SD, standard deviation

b. Presentation and comorbidities

Table 2 shows that eight patients had complete heart block (CHB), necessitating implantation of permanent pacemakers (PPM). Eleven (31%) patients presented with ventricular tachycardia (VT), with subsequent implantable cardioverter defibrillator (ICD) implantation. Two (5.7%) patients presented with decompensated heart failure (HF). Other comorbid conditions included hypertension in 3 (8.6%) and diabetes mellitus in 1 (2.9%).

Table 2. Clinical presentation and comorbidities of the study population (N=35)

Characteristic	Descriptive statistics
Hypertension, n (%)	3 (8.6)
Diabetes mellitus, n (%)	1 (2.9)
Heart failure, n (%)	2 (5.7)
Dyslipidaemia, n (%)	0
Complete heart block, n (%)	8 (22.9)
Ventricular tachycardia, n (%)	11 (31.4)

c. CMR findings

The median LVEF was 56% (IQR 33-62). LV mass and volumes are presented in Table 3. RVEF was 44±14%. Mean LA area and median RA area were 24±7 cm^2 and 21 (17-21) cm^2, respectively.

Table 3. CMR findings in the study population (N=35)

Characteristic	Descriptive statistics
LVEF, %, median (IQR)	55.5 (33-62)
LVEDV, ml, median (IQR)	183 (123-236)
LVESV, ml, median (IQR)	83 (48-153)
LVSV, ml, mean (±SD)	81.8 ± 24.1
LV mass, g, mean (±SD)	136.4 ± 36.4
LV mass index, g/m^2, mean (±SD)	69.2 ± 16.5
RVEF, %, mean (±SD)	43.9± 14.1
RVEDV, ml, median (IQR)	152 (121-198)
RVESV, ml, median (IQR)	97 (50-139)
RVSV, ml, median (IQR)	68 (50-85)
LA area, cm^2, mean (±SD)	23.6± 6.5
RA area, cm^2, median (IQR)	21 (17-28)

LA, left atrium/atrial; LV, left ventricle/ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; RA, right atrium/atrial; RV, right ventricle/ventricular; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volumes; RVSV, right ventricular stroke volume.

d. Tissue characteristics on CMR

Table 4 summarises the CMR tissue characteristics. Ten (29%) participants had imaging protocols that included T1, T2 and extracellular volume (ECV) mapping. Therefore, results of mapping techniques are not reported in this analysis. Myocardial oedema, demonstrated by elevated T2-weighted signal intensity ratio, was noted in 11/35 (31%) patients. Focal fibrosis, demonstrated by LGE, was detected in 31/34 (91%) patients who underwent LGE CMR (Figure 1).

