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Cardiac Sarcoidosis: A Clinical Review

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Abstract

Cardiac sarcoidosis represents one of the most consequential manifestations of systemic sarcoidosis, associated with significant morbidity and mortality. This review examines the epidemiology, pathophysiology, clinical presentation, diagnostic approach, and management of cardiac sarcoidosis, illustrated by a clinical case. We challenge the traditional framing of sarcoidosis as primarily a respiratory disease and highlight the importance of recognising cardiac involvement, which may occur in isolation or precede pulmonary manifestations. Contemporary diagnostic advances, particularly cardiac magnetic resonance imaging and 18 F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT), have transformed our ability to detect and monitor cardiac disease. Management remains largely eminence-based, though emerging evidence supports aggressive immunosuppression with corticosteroids and steroid-sparing agents. We discuss the role of implantable cardiac defibrillators, risk stratification using advanced imaging, the importance of serial monitoring with soluble interleukin-2 receptor and FDG-PET/CT imaging, and the emerging use of tumour necrosis factor inhibitors for refractory disease.

Case Presentation

A 44-year-old man was brought to the emergency department following an out-of-hospital cardiac arrest. Paramedics reported ventricular tachycardia responsive to defibrillation. Initial investigations were largely unremarkable: chest radiograph was normal, electrocardiogram showed non-specific T-wave changes, and routine blood tests were within normal limits apart from mildly elevated C-reactive protein and raised troponin.

A further episode of ventricular tachycardia in the emergency department proved refractory to initial defibrillation, necessitating amiodarone infusion. Following stabilisation, computed tomography (CT) of the chest revealed bilateral hilar lymphadenopathy without parenchymal lung abnormalities. Transthoracic echocardiography demonstrated mild left ventricular systolic impairment with an ejection fraction of 45%, basal septal hypokinesis, and normal right ventricular function.

Coronary angiography showed no significant atherosclerotic disease. Cardiac magnetic resonance imaging (cMRI) demonstrated multifocal late gadolinium enhancement (LGE) in a non-ischaemic pattern, predominantly affecting the basal interventricular septum with extension to the right ventricular aspect – a distribution highly characteristic of cardiac sarcoidosis. There was associated myocardial oedema on T2-weighted imaging, suggesting active inflammation. Soluble interleukin-2 receptor was markedly elevated at 4,322 U/mL.

He was commenced on pulse methylprednisolone followed by oral prednisolone 40 mg daily. An implantable cardiac defibrillator was inserted. Endobronchial ultrasound-guided biopsy of an enlarged mediastinal lymph node revealed non-caseating granulomatous inflammation, supporting a diagnosis of cardiac sarcoid. 18 F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) demonstrated high avidity within the myocardium corresponding to the areas of LGE on MRI, along with avid lymph nodes in the mediastinum alongside multiple skeletal, splenic, and hepatic lesions. Notably, there was no significant atrial FDG uptake.

Detailed occupational and environmental history revealed that he had worked in the building industry for over twenty years, with frequent exposure to silica insulation dusts, often without appropriate respiratory protection. He was a non-smoker with no family history of autoimmune disease or cardiomyopathy.

He was discharged on methotrexate 20 mg weekly with a tapering prednisolone regimen. At three-month follow-up, his implantable defibrillator had not discharged and echocardiography showed improvement in left ventricular ejection fraction to 52%. However, soluble interleukin-2 receptor remained elevated, and repeat FDG-PET/CT demonstrated persistent myocardial avidity, indicating inadequate suppression of inflammation. Treatment was escalated by adding intravenous infliximab at a dose of 5 mg/kg every eight weeks.

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At 12-month follow-up, FDG-PET/CT demonstrated complete suppression of myocardial avidity with resolution of extracardiac lesions, and soluble interleukin-2 receptor had fallen to within the normal range. Left ventricular ejection fraction had normalised at 58%. At two years of follow-up, he remains well with no ICD discharges and no symptoms on combination maintenance infliximab and 10mg weekly methotrexate.

Epidemiology

Population Incidence and Prevalence

The epidemiology of cardiac sarcoidosis has changed substantially in recent decades due to advances in diagnostic imaging. Data from Finland demonstrate a greater than 20-fold increase in annual detection rates between 1988 and 2012, with prevalence reaching approximately 2.2 per 100,000 adults[1]. By 2021, estimated prevalence had risen to 14 cases per 100,000 population[2].

In the United States, systemic sarcoidosis prevalence is approximately 35.2 cases per 100,000 population, with substantial geographic clustering[3]. The incidence is significantly higher in Black Americans compared with White Americans (35.5 versus 10.9 per 100,000 annually), with the Black Women's Health Study reporting an annual incidence as high as 71 per 100,000 and prevalence approaching 2%[4,5].

In England, a recent population-based study using linked primary care data identified 18,554 incident cases between 2003 and 2023, with age- and sex-standardised incidence increasing from 6.65 to 7.73 per 100,000 person-years[6]. Mortality was significantly elevated compared with the general population, with standardised mortality ratios of 1.8 in males and 2.1 in females.

A Danish registry study comparing 11,834 patients with sarcoidosis to matched population controls demonstrated excess cardiovascular risk at the population level[7]. Ten-year risks were elevated for heart failure (3.18% versus 1.72%), ventricular arrhythmias and cardiac arrest (0.96% versus 0.45%), pacemaker implantation and conduction disease (0.94% versus 0.51%), and atrial fibrillation (3.44% versus 2.66%). All-cause mortality was also increased (10.88% versus 7.43%). These data underscore the importance of cardiac surveillance in all patients with sarcoidosis.

Limited epidemiological data are available from South Asia. Sarcoidosis was historically considered rare in India, though increasing recognition suggests this may reflect under-diagnosis rather than true low prevalence[8]. Most available evidence comes from hospital-based series in tertiary centres, which may not be population-representative. These reports indicate that extrapulmonary manifestations, including cardiac involvement, may be more common than previously appreciated.

