GLOBAL VOICES

Diagnoses, management patterns, and outcomes of cardiac sarcoidosis in South Africa

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BACKGROUND Sarcoidosis is an idiopathic multiorgan disease characterized by tissue infiltration by noncaseating granulomas. Clinical cardiac involvement is reported in approximately 5% of patients. However, the frequency of cardiac involvement is found to be higher on autopsy and in advanced imaging studies such as cardiac magnetic resonance imaging.

OBJECTIVE The purpose of this study was to determine contemporary diagnoses, management, and outcomes of cardiac sarcoidosis (CS) in South Africa.

METHODS Clinical records of patients diagnosed with CS between January 2000 and December 2021 were reviewed.

RESULTS Twenty-two patients were diagnosed with CS during the study period. The patients had a mean (± SD) age of 45.2 ± 12.3 years at the time of presentation. CS diagnostic rates increased from 4.5% in 2000–2005 to 45.5% in 2016–2021. Fifteen of the 22 patients (68.2%) were newly diagnosed with sarcoidosis at the time of CS diagnosis, and 9 of the 15 (60%) had pulmonary involvement. Of the 22 patients diagnosed with CS, 13 (59.1%) presented in combination with heart block, 10 (45.5%) with ventricular arrhythmias, and 4 (18.2%) with heart failure. Five endomyocardial biopsies were performed, and all were nondiagnostic. However, 8 of 8 endobronchial ultrasound (EBUS)–guided biopsies of thoracic lymph nodes were diagnostic of sarcoidosis and, notably, excluded tuberculosis. Fourteen patients (63.6%) were treated with corticosteroids, 7 (31.8%) with azathioprine, 9 (40.9%) with amiodarone, and 16 (72.7%) with a cardiac implantable electronic device. After a mean follow-up period of 64.5 ± 50.5 months, no deaths had occurred.

CONCLUSION CS diagnostic rates have increased over time. Diagnostic endomyocardial biopsies have a low diagnostic yield, whereas EBUS-guided biopsy of thoracic lymph nodes is of crucial diagnostic utility.

KEYWORDS Cardiac implantable electronic device; Cardiac sarcoidosis; Heart block; Heart failure; Ventricular tachycardia

Introduction

Sarcoidosis is a multisystem granulomatous disease pathologically characterized by tissue infiltration with noncaseating granulomas.[1] Sarcoidosis is 3 times more common in Black people than in White people.[2] Furthermore, Black patients tend to present with more acute and severe disease than their White counterparts.[3] Because pulmonary involvement is the predominant manifestation of sarcoidosis,[4,5] in South Africa the diagnosis of pulmonary sarcoidosis frequently is delayed or is misdiagnosed as pulmonary tuberculosis (TB).[6] For example, in a recent South African study, 17% of patients with pulmonary sarcoidosis initially were diagnosed as having, and were treated for, TB before the correct diagnosis of pulmonary sarcoidosis was made,[6] thus highlighting the challenges of accurately diagnosing sarcoidosis. In cases of extrapulmonary involvement, the delays in accurately diagnosing sarcoidosis can be as long as 20 years.[7] Cardiac sarcoidosis (CS) is the leading cause of death among patients with sarcoidosis.[8,9] Although clinically manifest cardiac involvement occurs in at least 5% of patients with sarcoidosis,[10] autopsy and imaging studies with cardiac magnetic resonance (CMR) suggest as high as 55% of patients have asymptomatic cardiac involvement.[11–13] The management patterns and outcomes of patients with manifest CS in low-resource areas are unknown.

Methods

To determine the management and clinical outcomes of patients diagnosed with CS in South Africa, we performed a retrospective study of all patients diagnosed with CS at

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KEY FINDINGS

- Diagnostic rates of cardiac sarcoidosis are increasing.
- Multiorgan sarcoidosis is common in Black South Africans.
- Frequent presentations of cardiac sarcoidosis are a combination of ventricular arrhythmias, heart block, and heart failure.