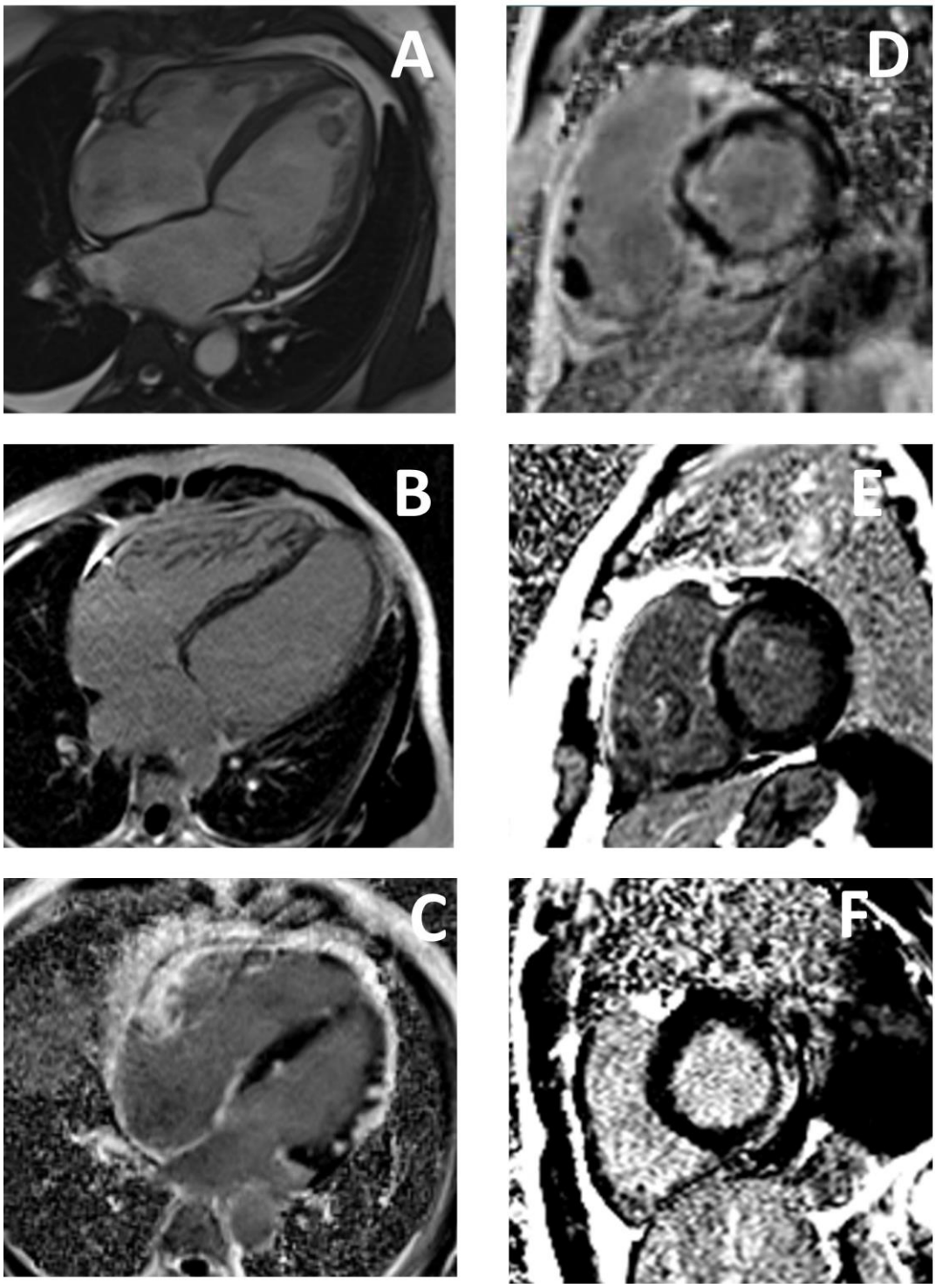

Figure 1. Representative cine (a) and late gadolinium enhancement (b-f) CMR images in patientswith sarcoidosis

A. balanced steady state free precession horizontal long axis (HLA). image showing dilated left and right ventricles with thrombus in apex of left ventricle; B. Phase-sensitive inversion recovery (PSIR) late gadolinium enhancement (LGE) HLA image showing dilated LVE with linear mid-wall enhancement in the interventricular septum; C. PSIR LGE HLA image showing nodular patterns of enhancement in the

interventricular septum, the inferoposterior wall of theLV, enhancement of the basal aspect of the right ventricular endocardial aspect of the septum,and enhancement of part of right ventricular free wall; D. PSIR LGE short axis (SAX) image showing enhancement of the right ventricular aspect of the inferior septum and enhancementof the right ventricular free wall; E. PSIR LGE SAX image showing multiple patterns of enhancement including 50% subendocardial enhancement in the anterior septum, the anterolateral papillary muscle, the right ventricular aspect of the septum and the right ventricular free wall; and F. PSIR LGE SAX image showing subepicardial enhancement of theinferolateral wall of the left ventricle.

Table 4. CMR tissue characteristics

Characteristic	**Descriptive statistics**
T2-weighted SIR >1.9 (%)	11/35 (31.4)
LGE (%)	21/34 (91.2)

LGE, late gadolinium enhancement; SIR, signal intensity ratio

e. Pericardial involvement on CMR

Patients with pericardial involvement are shown in Table 5. All patients had normal pericardial thickness. Small pericardial effusions (< 1 cm) were observed in 17/35 patients (49%).

