Different Impact of Immunosuppressive Therapy on Cardiac Outcomes in Systemic versus Isolated Cardiac Sarcoidosis

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CLINICAL STUDY

Different Impact of Immunosuppressive Therapy on Cardiac Outcomes in Systemic Versus Isolated Cardiac Sarcoidosis

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Summary

Isolated cardiac sarcoidosis (iCS) is increasingly recognized; however, its prognosis and the efficacy of immunosuppressive therapy remain undetermined. We aimed to compare the prognosis of iCS and systemic sarcoidosis including cardiac involvement (sCS) under immunosuppressive therapy.

We retrospectively reviewed the clinical data of 42 patients with sCS and 30 patients with iCS diagnosed at Kyushu University Hospital from 2004 through 2022. We compared the characteristics and the rate of adverse cardiac events including cardiac death, fatal ventricular tachyarrhythmia, and heart failure hospitalization between the 2 groups. The median follow-up time was 1535 [interquartile range, 630-2555] days, without a significant difference between the groups. There were no significant differences in gender, NYHA class, or left ventricular ejection fraction. Immunosuppressive agents were administered in 86% of sCS and in 73% of iCS patients (P = 0.191). When analyzed only with patients receiving immunosuppressive therapy (sCS, n = 36; iCS, n = 21), the cardiac event-free survival was significantly lower in iCS than sCS (37% versus 79%, P = 0.002). Myocardial LGE content at the initial diagnosis was comparable in both groups. The disease activity was serially evaluated in 26 sCS and 16 iCS patients by quantitative measures of FDG-PET including cardiac metabolic volume and total lesion glycolysis, representing 3-dimensional distribution and intensity of inflammation in the entire heart. Although iCS patients had lower baseline disease activity than sCS patients, immunosuppressive therapy did not attenuate disease activity in iCS in contrast to sCS.

iCS showed a poorer response to immunosuppressive therapy and a worse cardiac prognosis compared to sCS despite lower baseline disease activity.

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Key words: Systemic sarcoidosis, FDG-PET

Sarcoidosis is a systemic granulomatous disease of unknown etiology, involving multiple organs such as the lungs, nervous system, eyes, kidneys, and heart.[1)] Cardiac sarcoidosis (CS) is complicated by heart failure, fatal ventricular tachyarrhythmia, and sudden cardiac death.[1,2)] Therefore, early diagnosis and early therapeutic intervention for CS are extremely important for the improvement of poor prognosis.

Editorial p.789

The usefulness of magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) in diagnosing CS has been established. The diagnostic criteria for CS of the Heart Rhythm Society (HRS) or Japan Ministry of Health and Welfare (JMWH) have been widely used.[3,4)] The newest guidelines published by the Japanese Circulation Society (JCS 2016) include both MRI and FDG-PET findings as major criteria.[1)] In particular, the advocacy of the concept of isolated CS

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(iCS) has increased the number of early diagnosed cases.[1] On the other hand, many cases of iCS are clinically diagnosed based on the findings of MRI and FDG-PET due to its low histological diagnosis rate.

Left ventricular ejection fraction (LVEF), plasma B-type natriuretic peptide (BNP) level, history of ventricular tachycardia (VT)/ventricular fibrillation (VF), requiring ablation to treat VT, high-sensitivity cardiac troponin T or troponin I, serum soluble interleukin 2 receptor level, delayed-enhancement cardiovascular magnetic resonance, and right ventricular uptake of FDG are known as prognostic factors of CS.[5-9] A few small studies have reported that iCS may have a worse prognosis than systemic sarcoidosis with cardiac involvement (sCS);[10-12] however, whether the efficacy and prognostic impact of immunosuppressive therapy are equivalent between iCS and sCS still remains to be elucidated.

The aim of this study was to clarify the clinical features of patients with iCS and sCS receiving immunosuppressive therapy, and to determine its impact on disease activity and cardiovascular outcome.

Methods

Study population: The present study is a retrospective analysis of 96 consecutive patients who were suspected of having CS at the Department of Cardiovascular Medicine, Kyushu University Hospital between 2004 and 2022. Patients were classified as sCS or iCS based on the JCS 2016 guidelines.