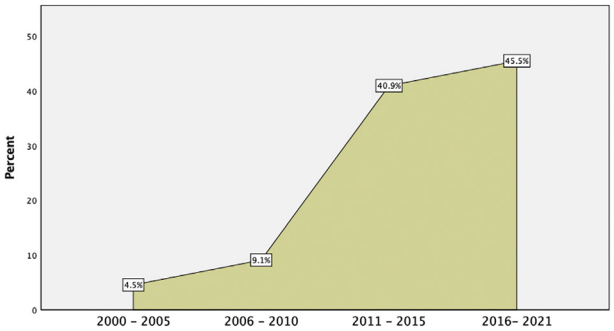

Figure 1 Area curve depicting the frequency of newly diagnosed cardiac sarcoidosis from January 2000 to December 2021 (N = 22).

Groote Schuur Hospital (GSH) cardiac clinic, Cape Town, South Africa. GSH is an 893-bed quaternary hospital affiliated with the University of Cape Town. Consecutive patients diagnosed with CS were identified from GSH cardiac implantable electronic device (CIED) records, CMR imaging reports, and heart failure clinic records from January 1, 2000, to December 31, 2021. The diagnosis of CS was based on the Japanese Ministry of Health and Welfare's set of criteria for the earlier cases and the Heart Rhythm Society (HRS) expert consensus statement on the diagnosis and management of arrhythmias associated with CS for the later cases.[1,14] The investigative management of potential CS was performed at the discretion of the treating cardiologist or electrophysiologist. However, a multidisciplinary team including cardiologists, imaging specialists, pulmonologists, and an electrophysiologist planned and executed treatment considerations. The investigations included an echocardiogram, serum angiotensin-converting enzyme (ACE) level, serum ferritin level, renal function test, complete blood count, and differential count. CMR imaging was performed before CIED implantation in stable patients, and 6 weeks after CIED implantation in unstable patients. CMR images were evaluated and reported by an experienced cardiac radiologist and a cardiac imaging specialist. Our unit did not have access to positron emission tomography during the study period. Patients implanted with a CIED as part of CS management underwent follow-up by an electrophysiologist at the GSH device clinic every 6 months. This study was undertaken in accordance with the ethical principles of the Declaration of Helsinki[15] and was approved by the University of Cape Town Human Research Ethics Committee (HREC No. 505/507/2019). The University of Cape Town Human Research Ethics Committee waived informed consent due to the retrospective nature of the study.

Statistical analysis

Normally distributed continuous variables are given as mean ± SD and as median [interquartile range] when skewed. Discrete data are given as number (percentage).

Results

During the study period, 22 patients receive a clinical diagnosis of CS. The number of new CS cases increased over time. Between the years 2000 and 2005, 1 case (4.5%) of CS was diagnosed; however, between the years 2016 and 2021, 10 cases (45.5%) were newly diagnosed with CS (Figure 1). Patient characteristics are given in Table 1. Mean patient age at the time of CS diagnosis was 45.2 ± 12.3 years; 50% were female, and 13.6% (3/22) had a history of a diagnosis and treatment for pulmonary TB. There was no evidence of microbiological or tissue biopsy results to prove active TB.

Seven of the 22 patients (31.8%) had a diagnosis of extracardiac sarcoidosis before the diagnosis of CS. However, 68.2% (15/22) were newly diagnosed with sarcoidosis at the time of CS diagnosis. Nine of the 15 patients (60%) with newly diagnosed sarcoidosis had pulmonary involvement, and 1 had hepatic involvement. CS presentation overlapped with a heart failure syndrome in 4 patients (18.2%), ventricular arrhythmias in 10 (45.5%), and heart block in 13 (59.1%) (Table 2). Biopsies were performed in 15 of the 22 patients (68.2%). Noncaseating granulomas were demonstrated in 10 patients with extracardiac biopsies (8/8 of the thoracic lymph node biopsies guided by endobronchial ultrasound [EBUS], 1/1 liver biopsy, and 1/1 eye biopsy demonstrated noncaseating granulomas), and 5 patients

Table 1 Patient characteristics (N = 22)