Table 5. Pericardial involvement in CS

Characteristic	**Descriptive statistics**
Normal pericardial thickness (%)	35 (100)
Pericardial effusions (< 1 cm) (%)	17 (48.6)

f. Extracardiac manifestations of sarcoidosis

Extracardiac findings of sarcoidosis noted included hilar lymphadenopathy(49%), pulmonary interstitial involvement (49%), and pleural effusions (11%), shown in Table 6.

Table 6. Extracardiac manifestations of CS

Characteristic	Descriptive statistics
Pulmonary involvement, n (%)	17 (48.6)
Lymph nodes, n (%)	17 (48.6)
Pleural effusion, n (%)	4 (11.4)

g. Outcomes of CS

There were no deaths in CS patients during the study period, with a median follow-up of 7.1 years. Three patients were treated for HF at follow-up. 54% of patients with rhythm abnormalities had implantable devices inserted.

Discussion

Sarcoidosis is a complex, granulomatous, systemic, multiorgan disorder that may involve the cardiovascular system. In this small retrospective analysis and first report on CS from South Africa, we identified 35 patients with CS who had undergone CMR. We observed that CS patients in South Africa were more likely to be male, relatively young (mean age at diagnosis: 50 years), and had frequent electrophysiological abnormalities, with a quarter presenting with CHB and a third with VT. Myocardial oedema was detected in a third and focal LGE in over 90%. Pericardial effusions and extra-cardiac involvement were noted in half of patients. Finally, survival was good following device implantation, with no mortality observed following a median follow-up of 7.1 years. These findings have major significance for low-resource settings, demonstrating that using CMR to identify sarcoid improves diagnostic certainty and that modern device therapies are linked to improved long- term survival.

In this study, 60% of individuals with CS were men, with a mean age of 50 years. CS can affect patients of all racial backgrounds and ages, with an average age at

presentation of approximately 50 years old.(11) Several reports indicate that the prevalence of CS in increasing.(11) However, it is unclear whether the changing epidemiology reflects an increase in disease prevalence or increased awareness and better identification of the condition.

Sarcoidosis is a heterogeneous disease of uncertain aetiology whose hallmark lesion is the non-caseating granuloma. Any segment of the heart may be affected by CS. Papillary muscles, atria, valves, coronary arteries, and pericardium have all been demonstrated to be affected, but the ventricular myocardium is most often involved. CS progresses from inflammatory lesions to fibrotic disease. Some individuals may only have a small area of inflammation or scarring and will not experience significant clinical sequalae. Other patients may progress to develop a pattern of extensive inflammation and scarring.

One of the common manifestations of CS is cardiac arrhythmia.(2) Such conduction defects range from AV block, bundle branch block and supraventricular tachycardia to more life-threatening arrhythmias like VT. In our study, a third of patients with CS presented with VT and a quarter with CHB.CHB has been identified as a frequent dysrhythmia in young individuals, in addition to being a cause of sudden cardiac death among CS patients. Symptomatic CHB was found in 44% individuals with histologically proven CS.(12) Patients with CS develop CHB at an earlier age than those with CHB from other causes.(13) Longer PR intervals (first-degreeAV block) are common and can progress owing to disease of AV node or bundle of His, as well as intraventricular conduction defects.(14) As a result, conduction system disease may be asymptomatic at first, and then develop to CHB.(15,16) VT (sustained or non-sustained VT, as well as ventricular premature beats) are the second most frequent clinical manifestation of CS,

accounting for around 30% of cases.(17, 12/8) Sarcoid granulomas or fibrosis in the myocardium can cause re-entrant arrhythmias by becoming focal points for aberrant automaticity or disrupting ventricular activation and recovery. Re-entrant arrhythmias can occur because of tissue scarring in the myocardium.(2)

In this study, 50% of patients had evidence of involvement in lung and mediastinal lymph node. Being a systemic disease, sarcoidosis may involve many organs in the body. The lung is the main site of involvement. Commonly affected organs, outside of the lung, include lymph nodes, liver, spleen, and skin. A review of 1,375 sarcoidosis patients, 64 presenting with CS, revealed lung parenchymal and/or intrathoracic lymph node involvement in all the 64 CS patients.(19) Similarly, lung and thoracic lymph node involvement are commonly reported in patients with CS.(20,22,23,24)

