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Isolated cardiac sarcoidosis: A focused review of an under-recognized entity

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Abstract

There is accumulating evidence for the existence of a phenotype of isolated cardiac sarcoidosis (ICS), or sarcoidosis that only involves the heart. In the absence of biopsy-confirmed cardiac sarcoidosis (CS), existing diagnostic criteria require the presence of extra-cardiac sarcoidosis as an inclusion criterion for the diagnosis of CS. Consequently, in the absence of a positive endomyocardial biopsy, ICS is not diagnosable by current guidelines. Therefore, there is uncertainty regarding the epidemiology, pathobiology, clinical characteristics, prognosis, and optimal treatment of ICS. This review will summarize the available data related to the prevalence and prognosis of ICS and will discuss challenges surrounding the diagnosis and management of this under-recognized entity.

Keywords

Cardiac sarcoidosis; cardiac PET; cardiac MRI

INTRODUCTION

Sarcoidosis is thought to be a systemic disease characterized by multi-organ infiltration by non-necrotizing granulomas. Sarcoidosis can affect any organ in the body, including the

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heart.¹ The prevalence of cardiac sarcoidosis (CS) among patients with systemic sarcoidosis is 20–27% in the United States^{2–4} and has been reported to be as high as 58% in Japan.⁵

There is accumulating evidence for a distinct clinical phenotype characterized by isolated cardiac involvement.^{6–22} Established criteria for the diagnosis of CS are insensitive for ICS since they require either evidence of extra-cardiac disease or a positive endomyocardial biopsy (EMB), which itself is highly limited in its sensitivity.^{23,24} Therefore, alternative diagnostic approaches to diagnose ICS would facilitate further investigation into the epidemiology, pathobiology, clinical course, and optimal treatment of ICS. The need for such alternative approaches is underscored by recent data suggesting that patients with ICS may have worse long-term outcomes as compared with patients with systemic sarcoidosis and CS.²⁰ If this is true, then early recognition of ICS and timely initiation of appropriate therapy would be of paramount importance.

This review will focus on 4 key questions related to ICS: 1. How common is it? 2. How does it present clinically? 3. What is the optimal approach to diagnosis?, and 4. What data exist to guide therapy and assess prognosis? Box 1 provides a summary of the current knowledge gaps in these areas. To address these knowledge gaps, we performed a comprehensive search of the literature using the search items “cardiac sarcoidosis” and “isolated cardiac sarcoidosis” and reviewed all relevant results.

Box 1

Summary of current knowledge about ICS

Epidemiology

As many as 25% of patients with CS may have ICS

Patients with ICS have worse LV systolic function at presentation as compared with patients with systemic sarcoidosis and CS

Diagnosis

The diagnosis of ICS is challenging, in part because the sensitivity of EMB is limited

Current clinical criteria do not provide a means of diagnosing ICS in the absence a positive EMB, even when advanced imaging techniques such as MRI or PET are abnormal

Therapy

ICD therapy is effective at aborting ventricular dysrhythmias in patients with ICS

Prognosis

Patients with ICS have more ventricular arrhythmias compared with patients with systemic sarcoidosis and CS

Patients with ICS may have worse event-free survival compared with patients with systemic sarcoidosis and CS

How Common is ICS?

Because established diagnostic criteria for CS are insensitive for the detection of ICS, the true prevalence of ICS is not known. Reported rates of ICS among patients with CS vary widely, and range from 27 to 54%.^{8,20–22,25} The frequency of ICS also appears to vary significantly depending on the diagnostic method and clinical presentation. For instance, ICS occurs at a higher frequency when the presentation is with advanced heart failure (52%),²² and at a lower frequency in cases of sudden cardiac death examined post-mortem (29%).²⁵

Tavora et al.²⁵ reviewed all autopsies performed at the Armed Forces Institute of Pathology from 1995 to 2008 on decedents with sudden cardiac death and either a history of, or findings at autopsy consistent with, CS. Of the 46 patients included, 41 had pathologic evidence of CS. Of these, 30 (73%) had no known clinical history of extra-cardiac sarcoidosis (ECS). However, only 12 (29%) were free of ECS on autopsy. Hence, in this autopsy study of patients with sudden death and known or suspected CS, the rate of ICS was 29%.