Challenging the Respiratory-Centric View

Historically, sarcoidosis has been framed as primarily a respiratory disease. This perspective warrants re-examination. The traditional emphasis on pulmonary disease reflects significant surveillance bias: sarcoidosis has been diagnosed predominantly by respiratory physicians, and the literature reflects patients seen in respiratory services.

Contemporary data suggest that a substantial proportion of patients do not have parenchymal lung disease but have significant involvement of other organs. The Finnish data, where two-thirds presented with clinically isolated cardiac disease, exemplify this point[1]. Importantly, cardiac involvement carries major prognostic significance and may surpass pulmonary disease in its impact: in an older study from Japan, cardiac sarcoidosis was found to account for up to 85% of sarcoidosis-related death[9].

The proportion of patients with systemic sarcoidosis who have cardiac involvement depends critically on detection methods. Clinical manifestations are encountered in only approximately 5% of patients[10]. However, when advanced imaging is employed, 20 - 25% demonstrate cardiac involvement[11]. Autopsy studies reveal even higher rates: 20-29% in the United States and 58-70% in Japanese series[9]. This discrepancy underscores the occult nature of much cardiac disease.

Importantly, up to half of cardiac sarcoidosis cases present as isolated cardiac disease without clinically apparent extracardiac involvement at diagnosis[1]. With systematic investigation, however, more than 80% of what are initially thought to be isolated cardiac cases are ultimately found to have extracardiac disease[12].

Environmental and Occupational Exposures

The aetiology of sarcoidosis remains incompletely understood, though epidemiological evidence suggests a role for environmental exposures in genetically susceptible individuals. Occupational exposures to inorganic dusts merit particular attention. The ACCESS study identified elevated odds of sarcoidosis among individuals with occupational exposure to insecticides, agricultural employment, and mould or mildew[13]. A Swedish registry study demonstrated increased risk among workers exposed to silica and other mineral dusts[14]. In the United States, sarcoidosis clusters have been reported among firefighters, particularly following the World Trade Center disaster[15].

The case presented illustrates the importance of obtaining a detailed occupational history. The patient's prolonged

exposure to inorganic dusts in the building industry, without adequate respiratory protection, represents a plausible environmental trigger. While such exposures cannot be proven to be causative in individual cases, identifying them serves two purposes: it may support the diagnosis of sarcoidosis in ambiguous cases, and it has implications for occupational health advice regarding future exposure avoidance.

Clinicians should actively enquire about occupational exposures to dusts (particularly silica and construction materials), agricultural work, and firefighting. A history of working in environments with poor ventilation or inadequate respiratory protection is relevant. These exposures are not included in diagnostic criteria but may increase clinical suspicion for sarcoidosis in patients presenting with compatible syndromes.

Pathophysiology

Cardiac sarcoidosis results from granulomatous infiltration of the myocardium. The non-caseating granulomas comprise epithelioid cells, multinucleated giant cells, and a surrounding rim of lymphocytes. These granulomas arise from a dysregulated T-cell immunological response with activation of type 1 T-helper cells and upregulation of cytokines including tumour necrosis factor-alpha, interferon-gamma, and interleukin-2[2]. The disease progresses through an active inflammatory phase, which may evolve to fibrosis and scarring.

The clinical manifestations depend upon location and extent of infiltration. Granulomas involving the basal interventricular septum may cause conduction abnormalities. Ventricular myocardial infiltration creates a substrate for arrhythmias through both active inflammation and scar formation. Extensive involvement may lead to ventricular dysfunction and heart failure.

Anatomical Distribution

The interventricular septum is the most frequently affected region in cardiac sarcoidosis. The basal septum is involved in approximately one-third of cases at autopsy and represents the most common site of involvement on cardiac MRI, where it may be the sole site of involvement[16,17]. The predilection for the basal septum explains the strong association between cardiac sarcoidosis and atrio-ventricular conduction disease. Enhancement involving the right ventricular aspect of the septum may produce a characteristic "hook" appearance, while a "basal inferoseptal triangular" pattern is considered highly suggestive of cardiac sarcoidosis[18]. In terms of myocardial layer distribution, subepicardial and mid-wall patterns predominate (approximately 40% and 30% respectively), while subendocardial and transmural enhancement are less common[19]. Crucially, the pattern does not correspond to coronary artery territories, helping to distinguish cardiac sarcoidosis from ischaemic heart disease. Differentiation from other forms of myocarditis is more challenging; sarcoidosis tends to favour the basal septum, whereas viral myocarditis more often involves the inferolateral subepicardial wall[20,21].

The most typical pattern on FDG PET/CT is a heterogeneous, multifocal distribution of focal inflammation throughout the left ventricle, with or without right ventricular involvement, that does not conform to a coronary artery territory (Fig. 1). Perfusion imaging can be used as an adjunct to interpretation and typically demonstrates reduced perfusion at sites of active inflammation. Although this multifocal pattern is most characteristic, a wide range of distributions may occur. Less common patterns, such as diffuse right ventricular and multifocal septal involvement, are rare but recognised manifestations of cardiac sarcoidosis and have been described on both cardiac MRI and FDG-PET/CT(Fig. 2)[22,23].

Pericardial involvement is uncommon and usually occurs through direct extension from adjacent myocardial inflammation, while clinically significant pericarditis is rare[24]. Atrial involvement may occur and is associated with an increased risk of atrial arrhythmias, particularly atrial fibrillation[25]. Involvement of the papillary muscles can lead to valvular dysfunction.

Patient Characteristics

Sarcoidosis classically presents between 25 and 60 years. Recent studies have identified two incidence peaks: the third and fourth decades, and women over 50 years[26]. Cardiac sarcoidosis presents at a mean age of around 50 years. Age is clinically important when evaluating rhythm disturbances; in younger patients, idiopathic fibrosis of the conduction system is uncommon, therefore high-grade atrioventricular block in individuals under 60 years should prompt investigation for secondary causes, including sarcoidosis.

