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Cardiac sarcoidosis: phenotypes, diagnosis, treatment, and prognosis

Jukka Lehtonen [1]*, Valtteri Uusitalo [2], Pauli Pöyhönen [1], Mikko I. Mäyränpää [3], and Markku Kupari [1]

[1]Heart and Lung Center, Helsinki University Central Hospital and University of Helsinki, Haartmaninkatu 4, 00290 Helsinki, Finland; [2]Clinical Physiology and Nuclear Medicine, Helsinki University Central Hospital and University of Helsinki, Haartmaninkatu 4, 00290 Helsinki, Finland; and [3]Department of Pathology, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 3C, 00290 Helsinki, Finland

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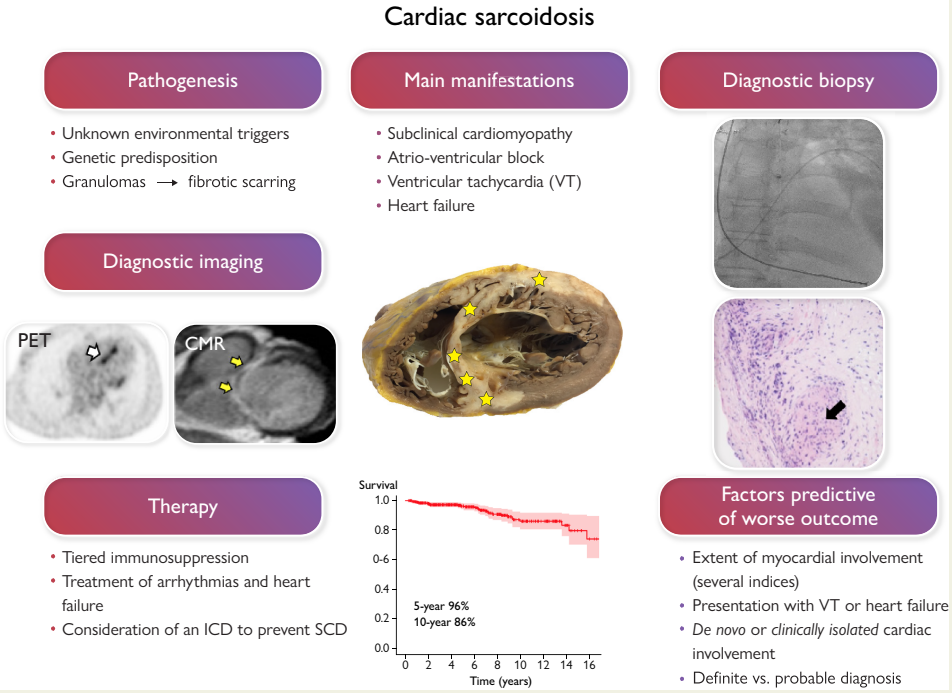
Graphical Abstract



In cardiac sarcoidosis (CS), inflammatory granulomas invade the heart leading to injury and fibrosis (yellow stars in the section of a sarcoidotic heart in the middle of the graph). CS is often subclinical, but, when clinically manifest, presents commonly with slow or fast arrhythmias or heart failure. On the left of the figure, positron emission tomography (PET) exposes focal septal uptake of 18-F fluorodeoxyglucose suggesting active inflammation (white arrow), and contrast-enhanced cardiac magnetic resonance (CMR) shows septal late gadolinium enhancement (arrows) indicating replacement fibrosis. Both constitute major diagnostic criteria for CS and entitle probable CS diagnosis if accompanied by confirmed extracardiac histology of sarcoidosis. Yet, the only way to definite diagnosis, demonstrated on the right, is myocardial biopsy showing non-necrotic granulomas (black arrow). The therapy of CS is based on immunosuppression and management of heart block, ventricular arrhythmias, and heart failure. The risk of sudden cardiac death (SCD) needs assessment and consideration of an implantable cardioverter-defibrillator (ICD). With current therapy, expected 5-year survival is well above 90% as shown by the Kaplan–Meier graph of a 398-patient Finnish CS cohort.

* Corresponding author. Tel: +358 504279869, Email: jukka.lehtonen@hus.fi

Abstract

Cardiac sarcoidosis (CS) results from epithelioid cell granulomas infiltrating the myocardium and predisposing to conduction disturbances, ventricular tachyarrhythmias, and heart failure. Manifest CS, however, constitutes only the top of an iceberg as advanced imaging uncovers cardiac involvement 4 to 5 times more commonly than what is clinically detectable. Definite diagnosis of CS requires myocardial biopsy and histopathology, but a sufficient diagnostic likelihood can be achieved by combining extracardiac histology of sarcoidosis with clinical manifestations and findings on cardiac imaging. CS can appear as the first or only organ manifestation of sarcoidosis or on top of pre-existing extracardiac disease. Due to the lack of controlled trials, the care of CS is based on observational evidence of low quality. Currently, the treatment involves corticosteroid-based, tiered immunosuppression to control myocardial inflammation with medical and device-based therapy for symptomatic atrioventricular block, ventricular tachyarrhythmias, and heart failure. Recent outcome data indicate 90% to 96% 5-year survival in manifest CS with the 10-year figures ranging from 80% to 90%. Major progress in the care of CS awaits the key to its molecular–genetic pathogenesis and large-scale controlled clinical trials.

Keywords Cardiac sarcoidosis • Inflammatory heart disease • Heart failure • Pacemaker • Implantable cardioverter-defibrillator

Introduction

Sarcoidosis is an enigmatic disease for many reasons, not least due to its exact cause and pathogenesis remaining hidden despite decades of focused research. Hypotheses abound, however, the overarching one being that the disease results from environmental antigens—infectious, occupational, or other—triggering a dysregulated T cell-driven immunologic response in a genetically predisposed individual.[1] The response generates non-necrotic inflammatory granulomas that may appear anywhere in the body leading to local injury and fibrosis—or resolving spontaneously.[1] Cardiac sarcoidosis (CS) usually presents in tandem with extracardiac involvement but can be the first or even isolated sign of sarcoidosis.[2] No cardiac structure is safe from granulomas, but myocardial infiltration does most of the harm. The clinical spectrum of CS extends from silence to sudden cardiac death (SCD),[2] the predominant manifestations being impaired conduction, ventricular arrhythmias (VAs), and heart failure. The main challenges of CS are—no less than—diagnosis and treatment (*Graphical Abstract*). As confirming the presence of myocardial granulomas is challenging, different sets of criteria[3–5] are used for clinical CS diagnosis, yet none are validated or universally adopted. Further, CS being rare and unknown for pathogenesis, precision therapy has not been possible and no controlled trial data exist. The many unknowns and uncertainties about CS puzzle even the most astute clinician. The present review updates the current knowledge of CS focusing on clinical aspects. Readers wishing deeper insight into its possible molecular–genetic mechanisms are referred to recent reviews elsewhere.[1,6]

Phenotypes

CS hidden until autopsy

A perceptible segment of CS presents as an unexpected SCD and is diagnosed only at autopsy.[7,8] These individuals have been free of both known sarcoidosis and cardiac manifestations while alive, or their symptoms and signs of heart disease have been misdiagnosed on lifetime examinations. Among the 351 cases of CS detected in Finland from 1998 to the end of 2015, 62 were diagnosed postmortem, and in 38 (11% of all cases) SCD was the first and only manifestation of CS.[8]

CS with dominant extracardiac sarcoidosis and no or minimal cardiac symptoms

The typical patient is one with known sarcoidosis found to have cardiac involvement on routine screening or in examinations for mild symptoms and/or abnormalities on a 12-lead electrocardiogram (ECG). Postmortem[9] and cardiac magnetic resonance (CMR) studies[10–12] have uncovered myocardial involvement in 25% to 30% of all sarcoidosis and even in 9% of patients without symptoms or ECG abnormalities.[12] Yet, in a screening study of 2163 patients with extracardiac sarcoidosis, only 3.2% had CS detectable by clinical means alone.[13]