Kandolin et al.⁸ studied a series of 74 consecutive patients treated for definite or suspected CS at a single center in Finland from 2000 to 2010. Using EMB, explant pathology at cardiac transplantation, or autopsy as the basis for diagnosing CS, and using clinical evaluation, chest x-ray, and liver enzymes as the basis for excluding ECS, these authors reported a rate of ICS of 33 out of 74 patients (45%). However, 15 of these 33 patients underwent whole-body positron emission tomographic (PET) imaging with F-18 fluorodeoxyglucose (FDG), which demonstrated focal extra-thoracic uptake in 7. If, based on this, it is assumed that the rate of clinically silent but radiographically evident ECS among those initially suspected to have ICS is approximately 50%, then the estimated rate of ICS in this study would fall to approximately 23%.

In a subsequent analysis, Kandolin et al.²⁰ studied all patients with a histologic diagnosis of CS in Finland from 1988 to 2012, a total of 110 patients. The diagnosis of CS in this analysis required either positive cardiac histology (EMB, mediastinal lymph node biopsy, explant pathology at cardiac transplantation, or autopsy) or histologic evidence of ECS plus clinical and imaging findings consistent with CS (e.g., late gadolinium enhancement on cardiac magnetic resonance imaging). The exclusion of ECS was based on clinical evaluation and chest X-ray. The authors reported a rate of ICS of 71 out of 110 patients (65%). However, 30 of these 71 were additionally studied with whole-body FDG PET, and 12 were found to have focal extra-cardiac FDG uptake. If, based on this, it is assumed that the rate of clinically silent but radiographically evident ECS among those initially diagnosed with ICS is approximately 40%, then the estimated rate of ICS in this study would fall to approximately 26%.

Tezuka et al.²¹ studied 83 consecutive patients with a clinical diagnosis of sarcoidosis treated at a single center in Japan from 1997 to 2013. The diagnosis of CS was based on the 2006 Japanese Ministry of Health and Welfare criteria (JMHW). The method of excluding ECS, which was only described for the 11 patients with ICS, included clinical skin examination and clinical ophthalmologic examination. Of the 83 patients studied, 41 had CS

by JMHW criteria. Of these, 11 (27%) had no evidence of ECS. Hence, in this study, the rate of ICS was 27%.

Lastly, Sperry et al.²² reported 27 cases of individuals presenting with advanced heart failure and biopsy-proven CS, usually at the time of heart transplantation. Among these, only 30% met JMHW criteria for CS before cardiac biopsy, and only 48% had known extra-cardiac involvement. Table 1 summarizes the current data regarding the prevalence of ICS.

How Does ICS Present Clinically?

Owing to the lack of consensus on diagnostic criteria for ICS, relatively little is known about its clinical features and if they differ from those of systemic sarcoidosis with CS. However, data from several studies suggest that patients with ICS may present with more advanced heart disease than those with systemic sarcoidosis and CS. In their 2011 study, Kandolin and colleagues found that 82% of patients with ICS had impaired left ventricular (LV) systolic function, defined as a an LV ejection fraction <50%.⁸ In their subsequent 2015 study, the same authors found that 69% of patients with ICS had impaired LV systolic function, compared with 41% of patients with systemic sarcoidosis and CS, a difference that was statistically significant.²⁰ Similarly, in their 2015 study described above, Tezuka and colleagues found that 82% of patients with ICS had impaired LV systolic function, compared with 50% of patients with systemic sarcoidosis and CS, a difference that was not statistically significant.²¹ Finally, Tavora et al.²⁵ reported that 10 out of 12 patients (83%) with ICS presented with sudden cardiac death attributable to CS. By comparison, 15 of 29 patients (52%) with systemic sarcoidosis presented with sudden cardiac death attributable to CS.