Age (y)	45.4 ± 12.3
Female	11 (50)
Black	22 (100)
Hypertension	7 (31.8)
Diabetes mellitus	4 (18.2)
Dyslipidemia	2 (9.1)
Previous diagnosis of pulmonary tuberculosis	3 (13.6)
HIV infection	1 (4.5)
Known diagnosis of extracardiac sarcoidosis	7 (31.8)
Pulmonary sarcoidosis	7 (31.8)
Thoracic lymph node sarcoidosis	7 (31.8)
Eye sarcoidosis	5 (22.7)
Liver sarcoidosis	1 (4.5)
Cutaneous sarcoidosis	1 (4.5)
Newly diagnosed sarcoidosis	15 (68.2)
Pulmonary sarcoidosis	9 (40.9)
Thoracic lymph nodes	9 (40.9)
Liver sarcoidosis	1 (4.5)

Values are given as mean ± SD or n (%).
HIV = human immunodeficiency virus.

Table 2 Clinical presenting syndrome (N = 22)

Heart failure	4 (18.2)
Ventricular arrhythmia	10 (45.5)
Ventricular tachycardia	9 (40.9)
Premature ventricular complexes	1 (4.5)
Heart block	13 (59.1)
Myopericarditis	1 (4.5)
Serum ACE, %	54.6 (39)
Elevated serum ACE	8 (36.4)
Serum calcium, mean ± SD (mmol/l)	2.4 (0.1)
PR interval (ms)	186 ± 54.0
QRS width (ms)	125 ± 43.0
LBBB	3 (13.6)
RBBB	8 (36.4)
First-degree AV delay	5 (22.7)
2:1 AV block	1 (4.5)
High-grade AV block	1 (4.5)
Complete heart block	6 (27.3)
CMRI LVED volume (ml)	166.4 ± 57.4
CMRI RVED volume (ml)	161 ± 49.9
CMRI LVEF, %	46.4 ± 17.0
CMRI RVEF, %	42.9 ± 17.1
T2 positive	7 (31.8)
LGE positive	22 (100)
Patchy LGE	16 (72.7)

Values are given as n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; AV = atrioventricular; CMRI = cardiac magnetic resonance imaging; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LVED = left ventricular end-diastolic; RBBB = right bundle branch block; RVED = right ventricular end-diastolic; RVEF = right ventricular ejection fraction.

who had cardiac biopsies had negative results (Figure 2). All 5 patients with negative endomyocardial biopsies presented with complete heart block and CMR imaging changes suggestive of CS. Notably, TB was excluded from all biopsies by microscopy, culture, and absence of caseating granulomas.

All 22 patients underwent CMR imaging as part of their diagnostic workup, and all had evidence of cardiac late gadolinium enhancement (LGE). Figure 3 illustrates the cardiac segments demonstrating LGE and the frequency of LGE per segment. Generally, all the cardiac segments had CMR evidence of CS involvement, but the most frequently involved segments were the basal

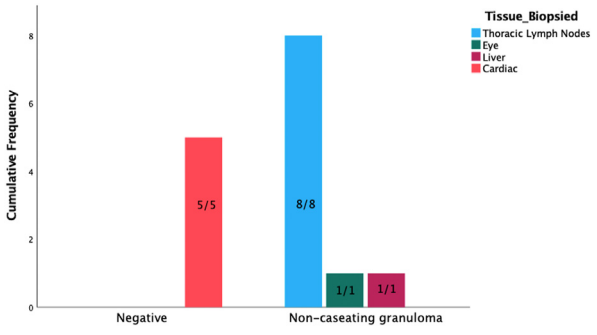

Figure 2 Clustered bar chart showing tissues or organs biopsied and the diagnostic yield (N = 15).

inferior septal segment, basal anterior septal segment, and basal anterior lateral segment; each of these segments was involved in 14 of the patients (63.6%) (Figure 4). Furthermore, papillary muscles were involved in 5 patients (22.7%), resulting in moderate-to-severe mitral valve regurgitation. The right ventricular free wall was involved in 11 patients (50%), a feature that could mimic arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). The basal inferior, midinferior, inferior apical, and apical cap showed no CS on CMR images. No repeat CMR imaging to monitor response to therapy was performed due to resource constraints.