Data collection and outcomes: Clinical data were obtained from the patient medical records. Baseline characteristics were obtained during the initial diagnostic process for CS. Baseline was defined as the time that patients were diagnosed with CS. In 2 patients, N-terminal prohormone of BNP (NT-proBNP) values were converted to BNP using the conversion formula: Log[BNP] = (Log[NT-proBNP] + 0.009 × [BMI] + 0.007 × [estimated glomerular filtration rate (eGFR)] − 1.21)/1.03.[13] The primary endpoint was a composite of all-cause death, hospitalization for heart failure, and fatal ventricular arrhythmia events. Fatal ventricular arrhythmia events were defined as documented VF, sustained VT lasting for more than 30 seconds, or appropriate implantable cardioverter-defibrillator (ICD) operation. Patients were followed until the date of the first documentation of cardiac events or the end of follow-up. Follow-up information was obtained by medical records and contact with the patients.

Echocardiographic measurement: All patients were evaluated by echocardiography. The parameters included left ventricular end-diastolic diameter (LVEDD), LVEF, the presence of aneurysm, and interventricular septum (IVS) thinning. LVEF was measured using the modified Simpson method. Basal IVS thinning was diagnosed when the basal thickness of IVS was 4 mm or less, or the ratio of basal thickness to one-third point near the annulus in IVS was 0.6 or less.[14] A left ventricular aneurysm was defined only if all of the following 3 criteria were met based on transthoracic echocardiography, contrast left ventriculography, or magnetic resonance imaging: the presence of a well-localized region of the left ventricle exhibiting either akinesis or dyskinesis, a discrete deformity in both systole and diastole, and normally contractile myocardium adjacent to the area of regional dysfunction.[15,16]

Cardiac MRI: MRI with a 3.0-T MR unit (Achieva 3.0 T TX or Ingenia 3.0 T; Philips Medical Systems, the Netherlands) and 32-channel phased-array coil was used for all patients. Cine and late gadolinium enhancement (LGE) MRI were performed with electrocardiographic gating while the patient held their breath. Cine MRI was performed using a steady-state free precession sequence in the 4CH, short- and long-axis orientations with the following parameters: repetition time (TR) = 2.9 millisecond (ms), echo time (TE) = 1.5 ms, flip angle = 45°, slice thickness = 8 mm, field of view = 380 mm × 434 mm, and acquisition matrix = 192 × 301. LGE-MRI were scanned at 10 minutes after 0.2 mmol/kg of gadolinium injection (Magnevist or Gadvist, Bayer Healthcare, Osaka, Japan) with the following parameters: TR = 3.9 ms, TE = 1.2 ms, flip angle = 15°, slice thickness = 10 mm, field of view = 300 mm × 343 mm, and acquisition matrix = 228 × 171. The inversion time was adjusted to optimally null the myocardium. LGE images were evaluated in the apical, mid, and basal segment of the LV short axis images.[17]

Quantification of LGE was performed using SYNAPSE VINCENT software (FUJIFILM Corp., Tokyo). The endocardial and epicardial contours were delineated in consecutive short-axis slices that covered the whole left ventricle. Hyper-enhanced areas considered LGE were determined as areas with signal intensities > 5 SDs above remote normal myocardial region, and then, the volume of LGE in the entire left ventricular myocardium was calculated.[18]

^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging: FDG-PET/computed tomography (CT) data were acquired using an integrated PET/CT scanner (Discovery STE, GE Medical Systems, Milwaukee, WI, USA; or Biograph Vision, Siemens Medical Solutions, Erlangen, Germany). Imaging was performed after at least 18 hours of fasting. Blood glucose levels were checked before the FDG injection. FDG was administered intravenously at a dose of 4 MBq/kg with the patient resting. A static PET scan was performed 60 minutes after the administration of FDG. A volume of interest (VOI) was inserted to encompass the entire heart, and the coronal and sagittal images were reviewed to ensure the entire myocardium and no adjacent non-cardiac FDG-positive structures were included. The maximal and mean standardized uptake value (SUV) voxel in this volume was automatically identified. An SUV > 3 was adopted as the cut-off threshold for inflammatory activity according to a previous study.[19] In addition, cardiac metabolic volume (CMV; analogous to metabolic tumor volume (MTV) in oncologic PET imaging) and total lesion glycolysis (TLG) were also calculated for the purpose of evaluating the total FDG-positive volume in the heart (Figure 1). CMV is a volume-based parameter such as inflammatory activity in patients with CS, defined as the volume within the VOI determined by the FDG uptake threshold.[20,21] TLG is calculated by multiplying CMV by SUVmean.[20] TLG represents the quantitative distribution volume and integrated intensity of inflammation in the entire myocardium.

