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Cardiac sarcoidosis: diagnosis and management

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Non-caseating granulomatous infiltration of the myocardium is the hallmark of cardiac sarcoidosis (CS). CS manifests clinically as conduction disturbance, ventricular arrhythmia, sudden cardiac death and/or heart failure with reduced ejection fraction. Other than confirmation through endomyocardial biopsy, a diagnosis of probable CS can be established by histological evidence of systemic sarcoidosis in addition to characteristic clinical or advanced imaging findings. Cardiac Magnetic Resonance imaging (CMR) and ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) are imaging modalities indispensable in the diagnosis and monitoring of CS. FDG-PET is the method of choice for identifying the active inflammatory phase of CS and in the monitoring and modifying of immunosuppressive treatment. CMR is better suited for assessing cardiac morphology and function. Both modalities are more effective in detecting CS when used in combination than either is alone. Management of CS is primarily based upon observational data of low quality due to a paucity of randomized controlled trials. Corticosteroid therapy and/or tiered-immunosuppression are the mainstays of treatment in reducing myocardial inflammation. Steroid-sparing agents aim to limit the unfavorable side-effects of a significant steroid burden. Antiarrhythmics and guideline-directed medical therapies are utilized for control of ventricular arrhythmia and left ventricular dysfunction respectively. CS necessitates multidisciplinary care in specialized centers to most effectively diagnose and manage the disease. Additional randomized trials are warranted to further our understanding of medical optimization in CS.

KEYWORDS

cardiac sarcoidosis, Cardiac Magnetic Resonance Imaging, late gadolinium enhancement, positron emission tomography, inflammatory heart disease

1 Introduction

Sarcoidosis is a multisystem granulomatous inflammatory disorder of unknown etiology. It is characterized typically by the presence of non-caseating granulomas that may develop in any part of the body, resulting in scarring and fibrosis or spontaneous resolution (1). Cardiac sarcoidosis (CS) is an infiltrative cardiomyopathy that presents concurrently in 20%–27% of patients with extracardiac disease or rarely as an isolated occurrence (2, 3). Isolated cardiac disease portends a poorer prognosis than CS with extracardiac involvement (4); patients with isolated CS suffer from worse LV systolic function at presentation and a greater burden of ventricular tachycardia (3). CS can manifest itself as aberrant atrioventricular conduction disturbances, ventricular arrhythmia or even sudden cardiac death (2). There are various criteria employed to confirm a clinical diagnosis of CS, however, none are validated or have garnered

TABLE 1 Guidelines for diagnosis of cardiac sarcoidosis based on the 2006 revised guidelines of the Japanese society of sarcoidosis and other granulomatous disorders.

Japanese society of sarcoidosis and other granulomatous disorders (2006)	
Histological diagnosis group	Clinical diagnosis group
Endomyocardial biopsy specimens demonstrate noncaseating epithelioid cell granulomas with histological or clinical diagnosis of extracardiac sarcoidosis	Extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies either of the following conditions: - ≥ 2 of the MAJOR criteria - 1 in 4 of the MAJOR criteria and ≥ 5 minor criteria
	Major criteria: - Advanced AV Block - Basal thinning of the interventricular septum - Positive ^{67}Ga uptake in the heart - Depressed ejection fraction of the ventricle ($<50\%$)
	Minor criteria: - Abnormal ECG: ventricular arrhythmias, complete RBBB, abnormal axis, abnormal Q wave - Abnormal echocardiogram: regional wall motion or morphological abnormality - Nuclear medicine: perfusion defect by ^{201}Tl or $^{99\text{m}}\text{Tc}$ myocardial scintigraphy - Gadolinium-enhanced CMR: delayed enhancement of myocardium - Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade

universal adoption (5–8) (Tables 1, 2). There currently exists a degree of uncertainty surrounding CS, influenced by factors such as the undetermined etiology of the disease, difficulties in establishing the presence of myocardial granuloma, and a lack of randomized controlled trials and personalized therapeutics. This article will review and elucidate the clinical diagnosis and management of CS.