Ethnicity plays a significant role in both occurrence and phenotypic expression. Cardiac involvement appears particularly prevalent in Japanese populations, where autopsy studies demonstrate higher rates of cardiac granulomas[9]. In the United States, Black patients are more likely to present with symptomatic heart failure compared with White patients, while ventricular arrhythmias are more frequent in males[27]. Black patients have more frequent multiorgan involvement, with odds ratios exceeding 3 for multiple organ system disease[28]. The reasons for these disparities remain largely unknown.

Clinical Presentation

The clinical manifestations of cardiac sarcoidosis can be categorised into three broad syndromes: conduction abnormalities, arrhythmias, and heart failure. Many patients remain asymptomatic, with cardiac involvement detected only through screening or incidentally.

Conduction Abnormalities

Conduction disease represents the most common clinical manifestation, found in 23 - 30% of patients with myocardial involvement[29]. High-grade atrioventricular block (Mobitz II or complete heart block) is characteristic. The predilection for the basal interventricular septum, which contains the atrioventricular node and bundle of His, explains this prevalence. At diagnosis, right bundle branch block is seen in 26 - 43% of cases[2].

A key clinical question is how often unexplained conduction block in young and middle-aged adults is due to sarcoidosis. The Finnish pacemaker registry provides compelling data: among 72 patients aged 18 - 55 years with initially unexplained second- or third-degree atrioventricular block, biopsy-verified cardiac sarcoidosis or giant cell myocarditis was found in 19% and 6% respectively[30]. A Canadian study found cardiac sarcoidosis in 34% of patients aged 18 - 60 years with unexplained high-grade block[31].

These data carry important implications: any patient under approximately 60 years presenting with unexplained high-grade atrioventricular block should be systematically evaluated for cardiac sarcoidosis. The Heart Rhythm Society specifically recommends screening in patients younger than 60 with unexplained Mobitz II or third-degree block[32].

Ventricular Arrhythmias

Ventricular tachycardia and ventricular fibrillation are life-threatening manifestations. As illustrated by the case presented, ventricular tachycardia may be the presenting feature, including in the context of cardiac arrest. These arrhythmias arise from re-entrant circuits created by patchy myocardial scarring interspersed with areas of inflammation

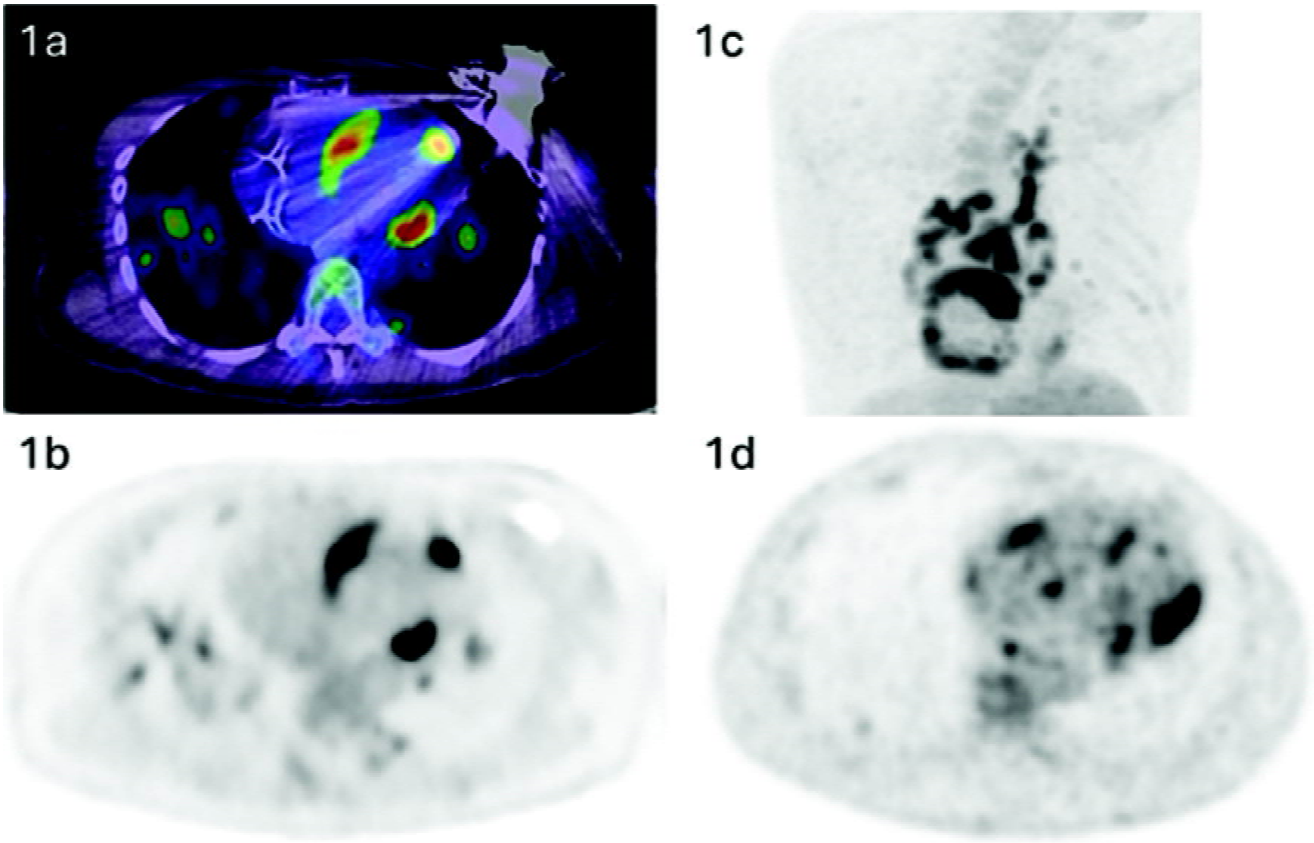

Fig. 1: *FDG-PET/CT patterns in cardiac sarcoidosis. (a) Axial fused PET/CT and (b) axial PET images from a patient with an implantable cardioverter-defibrillator (ICD), demonstrating multifocal left ventricular FDG uptake with FDG-avid pulmonary nodules. The presence of an ICD precludes cardiac MRI assessment, highlighting the role of serial FDG-PET/CT in monitoring treatment response and disease activity. (c) Maximum intensity projection (MIP) and (d) axial PET images from a second patient, showing the typical pattern of heterogeneous, multifocal biventricular FDG uptake with foci of atrial involvement. FDG-avid mediastinal and hilar lymphadenopathy is also seen, illustrating the ability of PET to identify extracardiac biopsy targets.*

and normal tissue. Right ventricular free wall involvement and multifocal myocardial enhancement on cardiac MRI are associated with a substantially increased risk of ventricular arrhythmias.