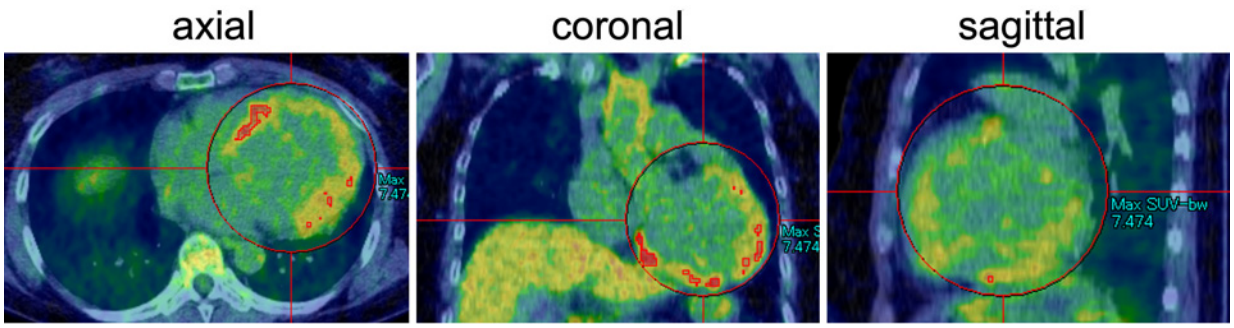

Figure 1. Measurement of cardiac metabolic volume (CMV) and total lesion glycolysis (TLG). A volume of interest (VOI) was inserted to encompass the entire heart, and the coronal and sagittal images were reviewed to ensure the entire myocardium and no adjacent non-cardiac FDG-positive structures were included (red circles). The maximal and mean standardized uptake value (SUV) voxel in this volume was automatically identified. SUV > 3 was adopted as the cut-off threshold for inflammatory activity. CMV was defined as the volume within the VOI determined by the threshold. TLG was calculated by multiplying CMV by SUV mean.

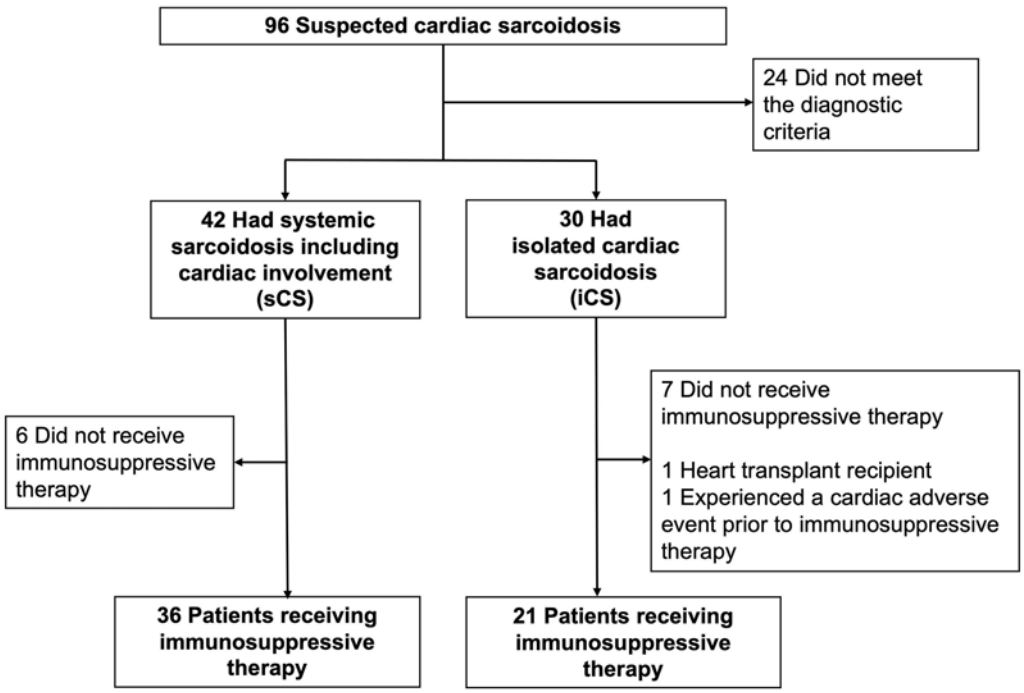

Figure 2. Flow diagram of the study patient selection.