In the evaluation of CS, CMR is the ‘gold standard' for measuring ventricular volume, ejection fraction, and myocardial mass. Overall, we found borderline or low normal LVEF and RVEF with preserved LV and RV volumes and mass. These findings are in keeping with what most investigators have reported.(10, 21, 25)

LGE CMR is a sensitive noninvasive diagnostic tool for CS. In our study, over 90% of participants had evidence of LGE. Kandlolin *et al*., in a 25-year national survey reported LGE in 85% of all CS patients; 95% LGE in individuals with isolated CS; and 62% in patients with CS with known extracardiac involvement.(8)

In this study, there were no deaths in CS patients after 7.1 years of follow-up. Overall, after 5 and 10 years after CS diagnosis, the survival rate was 93.6 percent and 89.6 percent, respectively.(10) Refractory HF and SCD from malignant ventricular arrhythmias or CHB lead to death in CS. In a different study, independent mortality indicators were New York Heart Association functional class (hazard ratio 7.72), LV end-diastolic diameter (hazard ratio 2.60), and sustained VT (hazard ratio 7.20).(26) The most important independent predictor of CS mortality is HF severity. The use of device therapies and corticosteroids prior to the onset of systolic dysfunction result in improved clinical outcomes.

A common complication of CS is HF, which is often associated with poor outcomes. Three individuals with CS were treated for HF in this study. In a Danish nationwide study of 11,834 patients with sarcoidosis during 1996 to 2016 (without HF or arrhythmias at baseline) who were matched based on their sex, age, and comorbidities with 47,336 healthy individuals without sarcoidosis in the population, those with sarcoidosis had a greater 10- year risk of HF (3.18 versus 1.72 percent),and also other adverse cardiac events including a combination of pacemaker insertion, atrioventricular block, and sinoatrial dysfunction, ICD implantation, ventricular arrhythmias, cardiac arrest, and atrial fibrillation or flutter.(8,24) Patients with sarcoidosis had a greater 10-year death risk (10.88% versus 7.43%).(8)

Limitations

The study had the following limitations:

Small sample size: the study is relatively small and may not be adequately powered to reflect true representation of the disease characteristics.

Referral bias: The study was conducted in tertiary centre raising the possibility of referral bias.

EMB and PET scan: These are not routinely used for the diagnosis and evaluation of CS in our institution.

Conclusion

Cardiac involvement has been said to be rare in sarcoidosis, and when it occurs, it usually affects young and middle-aged individuals. In this first report of CS from South Africa, we found that CS patients were more likely to be male, and with a mean age of 50 years at diagnosis, had frequent electrophysiological abnormalities, with a quarter presenting with CHB and a third with VT. Myocardial oedema was detected in a third and focal LGE in over 90%. Pericardial effusions and extra-cardiac involvement were noted in half of patients. Finally, survival was good following device implantation,with no mortality observed following a median of 7.1 years. These data have important implications for practice in low resource settings and demonstrate that use of CMR to diagnose sarcoid increases the diagnostic certainty and that modern device therapies are associated with good long-term survival.

References

1. Loke WSJ, Herbert C, Thomas PS. Sarcoidosis: Immunopathogenesis and Immunological Markers. International Journal of Chronic Diseases. 2013; 2013:1–13.

2. Blankstein R, Stewart GC. Clinical Manifestation and Diagnosis of Cardiac Sarcoidosis. UpToDate [Internet]. 2018;

3. Birnie DH, Kandolin R, Nery PB, Kupari M. Cardiac manifestations of sarcoidosis: diagnosis and management. Eur Heart J. 2017 Sep 14;38(35):2663–70.

4. Yoshida A, Ishibashi-Ueda H, Yamada N, Kanzaki H, Hasegawa T, Takahama H, et al. Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure. European journal of heart failure. 2013;15(2):166–75.

5. Greulich S, Deluigi CC, Gloekler S, Wahl A, Zürn C, Kramer U, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. JACC Cardiovasc Imaging. 2013 Apr;6(4):501–11.