While these comparisons are mostly underpowered due to the small sizes of the sub-groups compared, these data raise the question of whether patients with ICS are at greater risk for sudden cardiac death than their counterparts who have systemic sarcoidosis with CS. It is unclear if such differences are due to delayed recognition, and/or treatment of ICS vs. systemic sarcoidosis with CS, or if patients with ICS have a distinct clinical course. Lastly, a selection/detection bias effect cannot be excluded as increasing numbers of patients with systemic sarcoidosis are being “screened” for cardiac involvement, whereas ICS will generally come to clinical attention after the onset of cardiac symptoms due complete heart block, sustained ventricular arrhythmias, and/or significant left ventricular systolic dysfunction.

What Is the Optimal Diagnostic Approach to Cases of Suspected ICS?

The diagnosis of ICS is challenging for a number of reasons. First, the diagnosis of CS itself is fraught with difficulty, as the clinical manifestations of CS can be varied and non-specific, and existing diagnostic criteria have suboptimal sensitivity.²⁶ Second, because existing diagnostic criteria for CS require either positive EMB or evidence of ECS, the diagnosis of ICS in effect relies on EMB. However, the sensitivity of EMB for the diagnosis of CS is suboptimal at approximately 20–40%, which may in part be due to the patchy nature of the disease.^{8,21,23,24} Therefore, alternative methods for diagnosing ICS are needed.

Nery and colleagues reported an illustrative case of EMB guided by electro-anatomical mapping in the workup of suspected ICS.¹³ In this case, the patient fulfilled clinical criteria for arrhythmogenic right ventricular cardiomyopathy, but there was strong suspicion for CS based on intermittent heart block. An initial EMB was inconclusive. A repeat EMB was guided by electro-anatomical mapping, with samples taken from low-voltage regions in the right ventricular septum. This revealed the classic non-caseating granulomas of sarcoidosis. While such an approach would likely improve the diagnostic yield of EMB, it may not be appropriate for all cases of suspected ICS. First, not all patients may demonstrate low-voltage regions accessible from the right heart. Second, not all areas of low voltage may represent the active inflammatory phase of CS, and biopsies may be inconclusive in cases of non-specific fibrosis.

While mediastinal lymph node involvement would not be consistent with a strict definition of ICS, it is instructive to consider the diagnostic yield of lymph node (LN) biopsy in sarcoidosis that is limited to the mediastinum. Otsuka and colleagues reported the results of chest computed tomographic (CT) imaging in a series of 8 patients who underwent left ventriculoplasty for idiopathic dilated cardiomyopathy and were found to have evidence of CS on pathologic inspection of the resected myocardium.²⁷ On retrospective review of the CT imaging, all 8 patients had enlarged mediastinal LN. In their 2011 study, Kandolin et al.⁸ reported the results of mediastinal LN biopsies in 12 patients with suspected CS. Only-FDG positive nodes were sampled, which is salient in that lymph node enlargement may be due either to granulomatous infiltration or to heart failure physiology itself. Among the 12 biopsies, 11 had positive histology for sarcoidosis. Notably, 10 of these patients had negative EMB and 1 did not have EMB performed.

Despite potential strategies for improving the diagnostic yield of biopsies in the evaluation of suspected ICS, these procedures are invasive and the risk to benefit ratio remains undefined. On the other hand, advanced cardiac imaging, including cardiac magnetic resonance imaging (CMR) and cardiac PET, may provide non-invasive and sensitive techniques for the evaluation of suspected ICS.