Sudden cardiac death may be the first manifestation of sarcoidosis, which is an under recognised cause of sudden death in young adults. Data from the Finnish registry indicate a 9% five-year risk of sudden cardiac death even in patients presenting solely with atrioventricular block and preserved left ventricular ejection fraction greater than 50%[33]. This finding has important implications for device therapy decisions, as discussed below.

Atrial Arrhythmias

Although ventricular arrhythmias dominate discussions of cardiac sarcoidosis, supraventricular arrhythmias do occur and can be clinically significant. In a retrospective study of 100 patients with definite or probable cardiac sarcoidosis followed for a mean of 5.8 years, the prevalence of supraventricular arrhythmias was 32%, with atrial fibrillation being the most frequent[34]. Left atrial enlargement on echocardiography was the strongest predictor of supraventricular arrhythmia development.

Recent data suggest that FDG-PET/CT may identify patients at risk of atrial fibrillation. In a study of 118 patients who were in sinus rhythm at cardiac sarcoidosis diagnosis, atrial FDG uptake was an independent risk factor for incident atrial fibrillation: 55% of those with atrial uptake developed atrial fibrillation within five years compared with 18% of those without[35]. This observation has potential implications for anticoagulation decisions and rhythm monitoring strategies.

Heart Failure

Heart failure may result from extensive granulomatous infiltration causing ventricular dysfunction. Both dilated and restrictive patterns can occur. Left ventricular systolic dysfunction is present in approximately half of patients with cardiac sarcoidosis at the time of their diagnosis[1]. Right ventricular dysfunction may result from direct infiltration or pulmonary hypertension, which may be secondary to pulmonary disease or left ventricular failure. Importantly, heart failure has the potential to improve with immunosuppressive therapy when active inflammation predominates over irreversible scarring, a distinction that can be assessed by cardiac MRI and perfusion imaging.

Heart failure appears more prevalent among Black patients and women compared with White patients and men[27]. Clinicians should consider cardiac sarcoidosis in cases of unexplained cardiomyopathy, particularly in younger patients.

What Cardiac Sarcoidosis Does Not Typically Cause

Equally important is understanding atypical features. Pericarditis and clinically significant pericardial effusions are uncommon (although autopsy evidence of silent

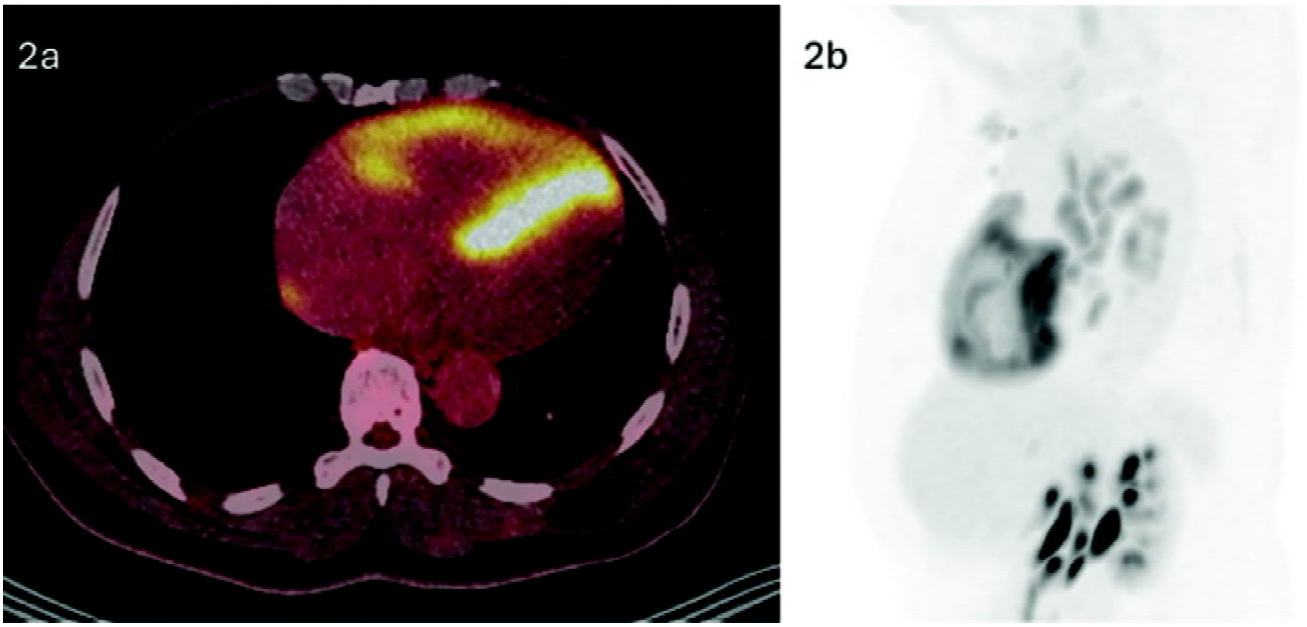

Fig. 2: *FDG-PET/CT in cardiac sarcoidosis demonstrating a rare but recognised pattern of diffuse right ventricular and septal FDG uptake. (a) Axial fused PET/CT image showing intense FDG avidity along the right ventricular free wall and interventricular septum. (b) Maximum intensity projection (MIP) image confirming diffuse cardiac uptake and demonstrating FDG-avid mediastinal and hilar lymphadenopathy.*

pericardial involvement is not infrequent)[24,36]. Valvular lesions are rare. Coronary arteritis does not typically occur and coronary angiography, in the absence of concurrent cardiovascular risk factors, is characteristically normal. Large vessel involvement such as aortitis is unusual. Significant aortitis should prompt consideration of alternative diagnoses including giant cell arteritis, Takayasu arteritis, and IgG4-related disease[37].