Clinically manifest CS

These patients are admitted for often acute and serious cardiac symptoms, undergo diagnostic assessment, and are found to have CS either on admission or during subsequent examinations. Although only a minority,[2,8] or one-half at most,[14,15] give a history of sarcoidosis, most are ultimately found to have multi-organ disease. The prevalence of isolated CS[16] has varied from 3%[17] to 43%,[18] the most common approximate being 20% to 25%.[16,19–21] Cardiac involvement as the first or only organ manifestation, i.e. *de novo* or *clinically isolated* CS, implies more serious disease than CS appearing on top of extracardiac disease.[2,14,15]

The manifestations of CS (*Table 1*) depend on the location and extent of granulomas, with high-grade atrioventricular block (AVB) and VAs being the most common initial signs.[8,22–25] Sustained ventricular tachycardia (VT) results from re-entry circuits in inflamed and scarred myocardial areas, but automatic and triggered arrhythmias are also possible.[26] Multiple VT morphologies are common. Heart failure reflects widespread left ventricular (LV) infiltration and systolic dysfunction, but restricted filling due to edematous or fibrotic LV walls can contribute. Mitral regurgitation results from LV or mitral annular dilatation, scarred LV wall restricting valve closure, or from granulomas invading the valve leaflets.[27] Infiltration of the right ventricle may masquerade as arrhythmogenic right ventricular cardiomyopathy.[28] Atrial fibrillation is rare at presentation but has a considerable later incidence.[29] Angina-like chest pain[30] can occur and is usually attributed to impaired coronary flow reserve[31] from compression of the myocardial microvasculature. However, granulomatous coronary arteritis is also possible and, rarely, CS presents as a full disguise of an acute myocardial infarction with angiography showing normal findings or either dissection or total occlusion of a single coronary artery.[27,32,33] Effusive and constrictive pericarditis are exceptional manifestations.[34]

The nationwide registry of Myocardial Inflammatory Diseases in Finland (MIDFIN) includes data on adult patients diagnosed with clinically manifest CS from the late 1980s onwards.[2,8,24] *Figure 1* shows an exponential rise in the 5-year detection rate of new cases ever since.

Table 1 Symptoms at presentation and main manifestations of cardiac sarcoidosis (CS) in two large cohorts

Symptoms in 383 Americans with CS[a]	%	Main manifestations in 289 Finns with CS[b]	%
Dyspnoea	50–70	High-grade atrioventricular block	46
Palpitation	40–60	Heart failure with LV dysfunction	18
Fatigue	30–45	Sustained VT	17
Chest pain	20–30	NSVT or frequent ventricular premature beats	7
Presyncope	15–30	Aborted sudden cardiac death	4
Syncope	15–20	Syndrome mimicking acute myocardial infarction[c]	4
Edema	5–10	Atrial tachyarrhythmia	1
Cardiac arrest	2–10	Other	3

NSVT indicates non-sustained ventricular tachycardia; VT, ventricular tachycardia.
[a]From the study of Rosenbaum *et al.*[22] involving a predominantly white (88%) male (63%) population aged on average 54 years. The diagnosis of cardiac sarcoidosis was based on the Heart Rhythm Society's (HRS) criteria[4] in 73% of the cohort, the rest having presumed CS without proof of sarcoidosis histology.
[b]From the study of Ekström *et al.*[8] involving a nationwide cohort with female predominance (74%) and a mean age of 50 years. All patients fulfilled the HRS diagnostic criteria.
[c]acute chest pain, ischemic ECG changes, and elevated cardiac biomarkers with a normal coronary arteriogram.

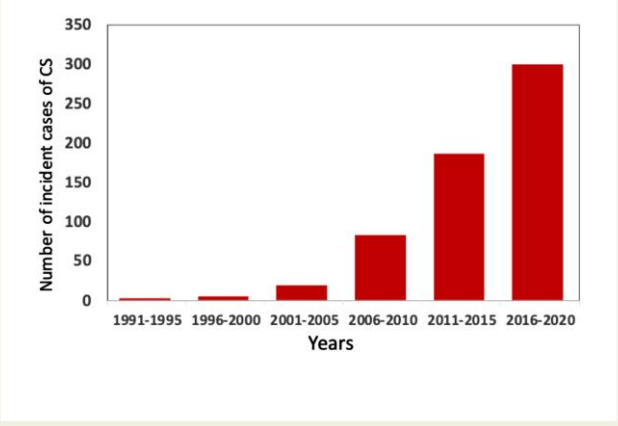


Figure 1 Incident cases of clinically manifest cardiac sarcoidosis (CS) in adults (>18 years) diagnosed in Finnish hospitals from 1991 through 2020. Curiously, 3 vs. 300 new cases were detected over the first and last 5-year periods, respectively. The population of Finland is 5.5 million with 4.5 million adults. The figure is based on Kandolin et al.[2] and unpublished data.

At the end of 2021, according to confirmed but partly unpublished entries, the registry included 703 cases, of which 641 were survivors giving a crude *prevalence of clinically manifest CS* at 14/100 000 population aged >18 y. Chow *et al.*[35] recently reported a CS prevalence of 4.4/100 000 for a small district in South Island, New Zealand, yet one-half of their patients did not have CS meeting the current diagnostic criteria.[3–5] No other CS-specific prevalence data exist, but the figures are likely to differ since the all-inclusive prevalence of sarcoidosis depends on geography and race, among other factors, being highest in the northern countries (Canada and Sweden, 140–160/100 000) and lowest in the East (Taiwan and Japan, 2-4/100 000).[36] The majority (≈70%) of Finns with CS are women in accord with recent observations from Europe and Japan.[11,12,25]

Diagnosis

Initial approach

The diagnosis of sarcoidosis rests on the triad of compatible clinical characteristics, proof of histology, and exclusion of other diseases. Suspicion of CS should arise, first, in patients with prevalent sarcoidosis presenting with cardiac signs or symptoms (*Table 1* and *Table 2*)[2,4,8,22,37–41] and, second, in all patients with initially unexplainable 2nd or 3rd degree AVB, sustained VAs, or heart failure. Though rare, CS has been shown to cause 20% to 34% of idiopathic high-grade AVB in middle-aged individuals,[42,43] a nearly similar proportion of idiopathic sustained VT,[44,45] and 5% of mixed VAs including frequent premature beats.[46] In pre-existing sarcoidosis, elevated cardiac troponins,[47] natriuretic peptides,[11,48] and, as newcomers, anti-heart and anti-intercalated disk antibodies[49] support the suspicion of CS. Echocardiography has limited sensitivity but can provide confirmatory evidence for the presence of CS (see *Table 2* and *Supplementary Figures 1 and 2*). Strain imaging improves its ability to detect myocardial involvement.[40,50,51] Still, both cardiac ultrasound and 12-lead ECG can look fully normal in CS.[52] In patients without known sarcoidosis, circulating lysozyme, angiotensin-converting enzyme, and soluble interleukin-2 receptor may help,[2,48,53] but only when abnormally elevated. Computed tomography of the chest can suggest intrathoracic sarcoidosis but, ultimately, the key studies involve advanced imaging with CMR and/or ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET).

Advanced imaging

^{18}F-FDG-PET

The rationale of ^{18}F-FDG-PET in suspected CS is that active inflammatory cells in sarcoid granulomas avidly take up glucose and its analogs.[37] Cardiac PET is usually combined with whole-body imaging to uncover extracardiac involvement. For diagnostic imaging, physiologic cardiac glucose metabolism is switched off by a low-carbohydrate/high-fat diet followed by fasting and, in some centers, by additional intravenous unfractionated heparin to raise the availability of fatty acids, although the contribution of heparin is unclear.[54] Regardless, 10%–15% of cardiac PET studies are diagnostic failures due to poor suppression of physiologic glucose uptake.[55] For assessment of LV scarring, parallel scanning with either PET or single-photon emission computed tomography is done using their respective perfusion tracers. PET is currently combined with chest computed tomography for co-localization and attenuation correction. Effective radiation doses approximate 7 mSv for cardiac and 10 mSv for whole-body ^{18}F-FDG-PET. In rest perfusion imaging, the doses are notably smaller.