At the time of CS presentation, 13 of 22 patients showed radiologic pulmonary sarcoidosis stage 2 (presence of lymphadenopathy and pulmonary infiltrates) (Figure 5). Upon the diagnosis of CS and exclusion of TB, 63.6% of the patients (n = 14) received treatment with corticosteroids, 31.8% (n = 7) with azathioprine, 40.9 (n = 9) with amiodarone, and 72.7% (n = 16) with a CIED (Table 3). The use of immunosuppressive therapy, including corticosteroids, was administered by a multidisciplinary team and guided by the presence of thoracic lymph nodes and/or edema on T2-weighted imaging. After a mean follow-up period of 64.5 ± 50.5 months, no deaths had occurred. Follow-up outcomes are given in Table 3.

Discussion

The major findings of this study are as follows. (1) The annual diagnostic rates of CS in South Africa are increasing. (2) Most South Africans with CS have evidence of extracardiac involvement, either preceding or at the time of CS diagnosis. (3) In our cohort, endomyocardial biopsy had limited diagnostic utility. (4) Although our patients had extensive sarcoidosis with a high frequency of extracardiac involvement preceding and at the time CS diagnosis, there were no deaths or cardiac transplantations.

The annual diagnostic rates of CS are increasing. This is partly due to increased physician awareness and the advent of, and access to, diagnostic modalities with better diagnostic sensitivity, such as CMR imaging.[12] For example, in a prospective evaluation of 81 consecutive patients with proven extracardiac sarcoidosis, delayed enhancement CMR imaging was 2-fold more sensitive in detecting CS than the consensus diagnostic criteria.[12] In addition, endomyocardial biopsy, a diagnostic guideline prerequisite for definitive diagnosis, has a low diagnostic yield.[1,14] Cardiac involvement in sarcoidosis often is patchy, midmyocardial or epicardial, perhaps explaining a negative biopsy result in patients with a high probability of CS on delayed enhancement CMR imaging or positron emission tomography.[16] In the current study, 5 of 5 of the performed endomyocardial biopsies were negative for CS. However, extracardiac tissue biopsies often were rewarding in making the diagnosis. For example, 8 of 8 EBUS-guided biopsies were positive for noncaseating granulomas. The extracardiac tissue biopsies usually are directed to visually abnormal tissue, rather than blind

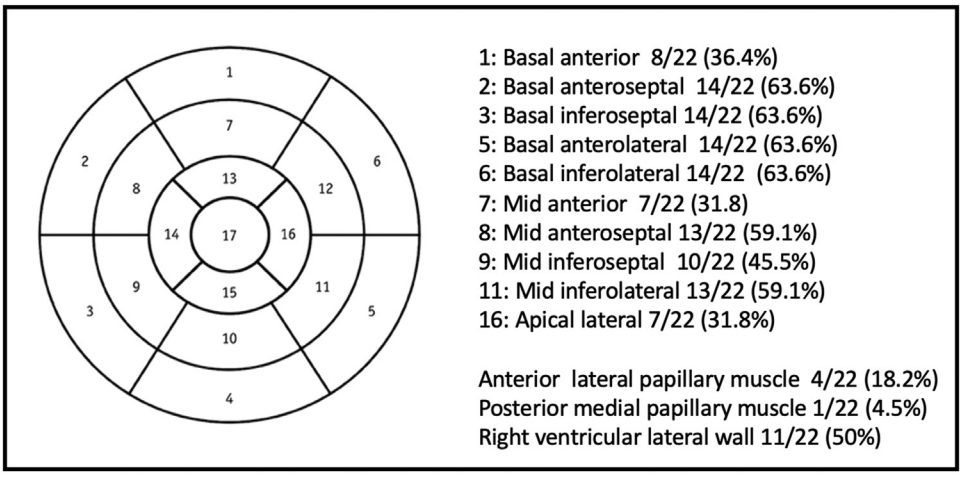

Figure 3 Cardiac segments demonstrating late gadolinium enhancement.