Diagnostic Approach

The diagnosis of cardiac sarcoidosis is supported by the demonstration of non-caseating granulomatous inflammation in involved tissue, combined with a compatible clinical syndrome. In practice, obtaining cardiac tissue confirmation is challenging, and clinicians frequently rely upon extra-cardiac tissue diagnosis with compatible cardiac findings.

Recognising the Possibility of Cardiac Sarcoidosis

Several features should heighten clinical suspicion. Cardiac manifestations typically follow a non-ischaemic pattern, with abnormalities that do not respect coronary artery territories on imaging. Age is also informative: a younger patient with high-grade atrioventricular block or unexplained ventricular arrhythmias warrants active investigation. Extracardiac clues are frequently present. Mediastinal or hilar lymphadenopathy and inflammatory eye disease (particularly uveitis) should strengthen suspicion. All patients in whom cardiac sarcoidosis is suspected should undergo formal ophthalmic examination.

Systematic Assessment for Multiorgan Involvement

If cardiac sarcoidosis is suspected, systematic search for involvement of other organ systems is warranted. FDG-PET/CT imaging allows comprehensive mapping of disease activity across multiple organs. PET/CT may reveal uptake in lung parenchyma, lymph nodes, liver, spleen, bone, joints, muscles, salivary glands and other organs. In our service, we additionally screen for endocrine involvement, in particular hypothalamic-pituitary involvement.

This systematic approach serves two purposes: it may identify more accessible sites for tissue diagnosis than the heart, and it defines the extent of systemic disease with implications for prognosis and management.

The Diagnostic Pitfall: Coincidental Granulomas

A critical diagnostic hallenge relates to interpretation of granulomatous inflammation. Sarcoidosis may present asymptomatically with mediastinal lymphadenopathy and can remain clinically silent for many years without consequence. This becomes particularly important when evaluating cardiac presentations. Consider a patient presenting with heart failure and mediastinal lymphadenopathy showing granulomas. It would be tempting to conclude cardiac sarcoidosis is the cause. However, the underlying cardiac pathology could instead represent an inherited cardiomyopathy in an individual with coincidental, previously asymptomatic extra-cardiac sarcoidosis. The presence of extracardiac granulomas should therefore be regarded as supportive evidence within the appropriate clinical context, rather than definitive proof of cardiac involvement.

Cardiac Imaging

Cardiac MRI and FDG-PET/CT have transformed diagnosis and management. Cardiac MRI with gadolinium-based contrast agents may demonstrate myocardial oedema on T2-weighted sequences (suggesting active inflammation), LGE (reflecting fibrosis or inflammation), wall motion abnormalities, and impaired left ventricular function. Sensitivity is 75 - 100%, and specificity is 76 - 78%[38].

FDG-PET/CT detects metabolically active inflammatory tissue. Suppression of physiological cardiac glucose uptake through dietary preparation and fasting to induce a mild ketotic state and suppress physiological myocardial glucose uptake via insulin dependent GLUT-4 transporters is essential. 24 hours of ketogenic diet should suppress myocardial FDG uptake in 80% of patients and 72 hours of ketogenic diet will achieve 95% suppression rates. FDG-PET/CT has the advantage of imaging the whole body, revealing extracardiac disease and providing biopsy targets.

A key distinction relates to monitoring treatment response. Cardiac MRI demonstrates fibrosis through LGE, which represents established scar and does not regress with immunosuppression. MRI can also detect myocardial oedema on T2-weighted imaging reflecting active inflammation however, its sensitivity and reproducibility for serial monitoring are more limited. In contrast, FDG-PET directly demonstrates metabolically active inflammation and is generally preferred for assessing inflammatory activity and monitoring response to immunosuppressive therapy. The joint Society of Nuclear Medicine and Molecular Imaging and American Society of Nuclear Cardiology 2017 Expert Consensus[39] the 2024 American Heart Association (AHA) position statement[2] recommend the use of repeat FDG PET/CT to ensure adequate response to therapy within 3 - 6 months of commencing immunosuppression.

Perfusion imaging can help identify areas of reduced perfusion due to inflammation and/or scar that do not correspond to a coronary artery territory. In the 2024 AHA scientific statement on cardiac sarcoidosis imaging, the

sensitivity and specificity of any FDG uptake pattern are reported as 100% and 33%, respectively[2]. In contrast, more typical imaging patterns, such as multifocal non-contiguous FDG-avid perfusion defects or myocardial FDG uptake in the presence of typical extracardiac sarcoidosis, have a sensitivity of 83% and specificity of 100%. In the absence of biopsy confirmation or extracardiac features of sarcoidosis, our experience is that diagnostic uncertainty often remains, and neither 100% sensitivity nor specificity is achieved with PET or other advanced imaging modalities.

Endomyocardial Biopsy

Endomyocardial biopsy (EMB) remains the gold standard but has important limitations. Patchy distribution means sensitivity is only 20 - 30% even with multiple biopsies[32]. Yield can be improved by targeting imaging abnormalities or using electro-anatomical mapping. Major complications include cardiac perforation, tamponade, and arrhythmia (1 - 5% risk)[40]. Given the low sensitivity and associated risks, EMB is typically reserved for uncertain cases.

In practice, diagnosis is usually established by demonstrating non-caseating granulomas in extra-cardiac tissue combined with compatible cardiac imaging. This approach is endorsed by the Heart Rhythm Society consensus statement[32]. However, awareness of the aforementioned diagnostic pitfalls is crucial; this is part of the art of diagnostic medicine.