Late gadolinium enhancement (LGE) on CMR has been well described as an imaging biomarker for myocardial fibrosis. In the 2011 study by Kandolin and colleagues described above, 16 of the 32 patients with ICS underwent CMR. Using EMB, explant pathology at cardiac transplantation, or autopsy as the reference standard, the presence of LGE in 15 of these patients corresponded to a sensitivity of approximately 94% for the diagnosis of ICS.⁸ In the subsequent 2015 study by Kandolin et al.,²⁰ 38 of the 71 patients with ICS underwent CMR. The presence of LGE in 36 of these patients corresponded to a sensitivity of approximately 95% for the diagnosis of ICS. However, given the dynamic nature of CS, with both active inflammatory and chronic fibrotic phases, LGE may be less sensitive for the detection of early inflammatory disease.

Cardiac PET, on the other hand, may be more useful in the detection of the active inflammatory phase of CS. The combination of both perfusion PET with either rubidium-82 or N-13-ammonia and FDG PET allows differentiation of the spectrum of CS. Either perfusion or FDG PET findings, or both, may be present in the active inflammatory phase of

CS and include patterns of focal, focal-on-diffuse, or diffuse FDG uptake, with or without perfusion defects.^{28–31} In the 2011 study by Kandolin and co-workers, 25 of 32 patients with ICS underwent cardiac PET imaging. The presence of focal FDG uptake with perfusion defects in 20 of these patients corresponded to a sensitivity of approximately 80% for the diagnosis of ICS.⁸ In their subsequent 2015 study, 46 of 71 patients with ICS underwent cardiac PET. The presence of focal FDG uptake in 34 of these patients corresponded to a sensitivity of approximately 74% for the diagnosis of ICS.²⁰

The combined use of CMR and PET in the evaluation of suspected ICS offers complementary data^{31–33} and may be particularly attractive given the fact that each imaging technique has different strengths and limitations.³⁰ When technically feasible, such an approach enables imaging of perfusion, inflammation, and fibrosis, while also allowing for the identification of extra-cardiac disease. As a result, combining CMR and PET imaging likely provides the highest diagnostic accuracy for detecting ICS.

Finally, the optimal method of excluding ECS in cases of suspected ICS has not been studied. An approach based solely on clinical history, physical examination, and laboratory testing will miss a significant amount of clinically silent but radiographically evident ECS. As described above, in both the 2011 and 2015 studies by Kandolin and co-workers, at least 40% of patients with suspected ICS undergoing whole-body PET were found to have clinically silent but radiographically evident ECS.^{8,20} Hence, an approach involving whole-body imaging is likely to provide the most reliable exclusion of ECS in the evaluation of suspected ICS. Importantly, ECS may develop after initial cardiac involvement in cases of apparent ICS. Adamson and co-workers reported a series of 18 patients treated for CS at a single center in New Zealand from 2005 to 2013. Among 3 patients initially thought to have ICS, 2 subsequently developed evidence of ECS. The time interval from initial negative assessment to the development of evidence of ECS was not reported.¹⁵ Table 2 summarizes the current evidence regarding the diagnosis of ICS.

What Data Exist to Help Assess Prognosis and Guide Therapy in ICS?

The complications of ICS are similar to those of systemic sarcoidosis with CS and include ventricular arrhythmias, heart failure, and conduction system disease.⁸

Patients with ICS have a risk of ventricular tachycardia (VT) that is at least as high as, and possibly greater than, the risk of VT among patients with systemic sarcoidosis and CS. In their 2011 study, Kandolin and co-workers reported that 36% of patients with ICS presented with VT and 6% presented with ventricular fibrillation.⁸ In their subsequent 2015 study, these authors reported that 38% of patients with ICS presented with VT, compared with 23% of patients with systemic sarcoidosis and CS; the statistical significance of this difference was not reported.²⁰

Among patients with ICS, the benefit of device therapy with implantable cardioverter defibrillators (ICD) for primary prevention of VT appears to be greater than that among patients with systemic sarcoidosis with CS. Kron and co-workers studied 235 patients with CS who had undergone placement of an ICD.³² Among these, 15 had suspected or definite ICS. Over 4 years of follow-up, 9 of these 15 patients (69%) received appropriate device

therapy (anti-tachycardia pacing or defibrillation), compared with 75 of 222 patients (34%) with systemic sarcoidosis and CS, a difference that was statistically significant. This again suggests that VT may occur more commonly in patients with ICS as compared with systemic sarcoidosis and CS, and that device therapy may be appropriate and effective in patients with ICS at risk for ventricular dysrhythmias.