2 Diagnosis

The diagnosis of CS necessitates a multi-pronged approach involving histological evidence, exclusion of other diagnoses, and the presence of particular clinical features. The histological diagnosis of definite CS can be made from endomyocardial biopsy demonstrating non-caseating granuloma without an alternative cause, as per the HRS consensus statement. The sensitivity of endomyocardial biopsy is poor however due to patchy myocardial involvement (9, 10) ranging from 25%–36%; this can be improved to 50% if intracardiac voltage mapping, ^{18}F -flurodeoxyglycose positron emission tomography (FDG-PET),

or Cardiac Magnetic Resonance imaging (CMR) guided biopsy is performed (9, 11). Given these limitations, diagnostic criteria for probable CS were formulated which include extracardiac histological identification of sarcoid and the presence of one of the following clinical characteristics not explained by other etiologies (Table 1). These clinical characteristics include ejection fraction less than 40%, sustained ventricular tachycardia, Mobitz type II or complete heart block, FDG-PET demonstrating patchy uptake, CMR showing late gadolinium enhancement or gallium scintigraphy showing positive gallium uptake (6).

Typical CS symptomatology that should necessitate further workup includes chest pain, palpitations, and (pre)syncope episodes. While diagnostic and prognostic biomarkers have not yet been established for CS, serum B-type natriuretic peptide levels have proven to be a useful diagnostic marker for cardiac involvement in systemic sarcoidosis; cardiac troponin I was also shown to be a predictor of fatal arrhythmia in CS patients in a single study (12, 13). Electrocardiography and cardiac event monitoring can aid in the detection of atrioventricular conduction disturbances and ventricular tachycardia in patients who present with palpitations. Traditional echocardiographic parameters do not show findings sensitive or specific for CS in early disease as focal myocardial involvement is usually too small to detect (9, 14). Two-dimensional-speckle tracking echocardiography is a more sensitive technique and can predict subclinical myocardial involvement in CS patients by way of left and right ventricular global longitudinal strain measurement (15). Typical echocardiographic findings of more advanced disease include LV dilation with systolic dysfunction, regional wall motion abnormalities in a noncoronary distribution, septal wall thinning and ventricular aneurysm formation (16).

Cardiac Magnetic Resonance imaging (CMR) is a multimodal, noninvasive assessment tool used for the evaluation of CS by demonstrating edema and scarring within the myocardium. While CMR can visualize structural abnormalities suggestive of CS such as ventricular septal wall thinning, ventricular aneurysm and local dyskinesia (17), the essential principle underlying CS

TABLE 2 HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis.

Heart rhythm society expert consensus statement (2014)
It is probable that CS is present if all 3 of the following conditions are met:
(a) There is a histological diagnosis of extracardiac sarcoidosis
(b) One or more of the following is present:
<ul style="list-style-type: none"> • Corticosteroid or immunosuppressant-responsive cardiomyopathy or heart block • Unexplained reduced LV ejection fraction (40%) • Unexplained sustained (spontaneous or induced) ventricular tachycardia, Mobitz type II second-degree heart block or third-degree heart block • Patchy uptake (of FDG) 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
(c) Other causes for the cardiac manifestation(s) have been reasonably excluded

detection by CMR is that of delayed postcontrast imaging (18). Delayed gadolinium contrast washout represents edema and inflammation in the acute setting and fibrous replacement in the chronic phase of CS relative to normal myocardial tissue (19, 20). CMR determines the presence of late gadolinium enhancement (LGE) in patterns characteristic of CS (Figure 1), most frequently in patchy, multifocal distributions seldom with subendocardial involvement. Subendocardial LGE is generally a sequela of ischemic heart disease infarct but can still be seen in CS (21). LGE findings most commonly involve the subepicardial right ventricular and basal left ventricular septal portions of the heart (17, 22). It is prudent to note that there are no diagnostic LGE patterns on CMR for CS, however. A recent meta-analysis has explicated the test characteristics of CMR. Of the studies included, 33 studies assessing the diagnostic accuracy of CMR and FDG-PET in CS have shown the sensitivity of CMR to be 95% with a specificity of 85% (20). LGE is an important prognostic marker and independent risk factor for death in CS. A prospective study following 155 patients with systemic sarcoidosis who underwent CMR for detection of possible cardiac disease reports a hazard ratio of 31.6 for death and aborted sudden cardiac death if LGE is present on imaging, which is greater than 30 times the ratios reported for LVEF or end-diastolic volume (23). The extent of LGE is also a sensitive