Soluble Interleukin-2 Receptor

Soluble interleukin-2 receptor (sIL-2R) has emerged as a useful biomarker. Serum levels are elevated in active sarcoidosis and correlate with disease activity[41]. Sensitivity and specificity for diagnosing sarcoidosis are approximately 88% and 85% respectively, superior to angiotensin-converting enzyme[42]. In cardiac sarcoidosis, elevated sIL-2R is associated with worse outcomes. We measure soluble sIL-2R levels at diagnosis and monitor them serially during treatment as a biomarker of disease activity and therapeutic response.

Differential Diagnosis

The differential diagnosis of cardiac presentations attributable to sarcoidosis requires a systematic evaluation for alternative causes, including other granulomatous diseases, inherited conditions, infections, and malignancy.

Tuberculosis: The Critical Distinction

In endemic regions including the Indian subcontinent, the most important differential diagnosis is tuberculosis. Both conditions cause granulomatous inflammation and distinguishing them has profound implications for management. The histopathological distinction rests on caseation: tuberculous granulomas classically demonstrate central caseous necrosis, whereas sarcoid granulomas are non-caseating. However, this distinction is not absolute. Non-caseating granulomas may be seen in tuberculosis, particularly in early or treated disease.

Clinical and laboratory features aid differentiation. Tuberculosis is typically associated with greater burden of constitutional symptoms, positive tuberculin skin test or interferon-gamma release assay, and identification of acid-fast bacilli on microscopy or culture. In practice, when tuberculosis cannot be excluded, many clinicians will commence anti-tuberculous therapy before considering immunosuppression for sarcoidosis. Immunosuppressing a patient with unrecognised tuberculosis carries serious consequences.

Although pulmonary involvement is most typical, tuberculosis can also affect the heart. Cardiac involvement may manifest as pericarditis or, less commonly, myocarditis. Pericardial involvement is more characteristic of tuberculosis than sarcoidosis[43]. Large pericardial effusions and constrictive physiology should raise particular concern for a tuberculous aetiology.

Other Infectious Causes

Several other infections warrant consideration. Rheumatic fever, though declining in developed countries, remains an important cause of cardiac disease in India and other parts of South Asia[44]. Rheumatic carditis primarily affects the valves rather than the myocardium, but differentiation may be required in patients with both valvular and myocardial abnormalities.

Viral myocarditis can present with ventricular arrhythmias and cardiomyopathy, though the acute presentation and preceding viral prodrome usually distinguish it from sarcoidosis[45]. In patients from Latin America, Chagas disease should be considered[46]. Lyme carditis is relevant in endemic regions of North America and Europe, presenting with fluctuating high-grade atrioventricular block[47].

Inherited Cardiomyopathies

With increasing availability of genetic testing, inherited cardiomyopathies have become essential considerations in the differential diagnosis of cardiac sarcoidosis. This is particularly relevant for patients presenting with apparent isolated cardiac disease without extracardiac manifestations.

Desmoplakin cardiomyopathy is an excellent example. Caused by mutations in the gene encoding desmoplakin, this arrhythmogenic cardiomyopathy is characterised by episodic myocardial injury, left ventricular fibrosis, and high

incidence of ventricular arrhythmias – features that overlap substantially with cardiac sarcoidosis[48]. Crucially, desmoplakin cardiomyopathy can present with myocarditis-like episodes associated with troponin elevation and myocardial inflammation on FDG-PET/CT, leading to misdiagnosis as cardiac sarcoidosis. The cardiac MRI findings can be similar, with subepicardial and mid-wall LGE.

Lamin A/C cardiomyopathy also shares clinical features with cardiac sarcoidosis, including conduction system disease, atrial arrhythmias, ventricular arrhythmias, and dilated cardiomyopathy[49]. The combination of atrioventricular block with atrial arrhythmias and mild ventricular dilatation in a younger patient should prompt consideration of laminopathy.

Distinguishing features favouring inherited cardiomyopathy over cardiac sarcoidosis include family history of cardiomyopathy or sudden death, absence of extracardiac sarcoidosis despite thorough investigation, and certain ECG patterns (low-voltage QRS complexes and poor R-wave progression may suggest laminopathy).

We are increasingly incorporating genetic testing for arrhythmogenic and dilated cardiomyopathy genes in patients with suspected cardiac sarcoidosis when extracardiac disease cannot be demonstrated, when family history suggests inherited disease, or when the clinical picture is atypical for sarcoidosis. The identification of a pathogenic variant fundamentally changes management, prognosis, and necessitates consideration of cascade screening and risk assessment in family members.

Malignancy

Lymphoma is an important differential, particularly given that both conditions can present with mediastinal lymphadenopathy and cardiac involvement. Pericardial effusion, which is common in cardiac lymphoma but unusual in sarcoidosis, provides a helpful distinguishing feature[50]. Extensive lymphadenopathy, hepato-splenomegaly, and constitutional symptoms should heighten suspicion for lymphoma. When lymph node biopsy is performed, the pathologist should specifically exclude lymphomatous involvement.

Others

In addition to inherited cardiomyopathies and infectious myocarditis, other potential causes of a false positive cardiac sarcoidosis imaging diagnosis include ischaemic hibernating myocardium, recent myocardial infarction, other infiltrative or autoimmune causes of dilated cardiomyopathy and incomplete suppression of physiological myocardial glucose uptake prior to scanning.

Management

The management of cardiac sarcoidosis remains predominantly eminence-based. There are no randomised controlled trials specifically addressing immunosuppressive treatment. Nonetheless, clinical experience strongly supports immunosuppression, and contemporary management involves a tiered approach.

The Case for Immunosuppression

Most clinicians agree that immunosuppression is necessary. In our experience patients with ventricular arrhythmias treated with device therapy alone often continue to experience recurrent discharges, whereas the addition of immunosuppression is associated with improved arrhythmia control. Dramatic improvement in left ventricular function and reversal of atrioventricular block have been reported following immunosuppressive treatment.

A systematic review of 34 retrospective studies found that corticosteroid therapy improved atrioventricular conduction in 43% of treated patients compared with none among untreated patients[51]. Data quality was insufficient to draw firm conclusions regarding impact on ventricular arrhythmias or mortality, but the direction of effect supports treatment. The American Heart Association endorses corticosteroids as first-line treatment for cardiac sarcoidosis with active inflammation[2].