The optimal approach to the medical management of heart failure associated with ICS has not been studied. Patients with systemic sarcoidosis and CS who are treated with prednisone may experience improvements in LV systolic function, especially those with mild to moderate dysfunction (e.g., LV ejection fraction of 30–55%).^{33,34} While changes in LV systolic function in patients with ICS receiving immunosuppressive therapy have not been separately reported, it would be reasonable to expect a similar benefit in such individuals.

In end-stage heart failure associated with ICS, cardiac transplantation may be a reasonable option. Chang and co-workers reviewed 411 cardiac transplantations at a single center in Taiwan from 1988 to 2011.⁹ Explanted hearts from 5 patients demonstrated pathology consistent with CS. None of these 5 patients had historical or clinical evidence of ECS; hence at least some may have had ICS. During up to 8 years of follow-up, none of these 5 patients demonstrated recurrent CS, clinically or on routine surveillance EMB, and none died. Given the small number of patients studied, these data should be interpreted with caution, but they suggest that when indicated, cardiac transplantation for end-stage heart failure associated with ICS may be appropriate. This observation is notwithstanding the limitation that in clinical practice the diagnosis of ICS in such cases may only be recognized following explantation. Moreover, it is noteworthy that recurrence of CS has rarely been reported following heart transplantation.^{35–38}

Data regarding overall prognosis and long-term survival of ICS vs. systemic sarcoidosis with CS are summarized in Table 3.

DISCUSSION

Based on our review of the available data, the rate of ICS among patients with CS appears to be approximately 25%. In addition, patients with ICS appear to have worse LV systolic function at presentation and a higher rate of incident ventricular tachycardia as compared with patients with systemic sarcoidosis with CS. Because of limitations in current diagnostic criteria, there is an important role for advanced cardiac imaging techniques in the evaluation of patients with suspected ICS. A combined approach using FDG PET and CMR may provide complementary data on both inflammation and scar or fibrosis, respectively (Figure 1). In addition to improved detection of earlier stages of ICS, a combined approach may provide enhanced diagnostic certainty and improved accuracy.^{39–41} Finally, by utilizing whole-body imaging, FDG PET may be a useful technique for screening for extra-cardiac involvement in cases of suspected ICS.

Challenges Related to Management of ICS

A challenging clinical scenario occurs when a patient has a clinical presentation and cardiac imaging consistent with CS, but no evidence of ECS, and the results of EMB—if performed

—are negative or inconclusive. In such cases, it is helpful to establish the likelihood of CS by integrating all clinical and imaging data. If the likelihood is >50% and significant inflammation by cardiac PET is present, a trial of immunosuppressive therapies may be reasonable. Importantly, myocardial inflammation should be conclusively demonstrated in such cases, as opposed to cases where non-specific FDG uptake or failure to suppress physiologic FDG uptake from the normal myocardium is present.⁴²

In keeping with the 2014 expert consensus statement on cardiac sarcoidosis from the Heart Rhythm Society, reduction in FDG uptake upon treatment could serve as a potential criterion to support the diagnosis of ICS.⁴³ Nevertheless, it is important to acknowledge that FDG uptake may be due to other conditions, including failure to suppress physiologic glucose uptake by normal myocardium, inflammatory myopathies associated with rheumatologic disorders and some subtypes of myocarditis.

Efforts to enhance clinical detection of ICS and to aid in the management of suspected ICS may benefit from guidelines for categorizing the likelihood of CS as probable (>50%) or highly probable (>90%). This approach is exemplified by the World Association of Sarcoidosis and Other Granulomatous Disorders Organ Assessment Instrument,⁴⁴ which establishes categories to assess the probability of individual organ involvement in patients with sarcoidosis.