Statistical analysis: Data are presented as the mean ± standard deviation for continuous variables, and as number and percentage for categorical variables. Differences between the 2 groups were analyzed by the t-test and the Mann-Whitney *U* test, if appropriate, for continuous variables, and the χ^2 test and Fisher's exact test for categorical variables. Cumulative event-free survival in the iCS and sCS groups was estimated using Kaplan-Meier analysis, and the difference was analyzed using the log rank test. Predictors of cardiac events were analyzed using Cox proportional hazard analysis. Variables for univariate and multivariate analyses included age, gender, LVEF, BNP, history of fatal ventricular arrythmia, cardiac implantable electronic device, and iCS. Hazard ratios are presented with 95% confidence intervals (CI). Statistical analysis was performed with JMP version 16.0 (SAS Institute Inc., Cary, NC, USA), and significance was defined as $P < 0.05$.

Ethics statement: This study was conducted according to the principles of the Declaration of Helsinki. The original study protocol was approved by the Institutional Review Board (IRB) of Kyushu University Hospital (#2022-129). Patients were offered the opportunity to opt out of the study. The authors had full access to the data and take full responsibility for the integrity of the data.

Results

Patient characteristics: The study profile is shown in Figure 2. Of the 96 patients with suspected CS, 24 were

Table I. Characteristics of Patients Receiving Immunosuppressive Therapy

	sCS (n = 36)	iCS (n = 21)	P value
Demographics			
Age (years)	62.1 ± 9.4	55.9 ± 11.7	0.034
Male	12 (33%)	10 (48%)	0.285
NYHA III/IV	10 (28%)	9 (43%)	0.245
No clinical symptom at diagnosis	9 (2%)	2 (10%)	0.185
Comorbidities			
Hypertension	9 (25%)	4 (19%)	0.749
Diabetes mellitus	7 (19%)	5 (24%)	0.744
Chronic kidney disease	10 (28%)	10 (48%)	0.130
Coronary artery disease	4 (11%)	1 (5%)	0.642
Laboratory data			
sIL-2R (U/mL) (n = 31, 15)	681 ± 406	427 ± 202	0.011
ACE (IU/L) (n = 35, 19)	11.5 ± 6.1	8.5 ± 4.6	0.066
Hemoglobin (g/dL) (n = 35, 20)	13.3 ± 1.6	13.4 ± 2.0	0.789
eGFR (mL/minute/1.73 m^2) (n = 35, 20)	65.1 ± 18.5	63.3 ± 18.5	0.738
Log BNP (pg/mL) (n = 33, 20)	2.1 ± 0.7	2.3 ± 0.8	0.503
Electrocardiographic findings			
Atrial arrythmia (AF/AFL/AT)	9 (25%)	4 (19%)	0.749
Advanced AVB/CAVB	15 (42%)	3 (14%)	0.041
Non-sustained ventricular tachycardia	17 (47%)	13 (62%)	0.284
Sustained VT/VF	1 (3%)	5 (24%)	0.022
Echocardiographic findings			
Left ventricular ejection fraction (%)	47.3 ± 19.2	40.6 ± 15.6	0.180
Left ventricular end-diastolic diameter (mm)	53.0 ± 11.0	57.1 ± 11.5	0.188
Aneurysm	8 (22%)	7 (33%)	0.358
Interventricular septum thinning	13 (36%)	13 (62%)	0.059
Endomyocardial biopsy (n = 33, 20)			
Presence of positive findings	6 (18%)	7 (35%)	0.168
Cardiac magnetic resonance			
Presence of LGE (n = 26, 16)	26 (100%)	15 (94%)	0.381
LGE extent (%) (n = 21, 13)	26.6 ± 13.1	26.6 ± 19.3	0.600
FDG-PET			
SUVmax (n = 28, 18)	9.2 ± 3.7	6.0 ± 1.8	0.001
SUVmean (n = 28, 17)	4.6 ± 1.0	3.8 ± 0.5	0.003
CMV (n = 28, 17)	151 ± 140	62 ± 66	0.041
TLG (n = 28, 17)	779 ± 778	245 ± 263	0.024