Induction Therapy with Corticosteroids

Our approach for induction therapy involves pulse methylprednisolone, typically 500 mg to 1 g intravenously daily for three days, followed by oral prednisolone. The pulse dose is individualised based on patient factors including diabetes, body weight, and age.

The optimal maintenance dose of oral corticosteroid is uncertain. Practice varies considerably between centres. Some experts recommend starting at 30 mg daily, citing concerns that higher doses (40 - 60 mg daily) are associated with greater adverse effects without clear evidence of superior efficacy. Others, including our group, favour higher initial doses (40 - 60 mg daily, approximately 0.5 - 1 mg/kg) in patients with significant inflammation or clinical instability, tapering to 10 - 15 mg daily over subsequent months. A systematic review found insufficient data to compare dosing regimens[51].

In the case presented, we initiated prednisolone at 40 mg daily given the severity of presentation with cardiac arrest. More modest presentations might reasonably be treated with lower initial doses. What is clear is that prolonged

high-dose corticosteroid therapy should be avoided: the adverse metabolic, skeletal, and infectious consequences are substantial, and steroid-sparing agents should be introduced early to facilitate dose reduction.

Steroid-Sparing Therapy: Methotrexate

Our first-line steroid-sparing agent is methotrexate. The PREDMETH trial demonstrated non-inferiority of methotrexate compared with prednisone for pulmonary sarcoidosis[52]. Evidence from neurosarcoidosis similarly supports efficacy. In a retrospective study of 28 patients with cardiac sarcoidosis treated with methotrexate, 88% demonstrated an initial reduction in cardiac FDG uptake, with complete resolution observed in 60%[53].

We aim for a target dose of 20 mg orally methotrexate once weekly. Dose adjustments are required based on patient characteristics; Japanese patients may require lower doses due to pharmacogenomic factors. Renal function must be carefully considered given methotrexate's renal excretion. Folic acid supplementation is standard. Mycophenolate mofetil represents an alternative steroid-sparing agent with some supporting data, though methotrexate is favoured as first-line[54].

Escalation to Tumour Necrosis Factor Inhibitors

For patients failing corticosteroids and methotrexate, we escalate therapy to a TNF inhibitor, typically infliximab. A multicentre study demonstrated significant reduction in prednisone dose and improvement in cardiac FDG uptake with TNF inhibition[55]. Prednisone decreased from 21.7 mg at initiation to 7.3 mg at 12 months. Among patients with cardiac FDG uptake, 62% showed complete or partial resolution. In the study by Rosenthal and colleagues, adalimumab was added in 19 patients with persistently active disease or methotrexate intolerance, with FDG uptake improvement in 84% and resolution in 63%[53].

An important caveat relates to TNF inhibitors in heart failure. The ATTACH trial demonstrated increased mortality when infliximab was used for non-sarcoid heart failure[56]. However, this concern may not apply to sarcoidosis, where treating the underlying inflammation may improve function. We use infliximab in cardiac sarcoidosis including patients with reduced ejection fraction, with close monitoring with echocardiography and serum NT-proBNP levels, and specialist cardiology input. Cost and availability may limit access to biologic therapy in some settings.

Implantable Cardiac Defibrillators

Implantable cardiac defibrillators play a central role in the management of cardiac sarcoidosis given the substantial risk of ventricular arrhythmias and sudden cardiac death. The indications for ICD implantation have been codified in the 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline, which includes specific recommendations for patients with cardiac sarcoidosis[57].

Secondary Prevention

ICD implantation is unequivocally indicated for secondary prevention in patients who have survived sustained ventricular tachycardia or cardiac arrest, as in the case presented. This group carries the highest risk of recurrent events with annualised rates of recurrent arrhythmia or sudden death approaching 80% in this population[58].

Primary Prevention

For primary prevention, ICD implantation is recommended in patients with cardiac sarcoidosis and left ventricular ejection fraction ≥35% despite optimal medical therapy[59]. This threshold aligns with indications for non-ischaemic cardiomyopathy. However, cardiac sarcoidosis presents a particular challenge: patients with preserved ejection fraction remain at significant risk of sudden death, and reliance on conventional ejection fraction thresholds may be inadequate for risk stratification.

The Heart Rhythm Society consensus statement recommends considering ICD implantation in patients with cardiac sarcoidosis who have syncope of suspected arrhythmic origin or imaging evidence of significant myocardial scar, even with preserved ejection fraction[32]. A study of 290 patients with biopsy-proven sarcoidosis found that LVEF >35% with any LGE had an annualised event rate of 2.1%, rising to 12.0% when LGE exceeded 5.7% of LV mass[58].

Risk Stratification Using Advanced Imaging

Contemporary risk stratification increasingly relies upon advanced imaging findings. LGE on cardiac MRI is associated with increased risk of death and ventricular arrhythmias. Importantly, the pattern of LGE may be as significant as extent: involvement of the right ventricular free wall, multifocal distribution, and subepicardial patterns are associated with particularly high arrhythmic risk[60].

Right ventricular abnormalities on cardiac MRI carry independent prognostic significance. In a study of 290 patients, reduced right ventricular ejection fraction was independently associated with all-cause death, whilst right ventricular LGE was independently associated with sudden cardiac death and significant ventricular arrhythmia[61].

FDG-PET/CT findings also predict adverse events. Patients with both abnormal myocardial FDG uptake and resting perfusion defects have substantially higher rates of ventricular tachycardia and death than those with normal imaging[62]. Right ventricular FDG uptake appears to confer particularly high risk.

Role of Electrophysiological Study

For patients without a clear indication for ICD implantation, electrophysiological study may inform risk stratification. Inducible sustained ventricular tachycardia predicts future arrhythmic events, and some centres use this to guide ICD decision-making in patients with preserved ejection fraction and equivocal imaging findings[63,64]. However, the added value of electrophysiological testing beyond imaging findings remains uncertain and is not routine in our centre.