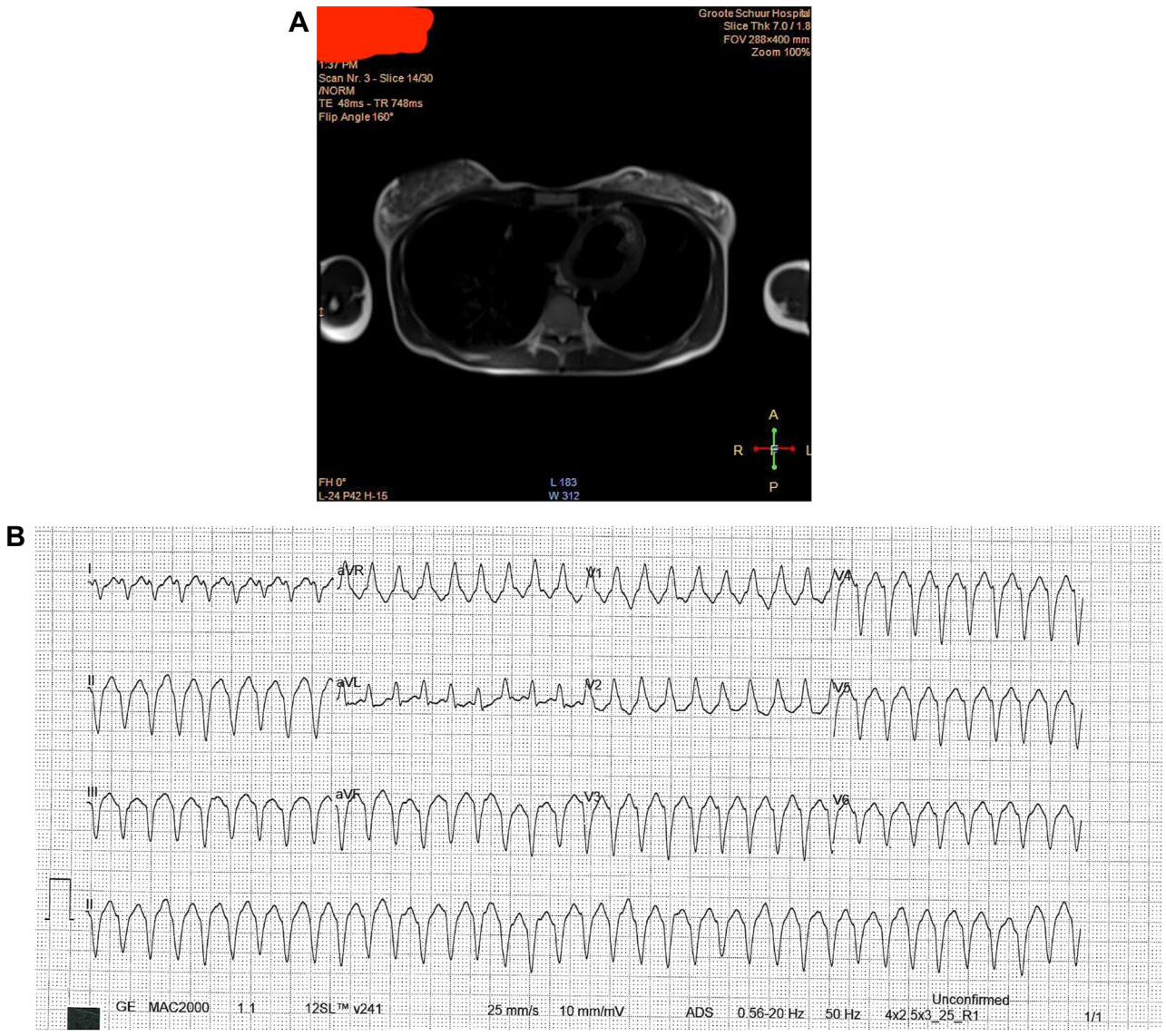

Figure 4 Cardiac magnetic resonance (CMR) image and electrocardiogram of a 26-year-old woman with no medical history, who presented with rapid regular palpitations and no syncope. **A:** Transmural late gadolinium enhancement (LGE) of the mid to apical left ventricular inferior walls that also involved the posteromedial papillary muscle (not shown). **B:** Monomorphic regular wide complex tachycardia, atypical left bundle branch morphology with superior axis suggestive of ventricular tachycardia from the left ventricular apex, consistent with the CMR findings. The patient had a very high serum angiotensin-converting enzyme level of 127 (normal 8–52) and hilar lymph nodes on high-resolution computed tomographic scan of the chest, which revealed noncaseating granulomas on endobronchial ultrasound–guided biopsy.