Data are shown as number (percent) or means ± SD. ACE indicates angiotensin converting enzyme; AF, atrial fibrillation; AFL, atrial flatter; AT, atrial tachycardia; AVB, atrioventricular block; BNP, B-type natriuretic peptide; CAVB, complete atrioventricular block; CMV, cardiac metabolic volume; eGFR, estimated glomerular filtration rate; iCS, isolated cardiac sarcoidosis; LGE, late gadolinium enhancement; NYHA, New York Heart Association; sCS, systemic sarcoidosis including cardiac involvement; sIL-2R, soluble interleukin-2 receptor; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; TLG, total lesion glycolysis; VF, ventricular fibrillation; and VT, ventricular tachycardia.

excluded because they did not meet the diagnostic criteria (JCS 2016). sCS was diagnosed in 42 patients, and iCS was diagnosed in 30 patients. Absence of extracardiac lesions was confirmed by the whole body FDG-PET scans in all the patients. The median follow-up time since diagnosis was 1535 [inter quartile range (IQR), 630-2555] days, and there was no significant difference between the groups. The time from symptom onset or documentation of abnormal laboratory results to the initial diagnosis of sarcoidosis was not significantly different between the groups. The clinical characteristics are shown in Supplemental Table I. The patients not receiving immunosuppressive therapy were excluded from further analysis. The reason for avoidance of immunosuppressive therapy included a very low level of myocardial FDG uptake (n = 7), normal cardiac function (n = 1), liver cancer (n = 1), and high risk of adverse effects (n = 4). A patient with relapse of cardiac sarcoidosis after heart transplantation and a patient who experienced a cardiac adverse event prior to initiation of immunosuppressants were also excluded (Figure 2).

The clinical characteristics of patients with sCS and iCS who received immunosuppressive therapy are shown in Table I and Supplemental Table II. Extracardiac lesions in 36 patients with sCS included pulmonary lesions (92%), ocular lesions (56%), skin lesions (17%), liver lesions (0.08%), stomach lesions (0.03%), and lymphadenopathies (0.03%). The iCS patients were significantly younger than the sCS patients. There were no significant differences in gender, NYHA functional class, or the prevalence of comorbidities including hypertension, diabetes mellitus, chronic kidney disease, and coronary artery

Table II. Treatment of Patients Receiving Immunosuppressive Therapy

	sCS (n = 36)	iCS (n = 21)	P value
ACEI/ARB/ARNI	25 (69%)	17 (81%)	0.534
β blocker	21 (58%)	18 (86%)	0.041
MRA	11 (31%)	7 (33%)	0.828
Diuretics	11 (33%)	7 (33%)	0.828
Antiarrhythmic agents	5 (14%)	8 (38%)	0.051
Immunosuppressive agents			
Prednisolone	36 (100%)	19 (90%)	0.132
Methotrexate	9 (25%)	3 (14%)	0.504
Azathioprine	2 (6%)	1 (5%)	1.000
Tacrolimus	0 (0%)	1 (5%)	0.368
Mycophenolate Mofetil	0 (0%)	1 (5%)	0.368
Immunosuppressive regimens - detail			
Prednisolone alone	27 (75%)	16 (76%)	
Methotrexate alone	0 (0%)	2 (10%)	
Prednisolone + Methotrexate	7 (19%)	0 (0%)	
Prednisolone + Methotrexate + Azathioprine	2 (6%)	1 (5%)	
Prednisolone + Tacrolimus	0 (0%)	1 (5%)	
Prednisolone + Mycophenolate Mofetil	0 (0%)	1 (5%)	
Catheter ablation for VT	0 (0%)	3 (14%)	0.046
CIED implantation			
PPMI	8 (22%)	3 (14%)	0.7292
CRT-P	2 (6%)	2 (10%)	0.6204
ICD/CRT-D	9 (25%)	11 (52%)	0.037

Data are shown as number (percent) or means ± SD. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CIED, cardiac implantable electrical device; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter-defibrillator; iCS, isolated cardiac sarcoidosis; MRA, mineralocorticoid receptor antagonist; PPMI, permanent pacemaker implantation; sCS, systemic sarcoidosis including cardiac involvement; and VT, ventricular tachycardia.