Abnormal cardiac PET is a key criterion in the diagnostic rubrics for CS[3–5] and typically involves one or more spots of increased ^{18}F-FDG uptake on suppressed or diffuse myocardial uptake (*Figure 2*). A 'hot spot' of ^{18}F-FDG overlapping a perfusion defect is a characteristic

Table 2 Possible abnormalities on 12-lead electrocardiogram and echocardiography in patients with cardiac sarcoidosis

Twelve-lead electrocardiogram	Echocardiogram
AVB, any degree	LV dysfunction (EF < 50%)
Fragmented or prolonged QRS complex	LV wall thickening or thinning
Complete bundle branch block	Local akinesia or dyskinesia
Abnormal Q-waves	LV aneurysm
T-wave inversions	Reduced global LV longitudinal strain
Frequent premature ventricular beats or NSVT	RV enlargement and reduced RV free wall strain
Epsilon-wave	Pericardial effusion

AVB indicates atrioventricular block; EF, ejection fraction; LV, left ventricular; NSVT, non-sustained ventricular tachycardia; RV, right ventricular.
The contents of the table have been compiled from several sources.[2,37–41]

finding ('mismatch pattern'). Perfusion defects result from either LV scarring or reversible impairment of microcirculation.[33] In addition to a visual review of PET images, quantification of inflammation is possible. 'Standardized uptake value' is calculated as radioactivity concentration in the region of interest relative to the injected dose and body weight.[37] Several metrics thereof exist describing either intensity and heterogeneity of ^{18}F-FDG uptake or myocardial metabolic volume and activity.[37,54] In a meta-analysis of 17 studies involving 891 patients with suspected CS, the sensitivity and specificity of PET were 84% and 83%, respectively.[56] However, the reference was not the gold standard (myocardial histology) but CS diagnosis by criteria[57] suffering from significant limitations.[10,58] Hibernating myocardium, other forms of myocarditis, rheumatologic diseases with cardiac involvement, and some genetic cardiomyopathies may also cause abnormal cardiac ^{18}F-FDG uptake. Absence of extracardiac uptake decreases the specificity of PET for CS.[59]

^{18}F-FDG-PET scanning has therapeutic and prognostic implications, too. Initiating immunosuppression for CS presupposes proof of inflammatory activity, and repeat scans may help identify response to and relapse after therapy.[60,61] The prognostic value of PET was confirmed in a recent meta-analysis of pertinent studies,[62] though not all works are supportive.[63,64] A 'mismatch pattern' (see *Figure 2*) and RV uptake are the key predictors of cardiac events.[58,65,66] Atrial ^{18}F-FDG uptake portends atrial tachyarrhythmias.[29] In the future, cardiac PET studies can involve tracers that work without dietary preparation, such as somatostatin analogs,[54] and hybrid PET/CMR imaging may improve diagnostic accuracy.[66,67]

CMR

In suspected CS, multimodal CMR imaging visualizes not only anatomy and function but also myocardial edema, necrosis, and scarring (*Figure 3*). Besides volumetric measurements, cine CMR enables identification of abnormalities in myocardial thickness and motion, such as septal thinning (*Figure 4A*), local dyskinesia, and ventricular aneurysms.[68–70] Myocardial edema is detectable on T_2-weighted imaging,[71] and inflammation can also be seen as myocardial gadolinium enhancement 3–5 min after contrast administration.[72] Delayed postcontrast (15 min) imaging, however, is the key CMR modality in CS. Late gadolinium enhancement (LGE) reflects extracellular expansion and delayed contrast wash-out related to necrosis and edema in the acute phase and replacement fibrosis in the chronic setting.[73] Typically, LGE involves basal LV segments and the RV side of the septum, but any part of the heart can be affected (*Figure 4*).[69,70,74] LGE is most often distributed in patchy, non-ischemic pattern, but subendocardial and even transmural involvement is possible.[75] A 'hook sign' (or 'hug sign') of septal LGE continuing into the RV free wall has been coined as an imaging biomarker for CS (*Figure 5*),[76] but an identical pattern can be seen in giant cell myocarditis.[77]

The presence of myocardial LGE constitutes a major diagnostic criterion for CS.[3–5] Studies on the performance of CMR[69,70,78] have yielded sensitivities between 75% and 100% and specificities from 77% to 85% with clinical CS diagnosis[57] surrogated for myocardial histology as the reference. On the other hand, Divakaran *et al.*[59] found that only 1 of 8 cases likely to have CS by pretransplant CMR imaging ultimately had CS in the study of the explanted heart. The repeatability of CMR appears fair in suspected CS. In a recent work, 2 experts agreed on myocardial LGE in 80% of cases, and Cohen's kappa was 0.59.[79]

In addition to visual assessment, quantification of the CMR findings is possible. Myocardial T1 and T2 relaxation times enable the detection of subclinical CS and quantification of diffuse interstitial fibrosis.[80–82] Their clinical utility remains unsettled, though. More importantly, the extent of LGE can be determined as the percentage of LV mass[83] or simply as the number of involved segments. The presence and extent of LGE predict serious events in suspected CS.[84]

Confirmation of sarcoidosis histology

Biopsies

For proof of sarcoidosis histology, the HRS guideline[4] recommends, and many centers prefer, extracardiac over endomyocardial biopsy (EMB) with arguments of better sensitivity and safety. The much-criticized sensitivity of only 19%–25% for EMB is not current, however, as it represents the obsolete technique of non-targeted RV biopsies.[85,86] Selecting the ventricle and the myocardial area for biopsy with help of cardiac imaging[87] and/or intracardiac voltage mapping[88] improves EMB's sensitivity. Its yield is higher if LVEF is impaired,[85,89] PET shows metabolism-perfusion mismatch,[58] or signs of RV involvement are present.[58,90,91] The risk of serious complications is <1%.[92,93] EMB also enables myocardial immunohistochemistry and transcriptomics that may help distinguish CS from other cardiomyopathies.[94–97] At our center, prior histology of extracardiac sarcoidosis is considered diagnostically sufficient but otherwise EMB is the procedure of choice (*Figure 6*). Exceptionally, if confirmation of isolated CS is considered imperative but EMBs fail, LV biopsies can be taken under direct visual control using video-assisted thoracoscopy.[98] Diagnosing isolated CS without histology[5] is questionable[16,99] because no cardiac manifestations or imaging findings are specific for myocardial granulomas.[59,88,100] Admittedly, views differ about the importance of histology,[22,33,101] some experts even considering emphasis on tissue diagnosis 'the largest limitation of the current guidelines'.[101]

Myocardial histopathology

In our unit, typically 10 heart muscle samples are taken in a diagnostic EMB session for suspected CS. Histopathology involves an examination of ca. 50–60 myocardial sections for routine histochemical stains and additional sections for immunohistochemistry (*Figure 7*). Findings in

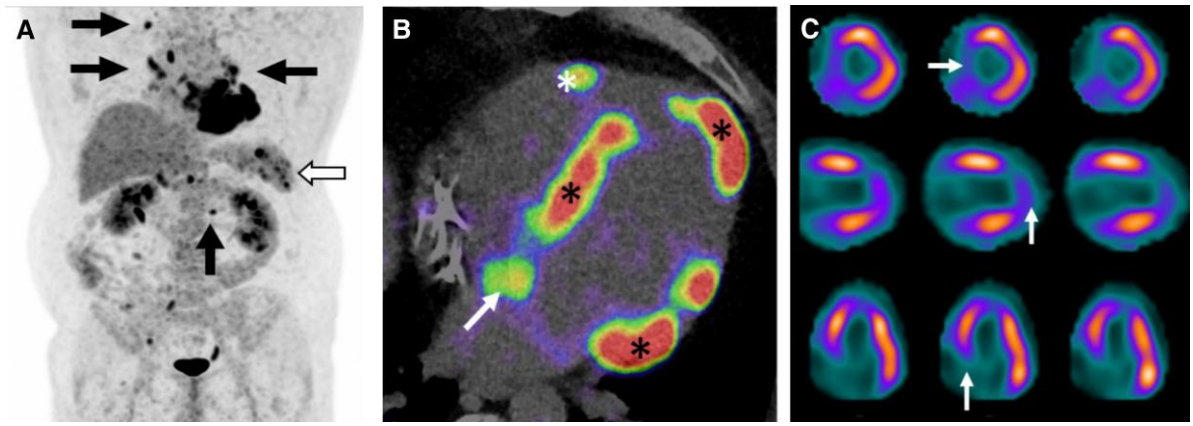


Figure 2 ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) scans of a patient with tri-fascicular block and depressed left ventricular (LV) function; cardiac sarcoidosis was verified by endomyocardial biopsy. (*A*) whole-body PET with ^{18}F-FDG positive lymph nodes (arrows) and splenic radiotracer accumulation (hollow arrow). (*B*) 4-chamber PET/CT image showing ^{18}F-FDG uptake on LV septum, apex, and basal lateral wall (asterisks), on right ventricular free wall (arrow), and on interatrial septum (arrow). (*C*) Single-photon emission computed tomography ^{99m}Tc-tetrofosmin scans showing perfusion defects (white arrows) on LV septum and apex overlapping areas of ^{18}F-FDG uptake on PET (mismatch pattern). From top to bottom, the rows represent short-axis, vertical, and horizontal views of the heart.