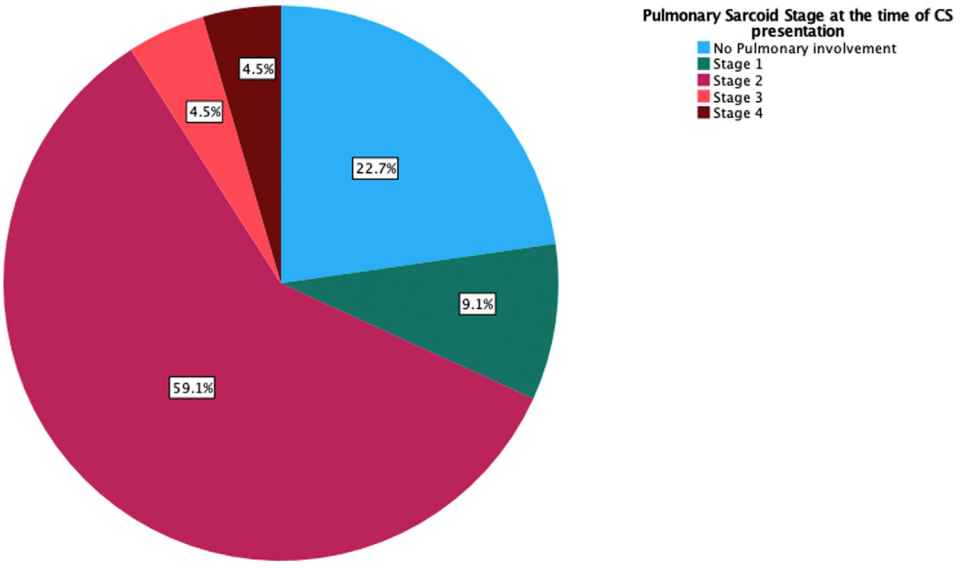

Figure 5 Pie chart demonstrating the radiographic pulmonary sarcoidosis stage at the time cardiac sarcoidosis (CS) diagnosis (N = 22).

endomyocardial biopsies, which frequently are fluoroscopically directed to the endomyocardial septum.[17] Novel techniques to improve the diagnostic yield of an endomyocardial biopsy have been described, such as biopsies of areas of low voltages and abnormal electrograms as indicated by 3-dimensional mapping.[18,19] The potential downside with 3-dimensional mapping–guided endomyocardial biopsy is the added complexity and cost, particularly in low-income countries such as South Africa.

Table 3 Treatment strategies instituted after diagnosis of cardiac sarcoidosis (N = 22)

ACE inhibitor/ARB	18 (81.8)
Beta-blocker	16 (72.7)
Spironolactone	9 (40.9)
Amiodarone	9 (40.9)
Corticosteroids	14 (63.6)
Azathioprine	7 (31.8)
Methotrexate	1 (4.5)
Single-chamber ventricular pacemaker	1 (4.5)
Dual-chamber pacemaker	6 (27.3)
CRT-D	1 (4.5)
Single-chamber ICD	10 (45.5)
Ventricular pacing % in single-chamber ICD	1 [0–11]
Follow-up outcomes and complications	
Appropriate ICD shocks	2 (9.1)
Inappropriate ICD shocks	1 (4.5)
Heart failure decompensation	3 (13.6)
CIED upgrade to ICD	1(4.5)
Follow-up ventricular tachycardia	5 (22.7)
Follow-up atrial fibrillation	4 (18.2)
CIED infection and extraction	1(4.5)

Values are given as n (%) or median [interquartile range].

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CIED = cardiac implantable electronic device; CRT-D = cardiac resynchronization therapy–defibrillator; ICD = implantable cardioverter-defibrillator.