Areas for Future Work

An important step towards further investigation in the area of ICS will be the development of improved diagnostic methods for both the detection of CS and the exclusion of ECS. Along with the important role of CMR and cardiac PET in the detection of ICS, radio-tracers targeting inflammatory cells such as F-18 fluorothymidine (FLT)⁴⁵ and Ga-68 DOTATOC⁴⁶ may provide additional and complementary information. Improved detection and diagnosis may facilitate a deeper understanding of the pathobiology, epidemiology, clinical characteristics, and prognosis of ICS. Given that ICS patients appear to present with more advanced left ventricular systolic dysfunction and may be at higher risk for the development of ventricular tachycardia, another important area of inquiry will be the role of early anti-inflammatory therapy and primary prevention device therapy in ICS. Box 2 lists selected questions that may represent opportunities for future research in ICS.

Box 2

Summary of key questions relating to ICS

Epidemiology

Do ICS and systemic sarcoidosis with CS occur with similar frequencies in male and female patients, in different age groups, in different racial and ethnic groups, and in different geographic locations?

Diagnosis

What is the optimal strategy for utilizing advanced cardiac imaging techniques in the workup of suspected ICS?

What is the optimal method of excluding extra-cardiac sarcoidosis?

Therapy

Which ICS patients should receive steroid therapy; when is the optimal time to initiate steroid therapy; and what is the best strategy for monitoring response to steroid therapy?

Which ICS patients should undergo device therapy with ICD placement?

Prognosis

What are the differences in long-term outcomes between ICS and systemic sarcoidosis with CS, and can medical and device therapy improve event-free survival?

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

CS	Cardiac sarcoidosis
ICS	Isolated cardiac sarcoidosis
ECS	Extra-cardiac sarcoidosis
EMB	Endomyocardial biopsy
FDG	Fluorodeoxyglucose
LGE	Late gadolinium enhancement
PET	Positron emission tomography

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Figure 1.

Example of the complementary value of CMR and cardiac PET imaging in detecting cardiac sarcoidosis. A 61-year-old male presented with systolic heart failure of unknown etiology. CMR showed late gadolinium enhancement in the basal and mid anterior, anteroseptal, and inferoseptal segments that extended into the right ventricle. Myocardial perfusion imaging showed mild perfusion defects in the mid inferoseptal and the mid anterior segments. There was FDG uptake involving the basal to mid anterior and anteroseptal, basal inferior and apical septal segments. In this case, the combined information provided by PET and CMR can enhance the diagnostic certainty for diagnosing cardiac sarcoidosis, as subsequently was also confirmed via biopsy.

Table 1

Summary of selected data on prevalence of ICS

Study	Population (n)	Method of diagnosing CS (n)	Method of evaluating for ECS (n)	Prevalence of ICS (%) [*]
Kandolin et al. ⁸	All patients treated for definite or suspected CS at a single center in Finland from 2000–2010 (74)	EMB (17) Explant (4) Autopsy (1) Mediastinal LN biopsy (11) Clinical evaluation (22) ^{**}	Clinical evaluation (74) Chest x-ray (74) Liver enzymes (74) Whole-body PET (21)	Definite or suspected: 55/74 (74%) Definite: 33/74 (45%)
Kandolin et al. ²⁰	All patients receiving a diagnosis of CS based on cardiac or other histology in Finland from 1988–2012 (110)	EMB (55) Explant (6) Autopsy (2) Mediastinal LN biopsy (18) CMR and/or PET (38) Other (9)	Clinical evaluation (110) Chest x-ray (110) Whole-body PET (39)	Clinical exclusion of ECS: 71/110 (65%) After whole-body PET exclusion of ECS: 59/100 (54%)
Tavora et al. ²⁵	All patients with sudden death and CS at autopsy at AFIP ^{***} from 1995–2008 (41)	Autopsy (41)	Autopsy (41) Clinical history (41)	After clinical/historical exclusion of ECS: 30/41 (73%) After pathologic exclusion of ECS: 12/41 (29%)
Tezuka et al. ²¹	All patients with a clinical diagnosis of sarcoidosis who were treated at a single center in Japan from 1997–2013 (83)	2006 JMHW Criteria (41) ⁺	Clinical evaluation including ophthalmologic and skin examination (11) ⁺⁺	11/41 (27%)
Sperry et al. ²²	Heart failure patients at the Cleveland clinic with CS proven by myocardial biopsy specimen from 2002–2014 (27)	Myocardial biopsies (27)	Clinical history Diagnostic biopsy Imaging findings, including FDG PET (16)	After clinical/historical exclusion of ECS: 30/41 (73%)