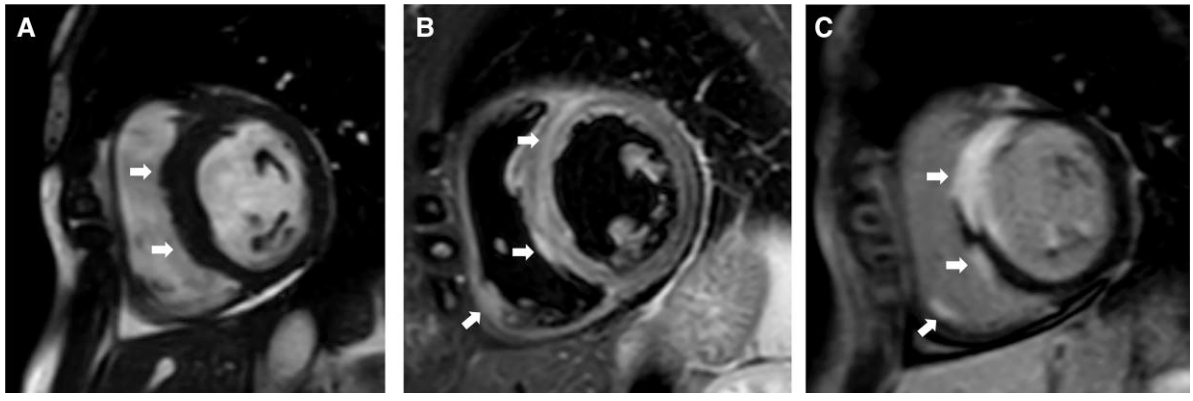


Figure 3 Magnetic resonance images of a patient with cardiac sarcoidosis, 3rd degree atrioventricular block, and normal left and right ventricular ejection fraction. The arrows highlight key findings. (*A*) short-axis cardiac cine image showing thickened ventricular septum. (*B*) T2-weighted image showing septal and local right ventricular edema indicating active inflammation. (*C*) late gadolinium enhancement image showing transmural septal, papillary muscle, and local right ventricular free wall involvement.

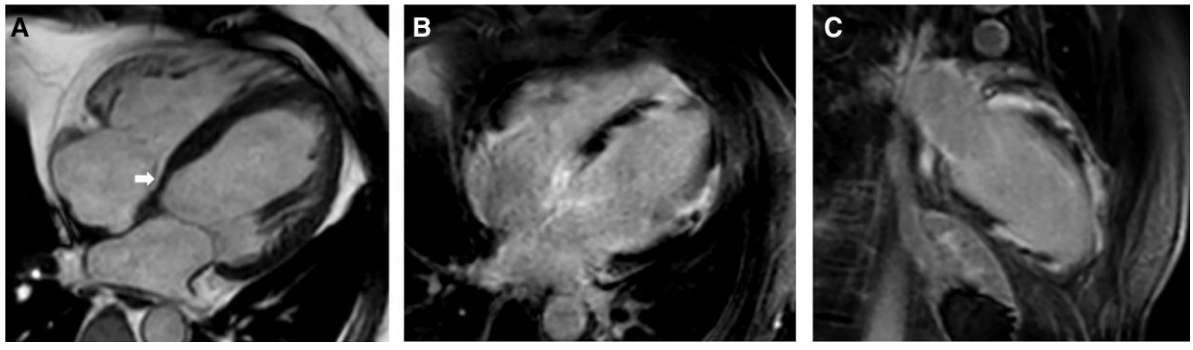


Figure 4 Magnetic resonance images of a patient with 3rd degree atrioventricular block and depressed left ventricular function; cardiac sarcoidosis was verified by endomyocardial biopsy. (*A*) apical 4-chamber cine image showing basal septal thinning (arrow) and thickened mid-septum. (*B* and *C*) apical 4- and 2-chamber images, respectively, of late gadolinium enhancement showing patchy left ventricular involvement.

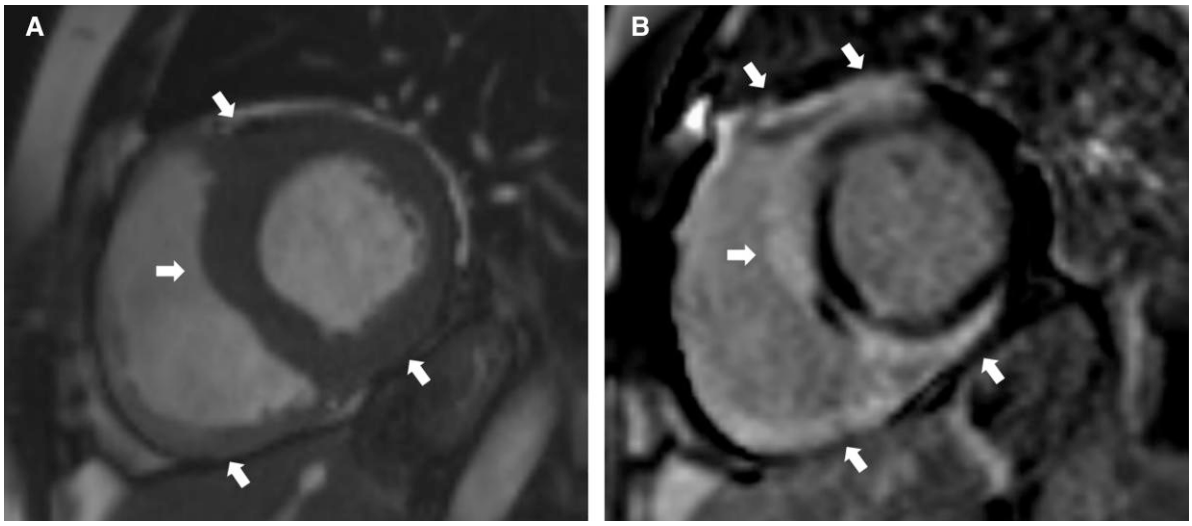


Figure 5 Magnetic resonance images of a patient with right bundle branch block, ventricular tachycardia, and depressed left and right ventricular function; cardiac sarcoidosis was verified by endomyocardial biopsy. The arrows point at key findings. (*A*) Short-axis cardiac cine image showing thickened left ventricular myocardium and inferior right ventricular wall. (*B*) A 'hook sign' pattern of cardiac sarcoidosis[76] characterized by late gadolinium enhancement in the septum continuing to ventricular insertion points and right ventricular free wall.

CS include non-necrotic granulomas and isolated giant cells with or without surrounding lymphocytic/granulocytic infiltration combined with myocardial fibrosis, sharply demarcated areas of involvement, and no extensive eosinophilia or myocyte necrosis. Non-necrotic granulomas *per se* signify sarcoidosis only if other causes are excluded.[4,5] Recently, indirect EMB signs of CS have been suggested,[102,103] including small collections of histiocytes ('microgranulomas'), lymphangiogenesis, and confluent fibrosis with fatty change.