disease (CAD) between the groups. Four patients with CAD in the sCS group underwent percutaneous coronary intervention for angina pectoris or silent myocardial ischemia, which were not the cause of left ventricular dysfunction. One patient with iCS had CAD, but coronary revascularization was deferred because of no evidence of ischemia. No patients with clinically diagnosed iCS had ischemic cardiomyopathy. Soluble interleukin-2 receptor (sIL-2R) levels were significantly lower in iCS than sCS. Hemoglobin level, eGFR, serum angiotensin-converting enzyme (ACE), and plasma BNP levels were comparable between the groups. Advanced and complete atrioventricular block were less prevalent in iCS than sCS; whereas sustained ventricular tachyarrhythmias were more common in iCS than sCS. There were no significant differences in echocardiographic findings including dimensions, morphology, and systolic function between the groups.

Endomyocardial biopsy was performed in all patients. The incidence of histopathological positive for epithelioid cell granulomas in myocardial biopsy samples were 18% in the sCS group and 35% in the iCS group. The remainder of the patients did not have any inflammatory cardiomyopathy or giant cell myocarditis findings. As shown in Supplemental Table III, there was no statistically significant difference in the proportion of iCS between the biopsy-positive and negative patients. Fewer biopsy-proven patients were asymptomatic at diagnosis compared to biopsy-negative patients. The biopsy-positive patients showed lower LVEF, higher BNP, and a greater amount of LGE on cardiac MRI than the biopsy-negative patients. No significant difference was observed in the FDG-PET parameters between the 2 groups.

Among patients with clinically diagnosed iCS, 1 patient underwent gene testing, which revealed no pathogenic genetic mutation related to cardiomyopathy. Almost all patients had evidence of LGE on cardiac MRI. In the quantitative analysis of FDG-PET, patients with iCS showed significantly lower values in all parameters including SUVmax, SUVmean, CMV, and TLG than sCS. CMV represents the 3-dimensional spatial distribution of inflammation and TLG represents the integral intensity of inflammation in the entire myocardium. These findings suggested that the patients with iCS had lower disease activity at baseline than sCS.

Treatment for CS: The prescription rates for angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, and diuretics were similar between the groups (Table II and Supplemental Table IV). The prescription rate of β-blockers was significantly higher in iCS than in sCS. Similarly, that of antiarrhythmics was slightly higher in iCS than in sCS. Ablation for ventricular tachycardia (VT) was performed in 3 iCS patients (14%), but not in any sCS patients. The rate of implantation of a cardiac implantable electronic device (CIED) was 53% in sCS and 76% in iCS (P = 0.132). The rate of implantation of an ICD or cardiac resynchronization therapy-defibrillator (CRT-D) was significantly

higher in iCS than in sCS. ICD implantation was not performed in 1 sCS patient due to very old age, nor in 1 iCS patient because of no history of ventricular arrhythmia including non-sustained VT. Prednisolone was administered as the main immunosuppressant in almost all patients (100% in sCS and 90% in iCS). The initial dose of prednisolone was 30 mg q.d. for the first 4 weeks, followed by tapering by 5 mg q.d. at intervals of 4 weeks to a maintenance dose of 5 to 10 mg q.d. according to the JCS 2016 guidelines.[1)] The median maintenance dose was 5.5 mg in sCS and 5.0 mg in iCS (P = 0.524). Although most patients were initially administered prednisolone, 2 patients refused to receive prednisolone therapy due to concerns about the adverse effects of steroids and were treated with methotrexate as the initial therapy. With the exception of these 2 cases, immunosuppressive agents other than a corticosteroid were added as second-line therapy. Other immunosuppressants included azathioprine, tacrolimus, and mycophenolate mofetil (Table II). Sixteen patients (44%) with sCS experienced relapse of sarcoidosis during the tapering of prednisolone, as did 6 (32%) with iCS (P = 0.35). The patients who relapsed were treated with up-titration of prednisolone or the addition of other immunosuppressive agents.