marker of prognosis. Patients with significant LGE burden (greater than 20% of LV mass) were shown to have an increased risk of cardiac mortality, arrhythmia, hospitalization from heart failure, and absence of LV functional improvement following steroid therapy (24). The addition of T2 mapping to CMR allows for the identification of the acute inflammatory response in myocardial tissue and potentially allows for the early detection of subclinical CS (25, 26). Earlier identification of disease may predict impending clinical deterioration and help tailor responses to immunosuppressive therapies (26, 27). Coupled with LGE findings in more advanced disease, T2 mapping permits comprehensive CMR evaluation in the CS workup.

¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) is an advanced imaging modality utilized in the diagnosis, prognostication and treatment monitoring of CS. The primary method of detecting CS by FDG-PET relies on identifying areas of increased ¹⁸F-FDG uptake in myocardial tissue which correspond to pathological cardiac inflammation (Figure 2). Inflamed sarcoid granulomatous tissue will readily take up glucose and its analogs (28), a process which can be mapped by multidimensional imaging and localize abnormal lesions. Pre-imaging preparation requires a high-fat, low-carbohydrate diet for 24 h prior to scanning to minimize dietary glucose-related competitive inhibition of ¹⁸F-FDG uptake (29). An area of

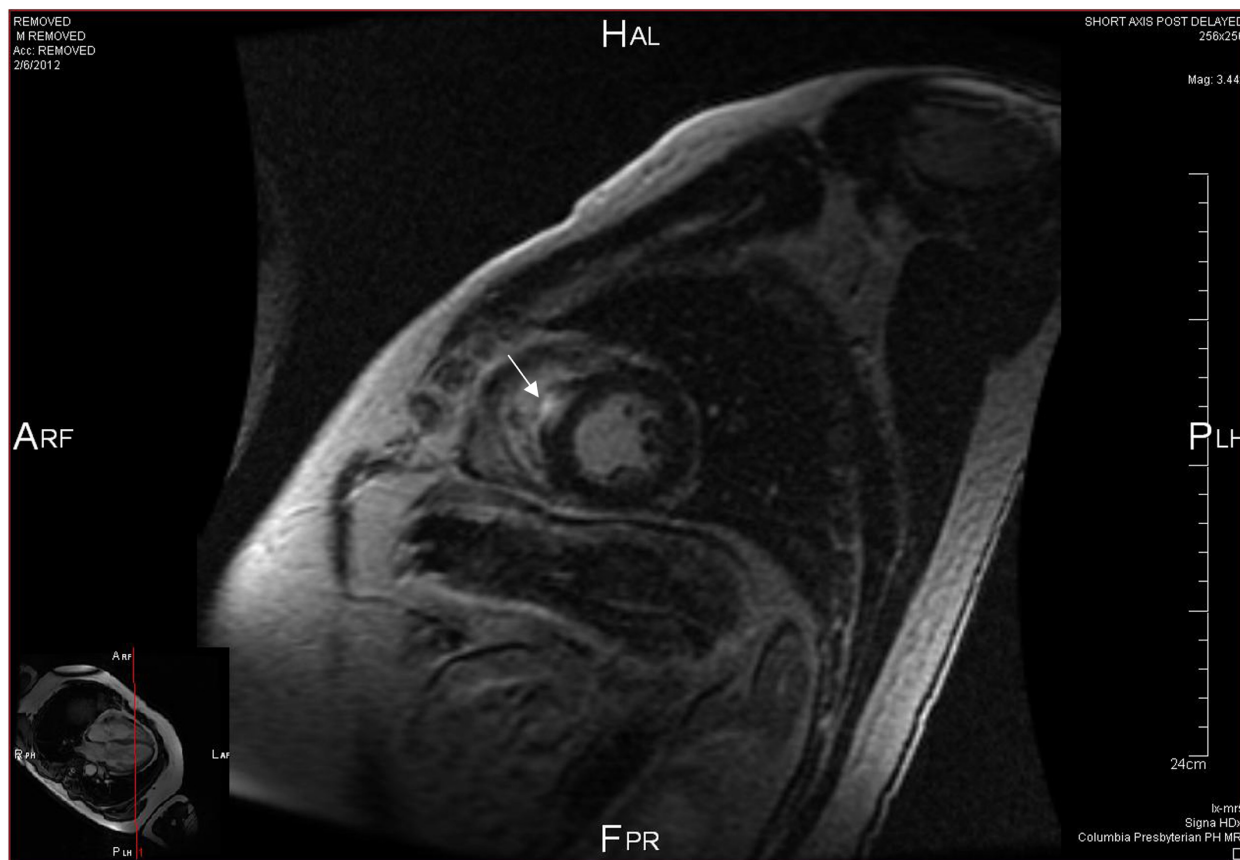


FIGURE 1
Cardiac MRI sagittal view at mid ventricle level showing focal late gadolinium enhancement (white arrow) in the interventricular septum.

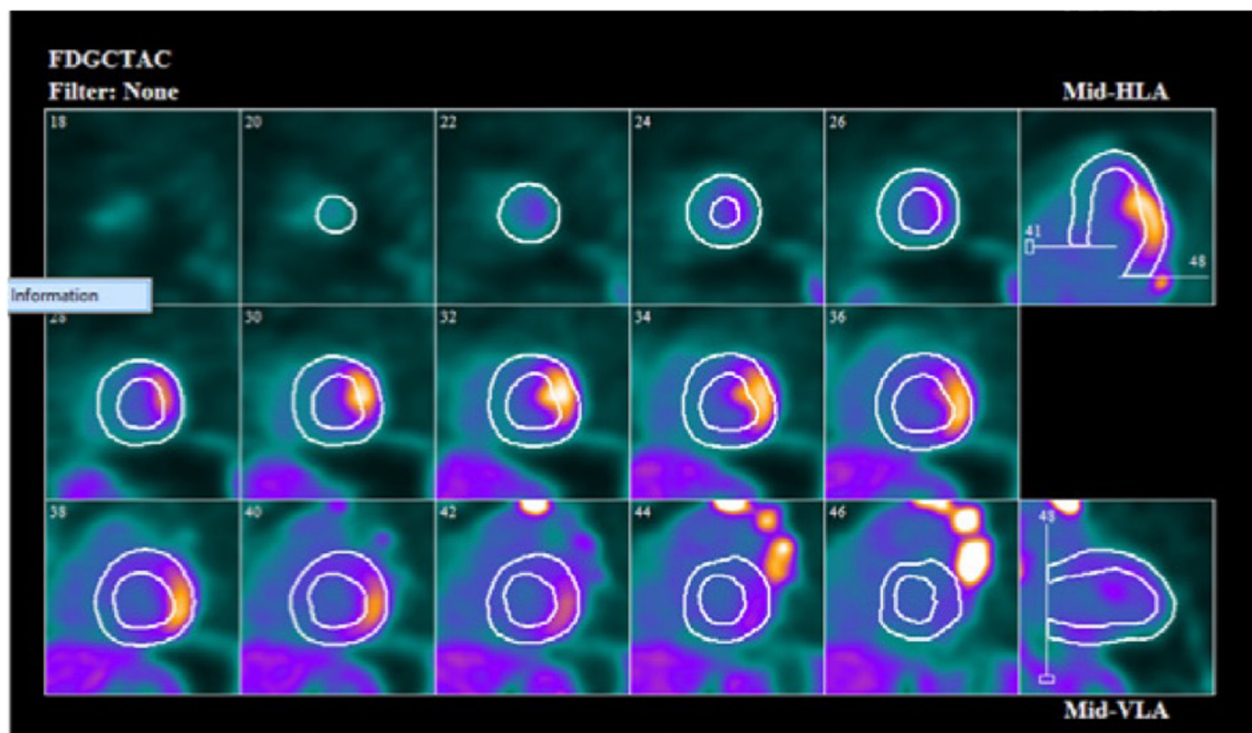


FIGURE 2
Cardiac F-18 FDG PET scan showing focal uptake of FDG in mid lateral wall on short axis, vertical long axis and horizontal long axis.