Diagnostic criteria in societal guidelines

There exist three current sets of diagnostic criteria for CS.[3–5] The ones from the World Association for Sarcoidosis and Other Granulomatous Disorders[3] and HRS[4] are nearly identical and straightforward. The updated criteria of the Japanese Circulation Society[5] are more complex but do not, unlike the other two,[3,4] require proof of histology. *Table 3* details the HRS criteria[4] that many centers are using including ours. Although probable CS (*Table 3*) is widely considered sufficient for clinical practice, the certainty of diagnosis is not indifferent as definite diagnosis has predicted worse outcome in many studies,[25,86,104–107] though not in all.[22] The differences across the diagnostic guidelines have resulted in CS cohorts that are not entirely comparable across countries or institutions.[108,109]

The challenging diagnosis of CS has led some centers to set up formal multidisciplinary diagnostic teams,[109] while others, emphatic about imaging, have generated a tandem analysis of CMR and PET images to classify CS diagnosis into categories of increasing likelihood.[110,111] Yet, imaging-based diagnosis of CS (probable-to-high likelihood) has shown limited specificity for definite CS.[59,100] Diagnostic collaboration across specialties is indispensable regardless of whether cardiologists or a multidisciplinary team are responsible for the diagnosis of CS.

Differential diagnosis

Lymphocytic, eosinophilic, and giant cell myocarditis with acquired and genetic cardiomyopathies and granulomatous infections constitute differential diagnostic alternatives to CS beyond ischemic heart disease. The distinction between CS and giant cell myocarditis defies the skills of clinicians and pathologists alike,[24,97] and whether they represent a one-disease continuum is debated. Although CS can disguise as a phenocopy of arrhythmogenic right ventricular cardiomyopathy, impaired AV conduction, LV dysfunction, septal LGE, and mediastinal lymphadenopathy are more common in the former.[112] Desmoplakin cardiomyopathy[113] can also imitate CS, and gene tests with pedigree analysis may be needed to distinguish CS from genetic cardiomyopathies. RV sarcoidosis must be distinguished from RV dysfunction due to sarcoidosis-associated pulmonary hypertension.[114] Advanced CS can be mistaken for dilated cardiomyopathy. Several transplant centers[115–117] have identically reported that all their cases of CS in the explanted heart had a pretransplant misdiagnosis of idiopathic dilated cardiomyopathy!

Screening

Given the notoriety of CS, cardiac screening of patients with extracardiac sarcoidosis appears desirable or even imperative.[118] Yet, whether detailed screening ultimately is beneficial, considering the conceivable harms and biases,[119] has not been thoroughly debated in the case of sarcoidosis. The American Thoracic Society[120] recommends symptom history and 12-lead ECG for routine screening, the HRS[4] advising echocardiography in addition; CMR and/or FDG-PET are recommended should abnormalities be noted. Dedicated screening studies, small as they are, suggest a low risk of serious events given absent cardiac symptoms and ECG abnormalities.[12,121–124] In a Danish epidemiologic study[125] of 11 834 sarcoidosis patients free of cardiac history, the 10-year risks were higher than in the background population but still only 3.18% for heart failure, 0.96% for VAs or implantation of a cardioverter-defibrillator, and 0.94% for slow arrhythmias or pacemaker implantation. All things considered, assessment of cardiac symptoms and 12-lead ECG on scheduled surveillance visits, followed by CMR in case of abnormalities, appears a sensible approach today.

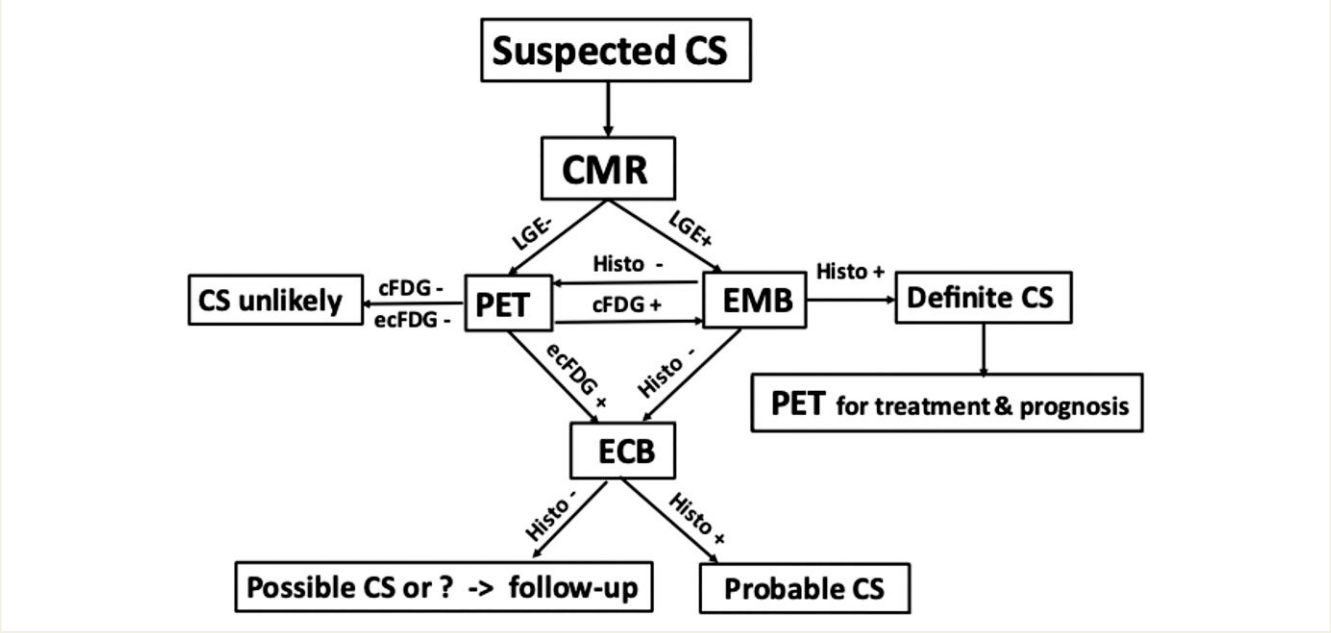


Figure 6 Flowchart for cardiac imaging and biopsies at Helsinki University Hospital for suspected cardiac sarcoidosis (CS) after exclusion of ischemic heart disease and in the absence of histologically verified extracardiac sarcoidosis. If cardiac magnetic resonance (CMR) shows late gadolinium enhancement (LGE), imaging-guided endomyocardial biopsy (EMB) is performed first. If either CMR or EMB is negative, whole-body positron emission tomography (PET) is done. PET being positive, either EMB or extracardiac biopsy (ECB) is performed depending on PET and CMR findings and patient's preferences. cFDG and ecFDG indicate cardiac and extracardiac uptake of fluorodeoxyglucose, respectively; histo, histology of sarcoidosis.

Treatment and follow-up

The care of clinically manifest CS involves immunosuppression to control the underlying myocardial inflammation and medical and device therapy for the consequences of cardiac injury and scarring. Although there exist societal guidelines for treatment,[4,5,126] their recommendations are based on evidence of low or very low quality. The care of CS should be handled in tertiary referral centers.

Immunosuppression

Initial therapy

In CS, unequivocal clinical manifestations with evidence of active inflammation on EMB or PET indicate initiation of immunosuppression.[4,5,126] In subclinical disease with absent LV dysfunction, the benefit of immunosuppression is unknown, and treatment decisions must be individualized in consideration of the extent of myocardial inflammation, other organ involvement, and risks of therapy.