^{*} Prevalence of ICS among patients with CS^{**} Among these 22, 9 had LGE on CMR, 12 had focal FDG uptake on cardiac PET, and 12 had resting perfusion deficits on SPECT. While the number of patients examined with each modality is reported, the number of patients studied with multiple modalities is not. Therefore, at least 12 of these patients had diagnoses of suspected CS based on advanced imaging, but it is not clear whether all 22 were diagnosed with advanced imaging^{***} AFIP, Armed Forces Institute of Pathology, Office of the Armed Forces Medical Examiner, and Office of the Chief Medical Examiner⁺ Revised 2006 Japanese Ministry of Health and Welfare Criteria⁺⁺ Method of excluding ECS was only reported for those with ICS

Table 2

Summary of selected data on the diagnosis of ICS

Study	Population	Reference Standard	Sensitivity
Endomyocardial biopsy			
Kandolin et al. ⁸	33 patients with histologically proven CS and no clinical evidence of ECS; 31 underwent EMB	Subsequent biopsy, explant pathology, or autopsy	11/31 or 34%
Tezuka et al. ²¹	11 patients with a clinical diagnosis of ICS; 5 underwent EMB	Clinical suspicion for and imaging features consistent with CS	2/5 or 40%
LGE on CMR			
Kandolin et al. ⁸	33 patients with histologically proven CS and no clinical evidence of ECS; 16 underwent CMR	EMB, explant pathology, or autopsy	15/16 or 94%
Kandolin et al. ²⁰	71 patients with a clinical diagnosis of ICS; 38 underwent CMR	EMB, explant pathology, or autopsy	36/38 or 95%
Focal FDG uptake on cardiac PET			
Kandolin et al. ⁸	33 patients with histologically proven CS and no clinical evidence of ECS; 25 underwent cardiac PET	EMB, explant pathology, or autopsy	20/25 or 80%
Kandolin et al. ²⁰	71 patients with a clinical diagnosis of ICS; 46 underwent cardiac PET	EMB, explant pathology, or autopsy	34/46 or 74%
Mediastinal lymphadenopathy on chest CT			
Ostuka 2007	8 patients who underwent cardiac transplant for DCM with evidence of CS on explant pathology; all 8 underwent chest CT	Explant pathology	7/8 or 88%

Table 3

Summary of selected data on prognosis in ICS

Study	Population (n)	Follow-up	Outcomes	ICS vs systemic sarcoidosis with CS
Kandolin et al. ²⁰	All patients receiving a histologic diagnosis of CS in Finland from 1988–2012 (110)	Median of 79 months, range of 12–303 months	Survival free of cardiac transplantation or aborted sudden death	1/71 in the ICS group vs 4/39 in the systemic sarcoidosis and CS group (log rank $P=0.005$)
Kron et al. ³⁴	Patients with CS and ICD implantation at multiple centers (time period not specified) (235)	Questionnaire mailed at a single time point	Appropriate device therapies (ATP or defibrillation)	9/13 in the ICS group vs 75/222 in the systemic sarcoidosis and CS group ($P=0.015$)
Tezuka et al. ²¹	All patients with a clinical diagnosis of sarcoidosis who were treated at a single center in Japan from 1997 to 2013 (83)	Mean of 18 months for ICS and 14 months for SCS	Survival	Reported as no difference; specific values not reported