abnormal ^{18}F -FDG uptake corresponding to a known perfusion defect is a distinguishing feature seen in CS, known as a mismatch pattern (5). Myocardial scarring or focal reversible vasoconstriction in arterioles adjacent to sarcoid granulomas are posited to lead to perfusion defects (30). The sensitivity and specificity for FDG-PET were shown to be 84% and 83% respectively as per a recent meta-analysis evaluating the diagnostic performance of the test across 17 studies and close to 900 patients with suspected CS (31). A final consideration prior to performing FDG-PET would be to exclude significant coronary artery disease (CAD). Myocardial ischemia from underlying CAD can result in both abnormal perfusion and ^{18}F -FDG uptake. Stress myocardial perfusion imaging would be of limited use given that resting perfusion defects may be attributable to either CS or CAD. The 2017 SNMMI/ASNC Expert Consensus Statement recommends CT coronary angiography or invasive angiography prior to FDG-PET to assess for anatomic stenoses once a patient's age and risk factors have been considered (32).

The preponderance of current available evidence confirms the prognostic value of FDG-PET. A contemporary meta-analysis performed by Bhatia et al. evaluated 40 studies with 495 participants to ascertain the prognostic significance of FDG-PET imaging in patients with suspected or diagnosed CS (33). Patients with abnormal ^{18}F -FDG uptake had higher odds of major adverse cardiac events, including sustained ventricular tachycardia and sudden cardiac death (OR 3.12, CI 1.9–5.01 $p < 0.00001$) as compared to known or suspected CS patients

with normal FDG-PET. Focal right ventricular uptake was shown to be an independent predictor of major adverse cardiac events (OR 5.24, CI 1.1–25.1, $p = 0.04$) (33, 34). The meta-analysis performed by Ahmed et al. showed odds ratios of 2.08 (CI 1.48–2.92) and 2.96 (CI 1.12–7.78) for abnormal LV and RV FDG-PET and major adverse cardiac events, respectively (35).

Quantification of ^{18}F -FDG uptake by myocytes is possible with calculation of the standardized uptake value (SUV) (28), allowing for objective assessment of treatment response over time (36, 37). Flores et al. showed that SUV can also be used to predict future clinical outcomes. Poisson regression analysis revealed that SUV at the time of CS diagnosis has significant associations with total cardiac events. Although OR for total cardiac events with maximum SUV was 1.068 (95% CI 1.024–1.114, $P = 0.002$), patients with higher SUV, particularly in basal segments, are at an increased risk of cardiac events. These events include ventricular tachycardia, AICD and PPM placement, worsening ejection fraction and death (38). The study concurs with an earlier prospective study following 23 patients over 2 years who were treated with corticosteroids (91%), angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (78%), and beta-blockers (83%) (39). Longitudinal regression demonstrated a significant inverse linear relationship between maximum SUV and LVEF, with EF increasing 7.9% per SUV decrease by 10 g/ml (-1) ($P = .008$). This data emphasizes the developing prognostic importance of quantitative FDG-PET data in relation to LVEF. Of interest, the study was also able to identify treatment non-responders who experienced decreases in LVEF with standard

therapies. This has real-world implications as it permits tailoring and escalation of therapy at an earlier stage if CS patients are not responding to the initial treatment regimen.