Nonspecific immunosuppression with corticosteroids constitutes the mainstay of treatment.[4,5,126,127] A review of 34 clinical reports involving >1000 patients concluded that corticosteroids improve AV conduction in 40% of patients and may prevent the deterioration of LV function, whereas their effects on arrhythmias and mortality remain ambiguous due to poor data quality.[127] Observations contradict whether corticosteroids benefit in severe LV dysfunction.[2,25,128,129]

In general, treatment is initiated with solo prednisone at a dose of 0.5 mg/kg/day. Yet, it is prudent to adjust the initial immunosuppression to the seriousness of the clinical manifestations. Rapidly progressive heart failure, life-threatening arrhythmias, and extensive inflammation on cardiac PET should prompt an upfront addition of another immunomodulator or intravenous pulses of methylprednisolone (500–1000 mg/day in 2–3 successive days).[130] Although there is no robust agreement on the detailed treatment protocol, prednisone is usually titrated down every 4 weeks in decrements of 5–10 mg until a maintenance dose of 10 mg/day is reached. The effect of treatment is checked initially at 3– 6 months intervals by assessing symptoms, LV function, 12-lead ECG, arrhythmia burden, and circulating cardiac biomarkers. ECG changes raising suspicion of active inflammation include worsening atrioventricular or intraventricular conduction, increased ventricular ectopy, non-sustained VT, and new ST-T changes; whereas decreasing EF, new wall-motion abnormalities, and increasing mitral regurgitation suggest persisting disease activity on echocardiography. In clinical follow-up, the toxic effects of steroids are also addressed with all other concerns the patient raises. Here the assistance of a nurse specialist is important. Regarding advanced imaging, follow-up CMR studies have a limited role due intracardiac devices causing troublesome image artifacts.[131,132] Instead, many centers repeat FDG-PET studies routinely to follow the activity of CS and to tailor treatment accordingly.[61,76,130,133] Sensible as it sounds, the 'routine PET strategy' has not been shown to improve either the quality of life or event-free survival, yet it exposes patients to cumulative ionizing radiation and may lead to treatment of images instead of patients. In a recent study of immunosuppression for suspected active CS, the rate of major cardiac events did not differ statistically significantly between patients showing a complete clearance of ^{18}FDG uptake vs. no response on early follow-up PET.[134] We prefer a 'selective PET strategy' where repeat studies are done if there are discrepant clinical observations or if either insufficient treatment response or relapse is suspected. In our practice, corticosteroids are discontinued after 12 to 16 months of therapy supposing absent signs of disease inactivity. Follow-up visits continue annually for 3–5 years and every other year thereafter. Late relapses are possible.

Second-line therapy

Second-line immunosuppressive agents, including methotrexate, azathioprine, mycophenolate mofetil, leflunomide, and cyclophosphamide, are initiated in

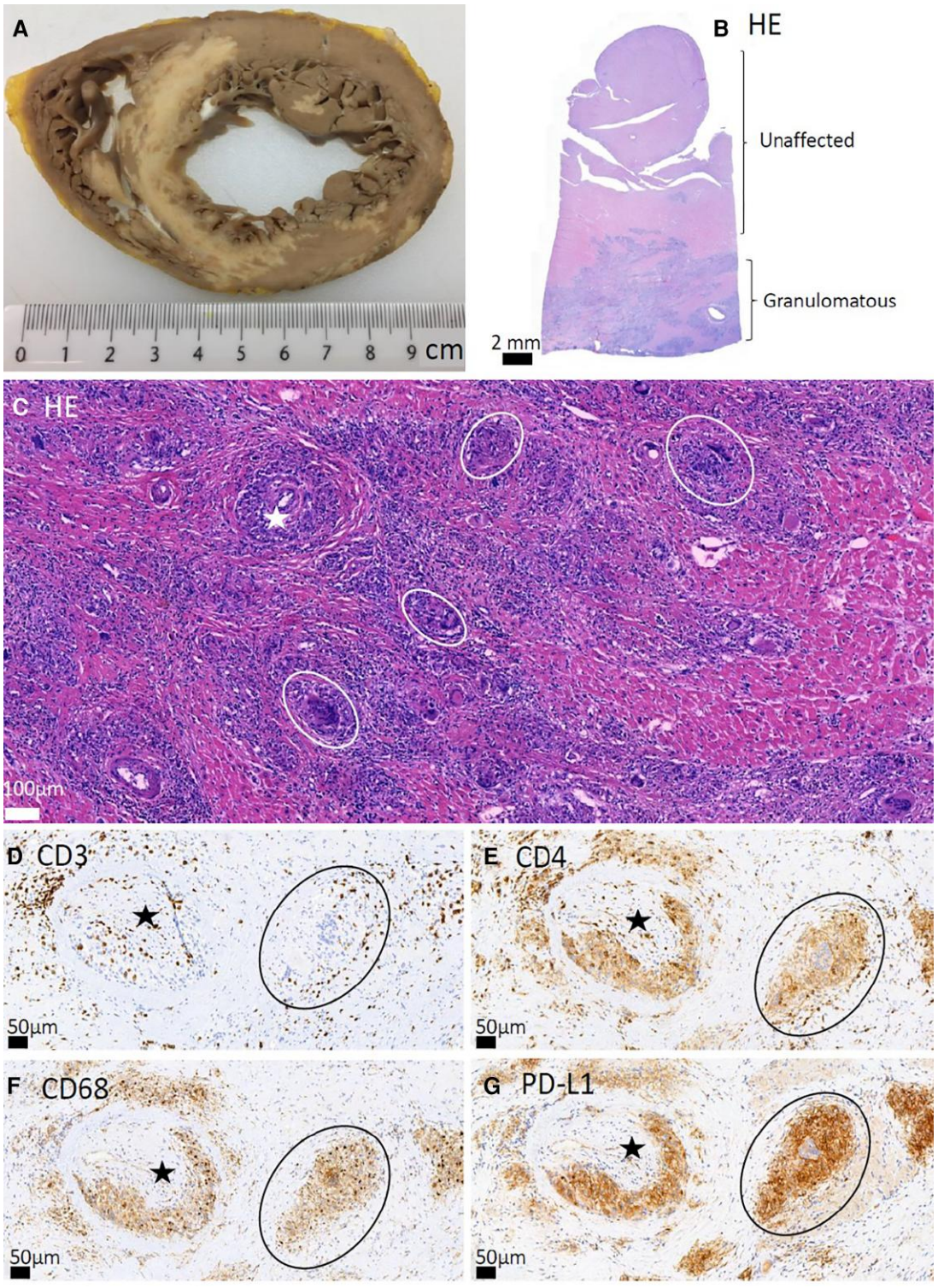


Figure 7 Histopathology of cardiac sarcoidosis. Sharply demarcated ('geographical') inflammatory lesions in a gross photo of an explanted heart (*A*) and in low-magnification hematoxylin-eosin (HE) staining (*B*). In panels (*C–G*), stars mark small coronary artery branches with vascular wall granulomas and circles encompass non-caseating granulomas. In panel **D**, CD3 immunostaining highlights T cells, and in panel **E**, CD4 antibody stains T cells intensely and macrophages and giant cells less strongly. Macrophages and giant cells can also be highlighted with CD68 (*F*) and PD-L1 (*G*) antibody staining. Scalebars are shown in each panel.

Table 3 The heart rhythm society's criteria for the diagnosis of cardiac sarcoidosis[4]

1. Histological diagnosis from myocardial tissue, *definite cardiac sarcoidosis*
requires presence of non-necrotizing granulomas with no alternative cause
2. Clinical diagnosis from noninvasive and invasive studies, *probable cardiac sarcoidosis*
requires histologic diagnosis of extracardiac sarcoidosis and presence of one or more of the following:
–cardiomyopathy or atrioventricular block responsive to immunosuppression
–unexplained reduced left ventricular ejection fraction (<40%)
–unexplained sustained ventricular tachycardia (spontaneous or induced)
–2nd degree (Mobitz type II) or 3rd degree heart block
–patchy uptake on dedicated cardiac 18-F fluorodeoxyglucose PET[a]
–late gadolinium enhancement on CMR[a]
–positive gallium uptake[a]
and exclusion of other causes for the cardiac manifestations

CMR indicates cardiac magnetic resonance; PET, positron emission tomography.
[a]in a pattern consistent with cardiac sarcoidosis.

case corticosteroids have insufficient efficacy or their dose needs a reduction to spare the patient their toxic effects. Although small studies[135,136] and some expert opinions[137] support combination therapy from the beginning, no good evidence for improved outcome exists.[126] Methotrexate in weekly doses of 10–20 mg is used most, while our preference has been azathioprine 1–2 mg/kg body weight per day. Both need precautions and careful follow-up for adverse effects including leukopenia, hepatotoxicity, and gastrointestinal complications.[138] Genetic defects in the activity enzymes degrading thioguanine increase the toxicity of azathioprine and need to be identified by genotyping before therapy or when problems appear.