The available diagnostic tests must be interpreted with caution and with awareness of the background epidemics of communicable and noncommunicable disease patterns in low- and middle-income countries such as South Africa, where there are high prevalences of TB and rheumatic heart disease. In a recent South African study, 17% of patients with pulmonary sarcoidosis initially were diagnosed as, and treated for, TB before the correct diagnosis of pulmonary sarcoidosis was made.[6] South Africa has an estimated TB incidence $\geq$500 per 100,000 in 2021, one of the highest in the world.[20] In communities with a high prevalence of TB, it is essential to exclude TB before patients are treated with immunosuppressive therapies, which in the case of TB could lead to worsening of symptoms and death. Important diagnostic clues for CS over TB are the presence of heart block and ventricular arrhythmias. In a large, multicenter, international trial of TB pericarditis in which 1503 electrocardiograms from 1160 patients with TB pericarditis were reviewed, the investigators found no cases of second- or third-degree atrioventricular (AV) block during the course of the study (some patients had multiple electrocardiograms recorded during the period of the study).[21] Although tuberculous multiorgan involvement occurs in up to 80% of patients infected with human immunodeficiency virus,[22,23] myocardial (not pericardial) involvement in TB is extremely rare.[24] In a necropsy study involving 13,000 patients over 27 years, tuberculous myocardial involvement was demonstrated in only 19 patients (0.14%).[24] These data suggest that myocardial and conduction manifestations such as AV block and ventricular arrhythmias in patients with TB are uncommon.

In the current study, CMR imaging demonstrated right ventricular free wall involvement in 50% of patients, a feature that mimics arrhythmogenic right ventricular cardiomyopathy (ARVC) in the absence of biopsy results.

Multiple reports have demonstrated the clinical overlap and challenge of discriminating between CS and ARVC.[25,26] However, important clinical clues can help to discriminate between CS and ARVC. Multiple well-designed studies have shown that AV block, as evidenced by PR prolongation or high-grade AV block, and left ventricular systolic dysfunction are important clinical markers for differentiating CS from ARVC.[27,28] Furthermore, in a small study of 13 CS and 23 ARVC patients presenting with ventricular tachycardias, an algorithm including PR interval $\geq$220 ms, presence of an R′ wave, and surface area of the maximum R′ wave in leads V_1 through V_3 $\geq$1.65 mm^2 had 85% sensitivity and 96% specificity for diagnosing CS.[29]

Sarcoidosis exhibits significant variations in regional and racial clinical manifestations that have implications for diagnostic workup and treatment. In a Finish retrospective study of 110 patients with histologically confirmed CS, 65% of the patients had isolated CS.[30] In the same study, there was 19% rate of mortality or cardiac transplantation after median follow-up of 6.6 years.[30] In contrast, 32% of our patient population had extracardiac sarcoidosis involvement predating the diagnosis of CS, and 41% had evidence of extracardiac sarcoidosis involvement at the time of CS diagnosis. Our findings are consistent with the ACCESS (A Case Control Etiologic Study of Sarcoidosis) registry data, which demonstrated that Black patients tend to have more extensive and multiorgan sarcoidosis involvement,[5] thus suggesting a proactive investigation for multiorgan involvement when the diagnosis of sarcoidosis is made.

Limitations

This study is limited by its retrospective nature and small sample size. During the study period, our institution did not have access to fluorodeoxyglucose (FDG)-positron emission tomography (PET) monitor treatment response to immunomodulatory therapies. Further, due to cost constraints, repeat CMRs were not done.

Conclusion

CS diagnostic rates have increased over time. Clinical presentation often is that of ventricular arrhythmias, heart block, and, less frequently, heart failure. Most patients with a sentinel presentation sarcoidosis as CS have evidence of pulmonary involvement. Diagnostic endomyocardial biopsies have a low diagnostic yield, whereas EBUS-guided biopsy of thoracic lymph nodes is of important diagnostic utility. With contemporary treatment modalities, including the involvement of a multidisciplinary management team, appropriate use of immunomodulatory therapies when clinically indicated, and CIED implantation for heart block treatment and secondary prevention ICDs, the outcomes are good with modest morbidity and no mortality on short-term follow-up.

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Patient Consent: The University of Cape Town Human Research Ethics Committee waived informed consent due to the retrospective nature of the study.

Ethics Statement: This study was undertaken in accordance with the ethical principles of the Declaration of Helsinki and was approved by the University of Cape Town Human Research Ethics Committee (HREC No. 505/507/2019).

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