6. Cain MA, Metzl MD, Patel AR, Addetia K, Spencer KT, Sweiss NJ, et al. Cardiac sarcoidosis detected by late gadolinium enhancement and prevalence of atrial arrhythmias. Am J Cardiol. 2014 May 1;113(9):1556–60.

7. Patel AR, Klein MR, Chandra S, Spencer KT, Decara JM, Lang RM, et al. Myocardial damage in patients with sarcoidosis and preserved left ventricular systolic function: an observational study. Eur J Heart Fail. 2011 Nov;13(11):1231–7.

8. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. Circulation. 2015 Feb 17;131(7):624–32.

9. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, McArdle BA, et al. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. J Cardiovasc Electrophysiol. 2014 Aug;25(8):875–81.

10. Fleming H. Cardiac Sarcoidosis. In: Sarcoidosis and Other Granulomatous Disorders James DG (Ed). New York: Dekker; 1994. p. 323.

11. Chapelon-Abric C, de Zuttere D, Duhaut P, Veyssier P, Wechsler B, de Gennes C, et al. Cardiac sarcoidosis: a retrospective study of 41 cases. Medicine. 2004;83(6):315–34.

12. Yoshida Y, Morimoto S, Hiramitsu S, Tsuboi N, Hirayama H, Itoh T. Incidence of cardiac sarcoidosis in Japanese patients with high-degree atrioventricular block. American heart journal. 1997;134(3):382–6.

13. Viles-Gonzalez JF, Pastori L, Fischer A, Wisnivesky JP, Goldman MG, Mehta D. Supraventricular arrhythmias in patients with cardiac sarcoidosis: prevalence, predictors, and clinical implications. Chest. 2013;143(4):1085–90.

14. Patel MB, Mor-Avi V, Murtagh G, Bonham CA, Laffin LJ, Hogarth DK, et al. Right Heart Involvement in Patients with Sarcoidosis. Echocardiography. 2016 May;33(5):734–41.

15. Lønborg J, Ward M, Gill A, Grieve SM, Figtree GA. Utility of cardiac magnetic resonance in assessing right-sided heart failure in sarcoidosis. BMC Med Imaging. 2013 Jan 11;13:2.

16. Chareonthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, et al. Joint SNMMI-ASNC Expert Consensus Document on the Role of 18F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring. J Nucl Med. 2017 Aug;58(8):1341–53.

17. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, et al. The WASOG Sarcoidosis Organ Assessment Instrument: An update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis. 2014 Apr 18;31(1):19–27.

18. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA, et al. Detection of myocardial damage in patients with sarcoidosis. Circulation. 2009 Nov 17;120(20):1969–77.

19. Doughan AR, Williams BR. Cardiac sarcoidosis. Heart. 2006 Feb;92(2):282–8.

20. Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. Clinic Rev Allerg Immunol. 2015 Aug 1;49(1):63–78.

21. Vita T, Okada DR, Veillet-Chowdhury M, Bravo PE, Mullins E, Hulten E, et al. Complementary Value of Cardiac Magnetic Resonance Imaging and Positron Emission Tomography/Computed Tomography in the Assessment of Cardiac Sarcoidosis. Circ Cardiovasc Imaging. 2018 Jan;11(1):e007030.

22. Yang Y, Zavodni A, Roifman I, Zia MI, Balter M, Dick A, et al. Myocardial extracellular space volume in patients with systemic sarcoidosis: quantitative measurement using a T1 mapping technique. Journal of Cardiovascular Magnetic Resonance. 2014 Jan 16;16(1):P279.

23. Smedema J-P, Snoep G, van Kroonenburgh MPG, van Geuns R-J, Dassen WRM, Gorgels APM, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol. 2005 May 17;45(10):1683–90

24. Zipse MM, Sauer WH. Cardiac sarcoidosis. Curr Cardiol Rep. 2014 Aug;16(8):514.

25. Cacoub P, Chapelon-Abric C, Resche-Rigon M, Saadoun D, Desbois AC, Biard L. Cardiac sarcoidosis: A long term follow up study. PLOS ONE. 2020 Sep 18;15(9):e0238391.

26. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol. 2001 Nov 1;88(9):1