Third-line therapy

Biologic anti-tumor necrosis factor (TNF) agents can prevent granuloma formation, and observational data support their efficacy in CS when other therapies have failed.[139–142] Infliximab is a chimeric TNF antibody which in doses <10 mg/kg is well tolerated even in patients with impaired LV function.[143] Before the start of therapy, comprehensive screening for tuberculosis and viral infections is needed, and vaccination status must be updated. In our practice, 5 mg/kg of infliximab is administered at weeks 0, 2, and 4, and every 8th week thereafter for one year or until signs of inflammation abide. Adjunct therapy with low-dose methotrexate or azathioprine reduces the production of neutralizing antibodies to infliximab. Adalimumab, a human monoclonal TNF antibody, is a subcutaneously administered alternative.[141,142] Although B lymphocyte-targeted therapy with rituximab has had some success in CS,[144] the experience remains small for conclusions. In biologic therapy, surveillance for infectious and other complications is critical.

Ongoing trials

A few prospective controlled studies, long overdue in CS, are underway on medical therapy. The CHASM-CS trial probes the hypothesis that a low-dose prednisone-methotrexate combination is as effective as a standard dose of prednisone.[145] The MAGIC-ART trial tests the influence of anakinra, an interleukin-1 receptor antagonist, on biomarkers of the activity of CS.[146] The J-ACNES trial compares the therapeutic effects of corticosteroids given alone or together with antibiotics based on the assumed pathogenetic role of *Propionibacterium acnes*.[147] The RESOLVE-Heart is an industry-driven trial focusing on the safety of namilumab, a monoclonal antibody targeting the granulocyte-macrophage colony stimulating factor, in active CS (https://clinicaltrials.gov/ct2/show/NCT05351554).

Control and prevention of symptomatic VAs and SCD

Symptomatic VAs

The observed effects of immunosuppression on symptomatic VAs in CS are unpredictable and partly confusing.[26,127,148] Still, corticosteroids are recommended if there is proof of inflammatory activity.[4] Antiarrhythmic drugs, mainly amiodarone or sotalol for VT, are started concomitant with immunosuppression or following an insufficient response. If medical therapy fails, catheter ablation can be considered.[4] In a meta-analysis of 15 studies involving >400 patients with refractory VT, freedom from recurrences was 45% after the first ablation and 63% after repeated procedures.[149] A varying proportion of patients, 13% to 40%, needed epicardial ablation. Importantly, VT ablation helps control stormy or incessant VTs.[150] Preceding ablation, intravenous methylprednisolone 40–80 mg/day is worth a trial if VT storm associates with active inflammation.[151] In cases refractory to medical and ablative therapy, bilateral cardiac sympathectomy may be considered.[152]

Prevention of SCD

Patients presenting with clinically manifest CS have a 10% risk of SCD over 5 years of follow-up.[107] In subclinical CS, the risk is unknown but likely much lower. As there is no good evidence for the preventive efficacy of any medical therapy, the question of when to recommend an implantable cardioverter-defibrillator (ICD) attains crucial importance. *Table 4* summarizes the pertinent recommendations given by the HRS,[4] the ACC/AHA/HRS consortium,[153] and the European Society of Cardiology (ESC).[154] All replicate the general ICD indications for secondary prevention and recommend implantation when LVEF is ≤35% or permanent pacing is needed. Of note, permanent pacing is recommended for high-grade AVB even despite improvement of conduction with steroid therapy.[4,155] History of syncope is an ICD indication by the North American guidelines[4,153] but not by the European one,[154] which also recommends programmed electrical stimulation (PES) and an ICD for inducible sustained VAs only in the presence of LV dysfunction (EF 35%–50%).[154] Both the AHA/ACC/HRS consortium and the ESC recommend ICD implantation if advanced cardiac imaging reveals signs of 'extensive' or 'significant' LV scarring, but, unfortunately, what quantities these qualifiers stand for remains undefined.[153,154] In our experience,[107] 85% of patients with clinically manifest CS meet the HRS indications, and practically all meet the ACC/AHA/HRS indications for an ICD at disease presentation. Those 15% judged not to benefit from the device by the HRS statement,[4] still have a combined risk of SCD, sustained VAs, and *de novo* ICD indications exceeding 50% at 5 years from presentation.[107] In such patients, long-term arrhythmia monitoring using an implantable loop recorder may help early detection of serious arrhythmias, but its prognostic impact remains unknown.[156]

Table 4 Current recommendations by expert societies for an implantable cardioverter-defibrillator in patients with cardiac sarcoidosis

Class[a]	2014 HRS Consensus Statement on Management of Arrhythmias in Cardiac Sarcoidosis[4]	2017 AHA/ACC/HRS Guideline for Management of Ventricular Arrhythmias and Prevention of Sudden Cardiac Death[153]	2022 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[154]
I	Prior aborted cardiac arrest, documented spontaneous sustained ventricular tachycardia, or LVEF ≤ 35%[b,c]		
IIa	LVEF > 35% with an indication for permanent pacemaker		
	History of syncope compatible with arrhythmogenic etiology		
	Inducible sustained ventricular arrhythmia at PES		Inducible sustained monomorphic ventricular arrhythmia at PES in a patient with LVEF 35%–50% and minor LGE at CMRI
		LVEF > 35% with evidence of myocardial scar (or 'extensive scar') by CMRI or PET[c]	LVEF >35% with significant myocardial LGE at CMRI after resolution of acute inflammation
IIb	LVEF 36%–49% or RVEF < 40%[b]		

ACC indicates American College of Cardiology; AHA, American Heart Association; CMRI, cardiac magnetic resonance imaging; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; PES, programmed electrical stimulation; PET, positron emission tomography; RVEF, right ventricular ejection fraction.

[a]Class I is recommended ('is useful/indicated/beneficial', 'should be performed'); Class IIa, modest recommendation ('can be useful/beneficial', 'should be considered'); and Class IIb, weak recommendation ('usefulness is unknown/uncertain', 'may/might be considered').

[b]2014 HRS guidance presupposes optimal medical therapy and a period of immunosuppression in the presence of active inflammation.

[c]2017 ACC/AHA/HRS guideline presupposes meaningful expected survival ≥1 year.

The use of PES to evaluate the risk of SCD is generally recommended in CS without severe LV dysfunction or other ICD indications for primary prevention.[4,153] The 2022 ESC guideline,[154] however, does not recommend PES if LVEF is >50% and there is no LGE on CMR imaging. A recent meta-analysis[157] found that non-inducibility is strongly associated with absence of future VAs. Yet, CS can progress, and further scarring may increase the initially low arrhythmogenicity. More research is needed focusing on the risk and predictors of SCD. Quantitative data from analyses of MRI, FDG-PET, and circulating biomarkers may help,[58,62,63,84,106,158,159] and involvement of the right ventricle needs more emphasis.[58,65,66,160] Whether the diagnosis of CS is definite or probable also deserves consideration.[107] In the future, artificial intelligence may help predict the SCD risk in CS.[161]

In Finland, the cumulative rate of ICD implantations in clinically manifest CS has been 75% over the last three decades.[107] Due to our recent observations,[107] and pending sharper risk assessment, we currently discuss implantation of an ICD with every patient having clinically manifest CS. Whether to ultimately implant or not rests on a shared decision with a patient fully informed of the risk of fatal arrhythmias, the conceivable benefits and harms of an ICD, and the uncertainties involved.

The complications following ICD implantations appear to be more common in CS than in the general ICD population.[162] Inappropriate therapies have been recorded in 15% to 24% of patients,[162,163] and the combined incidence of other complications, including lead problems and infections, has exceeded 15%.[162] It is prudent to start immunosuppression post-implantation to reduce the risk of device infections.