Benefits of CMR relative to FDG-PET include no patient exposure to ionizing radiation or need for patients to adhere to a specialized ketogenic preparatory diet. CMR is more readily available than FDG-PET although absolute numbers of physicians providing CMR services remain limited (1.0% of radiologists and 0.2% of cardiologists) (40). CMR can assess cardiac structure, function and tissue characterization, rendering it ideal to assess for alternative infiltrative disorders or cardiomyopathies that may account for a patient's clinical presentation. CMR also has a substantially lower rate of nondiagnostic studies compared to FDG-PET, with the latter approaching a 15% diagnostic failure rate secondary to insufficient suppression of physiologic glucose uptake (41). FDG-PET, conversely, benefits from a lack of interference from motion artifact or the inability of a patient to breath-hold. FDG-PET is, moreover, the preferred imaging modality of choice in patients with implantable cardiac devices or those with severely reduced renal function (42). Although T2 mapping has made CMR more adept at identifying CS at earlier stages, FDG-PET remains more proficient in diagnosing active inflammation in early disease, thus affording the physician an opportunity to initiate prompt immunosuppression. FDG-PET is also preferred over CMR for monitoring treatment response over time as SUV allows for the quantification of disease

activity (Figure 3). Finally, FDG-PET allows for detection of systemic sarcoidosis with concomitant full-body FDG imaging, a finding present in 97% of CS patients (43).

3 Management

Management of CS requires therapies targeting multiple aspects of the disease process. Active inflammation within the myocardium must be dampened with immunosuppressive agents and can be achieved by the use of corticosteroids, steroid-sparing agents, or a combination of both. Ventricular arrhythmia is treated with antiarrhythmics and ICD implantation can reduce the risk of sudden cardiac death in select patient populations. Left ventricular dysfunction can be managed with medical therapy to limit cardiac remodeling. These various avenues of treatment may be overlapping and occurring simultaneously. Every facet of CS management must be tailored to the individual, with particular focus on the clinical team's concern for disease activity, risk assessment and LV ejection fraction.

First-line treatment for CS involves nonspecific immunosuppression utilizing corticosteroids, which are initiated when evidence of active inflammation on EMB/PET/MRI and clear clinical signs and symptoms are manifested (6, 7, 44). A systematic review of more than 1,100 patients across 34 publications demonstrated that corticosteroids improve atrioventricular nodal conduction in 43% of patients and may promote left ventricular function recovery; the data on ventricular arrhythmias and