Pacemaker Indication

For patients with cardiac sarcoidosis requiring permanent pacemaker implantation for high-grade atrioventricular block, our practice is to favour implantation of a device with ICD functionality rather than a pacemaker alone. The Finnish registry demonstrated a 9% five-year risk of sudden cardiac death even among patients presenting with atrioventricular block and preserved ejection fraction above 50%[33]. This risk justifies the additional complexity and cost of an ICD in most cases.

Monitoring Treatment Response

Assessment requires a comprehensive approach that integrates clinical, biochemical, and imaging parameters. We routinely evaluate symptom burden, arrhythmia events, and heart failure status. Device interrogation provides objective documentation of arrhythmia frequency and burden, while serial measurement of sIL-2R serves as a biomarker of inflammatory activity.

FDG-PET/CT is the imaging modality of choice for monitoring. We typically perform FDG-PET/CT at approximately four to six months after treatment initiation to assess response. Persistent cardiac avidity despite treatment indicates inadequate control and should prompt escalation.

Duration of Treatment

The optimal duration of immunosuppressive treatment remains uncertain and represents an important knowledge gap. Unlike some phenotypes of pulmonary sarcoidosis that may remit spontaneously or tolerate treatment withdrawal, cardiac sarcoidosis carries significant risk of relapse upon treatment cessation.

Current evidence and clinical guidelines suggest that treatment should continue for at least one to two years[54]. Our approach is to continue treatment long-term, with shared decision-making regarding the risks and benefits. Serial FDG-PET/CT imaging guides treatment decisions, and treatment de-escalation should not be carried out if myocardial FDG avidity persists. If inflammation has resolved and remains suppressed on serial imaging, cautious de-escalation may be considered. We favour a phased approach: for patients on combination therapy, we would first withdraw the biologic agent while maintaining background methotrexate, with close monitoring for disease recurrence using sIL-2R levels and repeat FDG-PET/CT at approximately six months. Complete treatment withdrawal is undertaken with great caution and close surveillance, typically only after at least two years of sustained remission.

The patient in the case presented remains on maintenance infliximab and low-dose methotrexate at two years, with stable imaging appearances. We have not yet attempted treatment de-escalation given the severity of his initial presentation.

Prognosis

Cardiac sarcoidosis carries significant morbidity and mortality, though outcomes are highly variable depending on clinical presentation, extent of disease, and response to treatment.

Survival Data

The most comprehensive survival data come from the Finnish nationwide study. Among 110 patients with histologically confirmed cardiac sarcoidosis diagnosed between 1988 and 2012, overall transplant-free survival was 99.1% at one year, 93.5% at five years, and 89.3% at ten years[1]. However, outcomes varied substantially by presentation. Patients presenting with heart failure had markedly worse prognosis: transplant-free survival of 90%, 75%, and 52.5% at one, five, and ten years respectively. Patients presenting with arrhythmias or conduction disease had more favourable outcomes.

Prognostic Factors

Several factors predict adverse outcomes in cardiac sarcoidosis. New York Heart Association functional class and left ventricular end-diastolic dimension are independent predictors of death[65].

Advanced imaging findings carry prognostic significance independent of ejection fraction. LGE on cardiac MRI predicts death and ventricular arrhythmias even in patients with preserved ejection fraction[38]. FDG-PET/CT

abnormalities, particularly the combination of perfusion defects with increased FDG uptake, predict adverse cardiac events[62].

Right ventricular involvement, whether manifest as reduced right ventricular ejection fraction or right ventricular LGE, independently predicts adverse outcomes[61]. History of sustained ventricular tachycardia or cardiac arrest identifies patients at highest risk of recurrent arrhythmic events, justifying aggressive device and immunosuppressive therapy.

Prognosis with Treatment

While randomised data are lacking, observational evidence suggests that immunosuppressive therapy improves outcomes in cardiac sarcoidosis. Resolution of inflammation on FDG-PET/CT following treatment is associated with reduced arrhythmic events[66]. Improvement in left ventricular function following immunosuppression is well documented and, in our experience, can be dramatic when treatment is initiated before extensive fibrosis has developed.

The case presented illustrates the potential for excellent outcomes with aggressive multimodality management. Despite presenting with cardiac arrest and multiorgan disease, the patient achieved complete suppression of inflammation, normalisation of ventricular function, and remains free of arrhythmia at two years. Such outcomes are achievable but require prompt recognition, thorough staging, aggressive immunosuppression, appropriate device therapy, and meticulous longitudinal follow-up.

Conclusions

Cardiac sarcoidosis represents a challenging but increasingly recognised manifestation with substantial implications for morbidity and mortality. We must move beyond the traditional framing of sarcoidosis as primarily a respiratory disease. A substantial proportion of patients have significant extrapulmonary involvement, and cardiac disease may occur without parenchymal lung disease.

Clinicians should maintain a high index of suspicion, particularly in younger patients with unexplained arrhythmias, conduction disease, or cardiomyopathy. A detailed occupational history may reveal relevant environmental exposures. In endemic regions, distinguishing sarcoidosis from tuberculosis is the critical first step; immunosuppressing unrecognised tuberculosis carries serious consequences. The finding of granulomatous inflammation should support but not define the diagnosis of cardiac sarcoidosis; genetic cardiomyopathies must be considered when extracardiac disease cannot be demonstrated.

Management centres on immunosuppression combined with device therapy for arrhythmia protection. While evidence from randomised trials is lacking, clinical experience strongly supports corticosteroids, methotrexate, and TNF inhibitors. Risk stratification using advanced imaging informs ICD decisions, particularly in patients with preserved ejection fraction. Serial monitoring with sIL-2R and FDG-PET/CT guides therapy escalation and, eventually, cautious de-escalation.

Future research should focus on evidence-based treatment protocols through randomised trials, biomarkers predicting treatment response, and optimal strategies for treatment duration. In the meantime, a thoughtful, patient-centred approach combining aggressive immunosuppression with careful monitoring can achieve excellent outcomes, as exemplified by the case presented.

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