Treatment of heart failure

All guideline-directed medical therapies[164] can be used to treat CS-related congestive heart failure. Corticosteroids are indicated if there is proof of active myocardial inflammation. Aggressive immunosuppression and mechanical support may be needed in the rare cases of CS-related fulminant myocarditis.[165] Observations on the use of cardiac resynchronization thereapy (CRT) devices in CS have been somewhat disappointing.[166,167] Widespread scarring, suboptimal CRT pacing, and false CS diagnoses constitute possible causes for the considerable proportion of non-responders.[168]

LV assist devices and cardiac transplantation can be considered for CS-related terminal heart failure. Large registry studies have shown that patients with CS have as good post-transplant survival and a similar risk of late complications as the non-CS transplant recipients.[169,170] Recurrence of CS in the allograft is rare and has not resulted in graft failure.[171]

Long-term outcome and prognostic factors

Table 5 shows the 5-year and 10-year survival rates in recent CS cohorts with a comparative summary of the cohorts' characteristics.[25,38,105–107] Although the study populations differ in several key aspects, their 5-year survival prospects are consistently 90% or higher. In our 398-patient cohort of clinically manifest CS followed for a median of 5 years,[107] eight patients suffered a SCD, seven died of heart failure, nine suffered post-transplant deaths (of 25 undergoing transplantation), and nine died of non-cardiac causes. The overall survival estimate was 96% at 5 years and 86% at 10 years from presentation (*Figure 8A*). For transplant-free survival, the 5-year and 10-year estimates were 92% and 78%, respectively (*Figure 8B*).

The prognostic factors in CS fall into three main categories. One is the extent of myocardial involvement. The predictive values of LVEF,[2,25,63,106,172] quantity of LGE on CMRI,[173–175] summed rest score of segments with perfusion defects[63] or segments with perfusion-metabolism mismatch,[158] circulating natriuretic peptides,[106] LV global longitudinal strain,[51] and right ventricular EF[160] all reflect aspects of the extent of cardiac involvement. The second category relates to how CS shows itself. Presentations with sustained VT[25,63,106,172] or heart failure[2] imply poor outcome, while lone AVB is prognostically less ominous.[176] *De novo* and *clinically isolated* presentation also predict

Table 5 Contemporary cohort studies reporting long-term survival in cardiac sarcoidosis

	Cacoub et al[38]	Kusano et al[25]	Kitai et al[105] Nabeta et al[106]	Nordenswan et al[107]
Size of cohort, *n*	157	422	512	398
Nationality	French	Japanese	Japanese	Finnish
Time span of diagnoses	1980–2016	NA	2001–2017	1988–2017
Mean age at diagnosis, y	40	60	62	51
Female sex, %	41	68	64	72
Histology of sarcoidosis, %				
myocardial	2	18	11	48
extracardiac	98	39	52	52
missing	0	43	37	0
Presenting manifestation, %				
high-grade AVB	10	40	43	54
VT or VF	8	18	20	18
heart failure	10	NA	21	14
Impaired LVEF (<50%), %	26	48	52	44
Positive FDG-PET, *n* (%)[a]	12/37 (32)	273/406 (67)	324/342 (95)	236/265 (89)
LGE on CMRI (%), *n* (%)	39/91 (44)	184/216 (85)	282/307 (92)	201/208 (98)
Immunosuppressive treatment, %	96	84	88	96
ICD implantation rate, %	3	33	28	74
Heart transplantation rate, %	1.3	0.5	0	6.3
Median follow-up, y	8	5	2.9	5.0
Overall survival, %[b]				
5-year	94	90	90	96
10-year	90	81	82	86

AVB, indicates atrioventricular block; CMRI, cardiac magnetic resonance imaging; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NA, not available; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]focal or focal on diffuse myocardial uptake of ^{18}F-FDG suggestive of active inflammation.
[b]survival percentages are Kaplan–Meier estimates.

worse outcome, likely due to delayed diagnosis and more advanced disease.[2,14,15,18,21] The third prognostic category concerns the certainty of diagnosis: definite, myocardial histology-based CS diagnosis portends poorer outcome than probable diagnosis supported by extracardiac histology.[25,86,104–107] Whether the current treatment improves prognosis cannot be concluded from the data available today.

Challenges for future research

The prevailing challenges of CS relate to the unknown molecular–genetic etiopathogenesis with its diagnostic and therapeutic ramifications, the need and forms of cardiac screening, the prognosis of subclinical cardiac involvement and whether watchful waiting is safe, how to diagnose CS leaving as little room for doubt as possible, how to tailor immunosuppression and when to discontinue, and how to best assess the risk of SCD and identify patients benefiting from an ICD. As the first step, we would welcome universal adoption of a single set of diagnostic criteria. That would facilitate the much-needed larger prospective clinical trials.

Author contributions

J.L., V.U., P.P., M.I.M., and M.K. conceived and designed the contents of the review, drafted the manuscript, and made critical revision of the manuscript for key intellectual content.

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Supplementary data

Supplementary data is available at *European Heart Journal* Online.

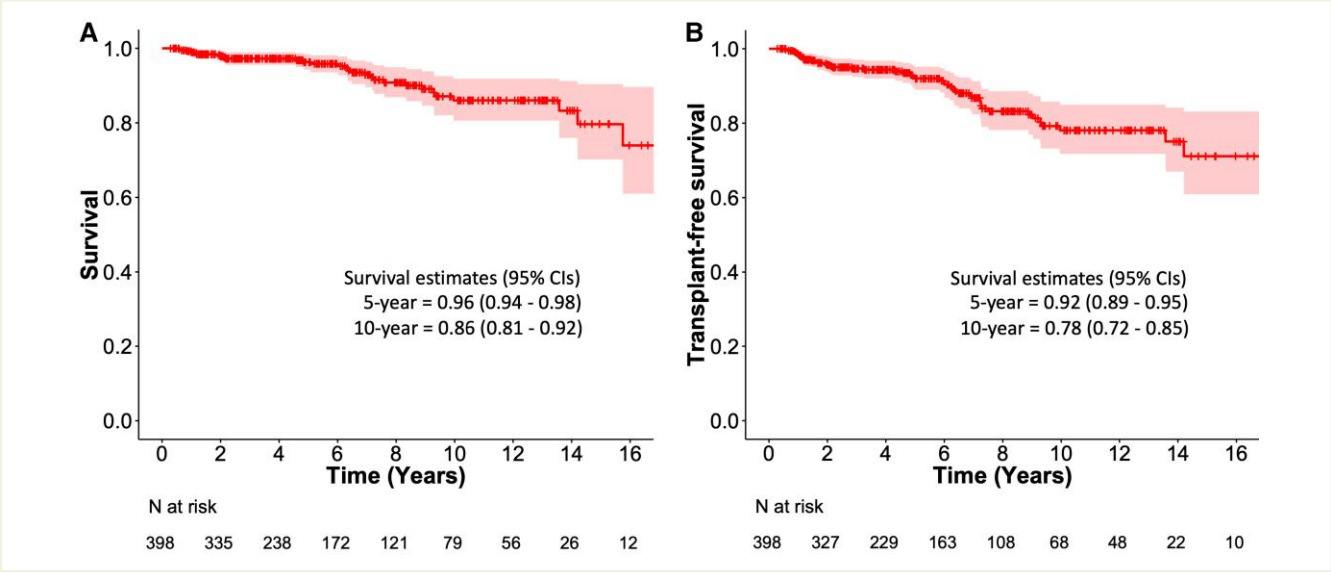

Figure 8 Kaplan–Meier curves of overall (*A*) and transplant-free (*B*) survival in a cohort of 398 patients with clinically manifest cardiac sarcoidosis diagnosed in Finland from 1988 through 2017 and followed for a median of 5.0 years. The figures are based on the data reported by Nordenswan et al.[107] and summarized in *Table 5*. The survival graphs reflect the care of cardiac sarcoidosis based on the following principles: requirement of diagnostic histology and pursuit of definite diagnosis, consistent use of corticosteroids with azathioprine and infliximab as the main additional immunomodulators, clinical follow-up with selective instead of routine repeats of positron emission tomography, frequent use of implantable cardioverter-defibrillators, and no sarcoidosis-specific restrictions to heart transplantation.

Data availability

No new data were generated or analysed in support of this review.

Conflict of interest

Lecture and/or advisory board fees from Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Takeda, Bayer, Amgen, Roche, and Aiforia technologies oy (M.I.M.). Lecture fee from Pfizer and research collaboration with GE healthcare (V.U.).

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