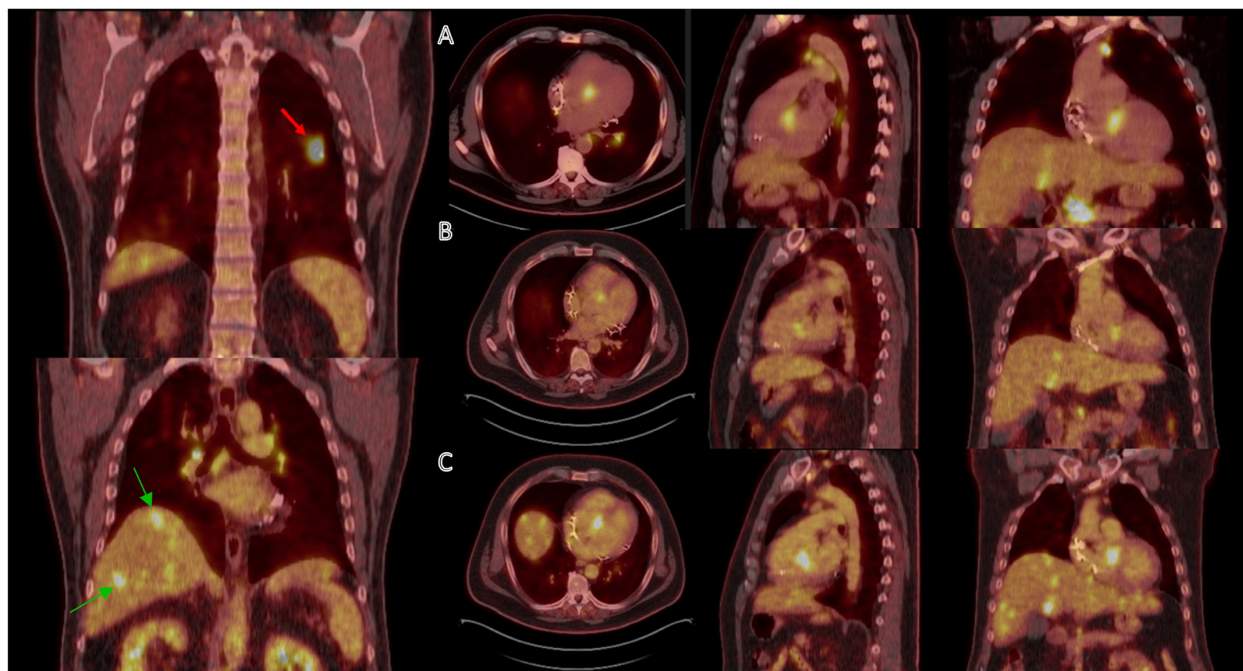


FIGURE 3

A 51-year-old man was found to have systemic sarcoidosis involving the lung (red arrow), liver (green arrows), and heart. (A) Before treatment, cardiac PET scan showed focal FDG uptake near the basal septum. (B) After 3 months of prednisone therapy, partial treatment response was achieved as evidenced by decreased FDG uptake in the myocardium. There was also a significant interval decrease in FDG-avid extra-cardiac lesions. (C) However, follow-up cardiac PET scan after a gradual 6-month prednisone taper demonstrated increasing FDG uptake in the myocardium and liver, suggesting relapse of sarcoidosis. Methotrexate was initiated.

mortality was too limited to draw any meaningful conclusions (45). There is some observational data to refute whether steroids have any benefit in patients with severe LV dysfunction (46, 47). The benefit of immunosuppression in subclinical disease in the absence of LV dysfunction has not yet been established. In these patients management decisions must be based on the presence of any extracardiac disease and the degree of active inflammation on advanced imaging. There are presently no standardized protocols or guidelines for the initiation and monitoring of patients with CS on corticosteroids. Lehtonen et al. in a recent clinical review has suggested tapering prednisone down by 5–10 mg every month until the patient is maintained on a dosage of 10 mg per day (5). Subsequently, corticosteroids would be discontinued at 12–16 months if there are no signs of disease activity. Serial annual follow-ups for 3–5 years with symptom evaluation, cardiac biomarkers, electrocardiogram and echocardiogram for left ventricular ejection fraction are recommended. The authors advise FDG-PET only if suspected relapse or treatment failure occurs, or if there are inconsistencies between clinical observations (5). This is in contrast to many institutes that perform routine FDG-PET to monitor disease activity and treatment response (48, 49). Pneumocystis Jirovecii prophylaxis with trimethoprim/sulfamethoxazole is encouraged once on corticosteroid doses greater than 20 mg daily (49). The Japanese Circulation Society recommends an initial prednisolone dose of 30 mg daily or 60 mg on alternate days for a 4-week period, followed by tapering of 5 mg monthly to reach a maintenance dose of 5–10 mg daily or 10–20 mg on alternate days by 6 months (7). Birnie et al. recommended starting with 30–40 mg of prednisone daily and tapering to 5–15 mg once an adequate treatment response was noted after 1 to 3 months. Treatment was continued for up to 12 months (50).

Corticosteroid sparing immunosuppressive therapies can be trialed to lessen the steroid burden or in the event of corticosteroid treatment failure, rapidly progressive heart failure, life-threatening arrhythmias or extensive inflammation on imaging. Rosenthal et al. demonstrated that low-dose prednisone (less than 10 mg) with either methotrexate or adalimumab is an effective maintenance therapy in patients after an initial response is confirmed (51). Such an approach would help to mitigate the unfavorable side-effects associated with chronic corticosteroid use. Methotrexate is the most widely used steroid-sparing agent in CS. Its common utilization as monotherapy or in combination with steroids in pulmonary sarcoidosis has been extrapolated to CS (52, 53). Vis et al. showed significant suppression of cardiac FDG uptake specifically in CS patients after 6 months of prednisone, methotrexate or combination therapy; there were no significant differences in clinical outcomes during follow-up over 24 months (54). This may be compared with other data suggesting improved outcomes with immunosuppressants utilized in combination with corticosteroids for the treatment of CS (55, 56). However, these selected studies are small and definitive conclusions cannot be drawn (44). Infliximab and adalimumab, both biologic anti-tumor necrosis (TNF) inhibitors, are third-line agents for CS and have shown promise in reducing cardiac inflammation when other treatment modalities have failed (48, 57). Anti-B-cell therapy with rituximab was shown to have a beneficial effect in a small case series involving 7 patients

with refractory CS, conclusions from such a sample size are naturally equivocal (58). All biologic agents require comprehensive screening and vaccination for tuberculosis prior to initiation, in addition to close monitoring for infection and other complications.

Treatment for left ventricular dysfunction in CS should be initiated with guideline-directed medical therapies (GDMT) as well as immunosuppression. GDMT has been recognized to limit deleterious cardiac remodeling in heart failure and includes beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and neprilysin inhibitor–angiotensin receptor combinations. Mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 inhibitors are also within the GDMT framework. Left ventricular systolic dysfunction on presentation has been reported as an independent predictor of adverse outcomes and mortality in CS patients (49, 59). It is judicious to note that data regarding GDMT use specifically in CS is lacking and has been extrapolated from established data on patients with heart failure with reduced ejection fraction (60, 61).

Ventricular tachycardia (VT) is a recognized clinical manifestation of CS. Re-entry circuits developing in fibrotic and inflamed myocardial tissue may generate sustained ventricular tachycardia, which can be seen in up to 17% of patients with active disease as evidenced by a Finnish registry (62). The HRS consensus statement advises antiarrhythmic medication, most commonly either sotalol or amiodarone, after immunosuppression initiation for unresponsive VT (6). Catheter ablation is reserved for patients refractory to medical therapy. In a meta-analysis of 401 patients with refractory VT across 15 studies, the recurrence rate of VT after first ablation was 55% and 37% after multiple procedures (63). Of reassurance, there is observational data to show that catheter ablation is able to control VT storm associated with CS (64).

The risk of sudden cardiac death in patients with manifest clinical disease is 10% over five years (65). Expert societies are largely in concordance over indications for implantable-cardioverter defibrillators (ICD) in patients with CS. Both the HRS/ACC/AHA consortium and the ESC list the following as indications for ICD insertion in patients with CS: LVEF <35% despite immunosuppression, cardiac arrest, history of syncope compatible with arrhythmogenic etiology, history of sustained VT or inducible sustained VT at programmed electrical stimulation, and LVEF > 35% with extensive myocardial scarring on advanced imaging (66, 67). Given that many patients will meet ICD insertion indications at the time of presentation with CS (54), prudent clinical risk stratification and honest conversation with patients are of the utmost importance to ensure these individuals receive access to the appropriate secondary prevention tools.

4 Conclusion

In summary, diagnosing CS in the absence of endomyocardial biopsy necessitates the usage of advanced imaging techniques. Both CMR and FDG-PET are integral to the diagnostic workup of CS, however, neither modality can assure a diagnosis of cardiac sarcoidosis in isolation. The two imaging modalities should be viewed as complimentary given that they identify different

pathological processes. FDG-PET is more adept at identifying the active inflammatory phase of CS and can help guide the initiation of treatment, whereas CMR best evaluates the chronic fibrotic phase of the disease via assessment of LGE. Indeed, hybrid CMR/FDG-PET was shown to be superior at detecting CS than both tests alone (68, 69). Management of CS consists of a stepwise approach utilizing corticosteroids, immunosuppressive medications and biologic agents. Antiarrhythmics should be used for VT unresponsive to immunosuppression. Specialized centers should be established to effectively manage CS patients; the diagnosis and care of these patients should be multidisciplinary in nature with experts in heart failure, cardiac imaging and electrophysiology involved. The results of the CHASM-CS randomized controlled trial are anticipated to expand current understanding concerning the effect of corticosteroid treatment on the clinical course of CS (70).

Author contributions

AA: Writing – review & editing, Writing – original draft. SS: Writing – review & editing, Visualization. ZA: Writing – review & editing. SB: Writing – review & editing, Supervision, Conceptualization.

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