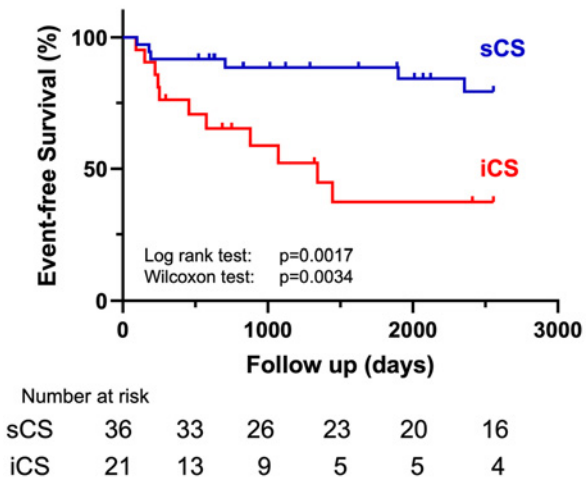

Figure 3. Cardiac event-free survival of the patients with sCS and iCS receiving immunosuppressive therapy. Kaplan-Meier event-free survival curves are shown. Adverse cardiac events included all-cause death, hospitalization for heart failure, and fatal ventricular arrhythmia events. sCS indicates systemic sarcoidosis with cardiac involvement; and iCS, isolated cardiac sarcoidosis.

Clinical outcomes: The median follow-up duration after the initiation of immunosuppressive therapy was 1394 days (IQR, 90-2555). Six patients (17%) with sCS experienced a major adverse cardiac event, including cardiac death, heart failure hospitalization, and fatal ventricular arrhythmia, as did 11 patients (52%) with iCS (P = 0.003). Three patients with sCS suffered sudden cardiac death and 3 were hospitalized for heart failure, however, no patient experienced a fatal ventricular arrhythmia event. On the other hand, 1 patient with iCS died of sudden cardiac death, 6 were hospitalized for heart failure, and 4 experienced a fatal ventricular arrhythmia event, including 3 ICD operations for VT and 1 VF episode. Among iCS patients with negative myocardial biopsy findings, 23% died of a cardiac cause and 31% experienced a fatal ventricular arrhythmia. No autopsies were performed in the deceased cases. Kaplan-Meier curves are presented in Figure 3 and Supplemental Figure 1. The event-free survival rate was significantly lower in the iCS group than in the sCS group even under immunosuppressive therapy (37% versus 79%, P = 0.002 for log-rank test). The results of univariate analysis using Cox proportional hazards model analysis are shown in Table III. iCS, LVEF, Log-transformed BNP, sustained ventricular tachyarrhythmia (VTA) including VT and VF, and ICD/CRT-D implantation were significantly associated with major adverse cardiac events; whereas age and gender were not associated with the cardiac outcome.

Multivariate analyses were performed using 3 models (Table III); model 1 that included general factors such as age and gender, model 2 that included heart failure-related factors, and model 3 that included arrhythmia-related factors. iCS was persistently an independent determinant for predicting major adverse cardiac events, after adjustment for age and gender (model 1), BNP and LVEF (model 2), and sustained VTA and ICD/CRT-D implantation (model 3). Multivariate analysis including all parameters used for univariate analysis also demonstrated that iCS and log BNP were independent predictors of the primary endpoint (Supplemental Table V). Although the rates of use of each immunosuppressive agent were not statistically different,

Table III. Cox Proportional Hazard Model for the Composite of Cardiac Events

	Univariate analysis		Multivariate analysis					
			Model 1		Model 2		Model 3	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
iCS	4.38 (1.60-12.0)	0.004	4.25 (1.52-11.9)	0.006	3.84 (1.29-11.5)	0.016	3.36 (1.18-9.55)	0.023
Age (years)	0.98 (0.94-1.03)	0.456	1.00 (0.96-1.05)	0.950				
Male	1.56 (0.60-4.06)	0.360	1.31 (0.48-3.58)	0.595				
Log BNP (pg/mL)	4.36 (1.74-13.5)	0.004			4.17 (1.16-17.1)	0.034		
LVEF (%)	0.97 (0.94-0.99)	0.015			1.00 (0.96-1.04)	0.876		
Sustained VT/VF	5.39 (1.72-16.9)	0.004					2.18 (0.61-7.74)	0.230
ICD/CRT-D	5.27 (1.92-14.4)	0.001					3.44 (1.12-10.5)	0.031

BNP indicates B-type natriuretic peptide; CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; iCS, isolated cardiac sarcoidosis; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; and VT, ventricular tachycardia.

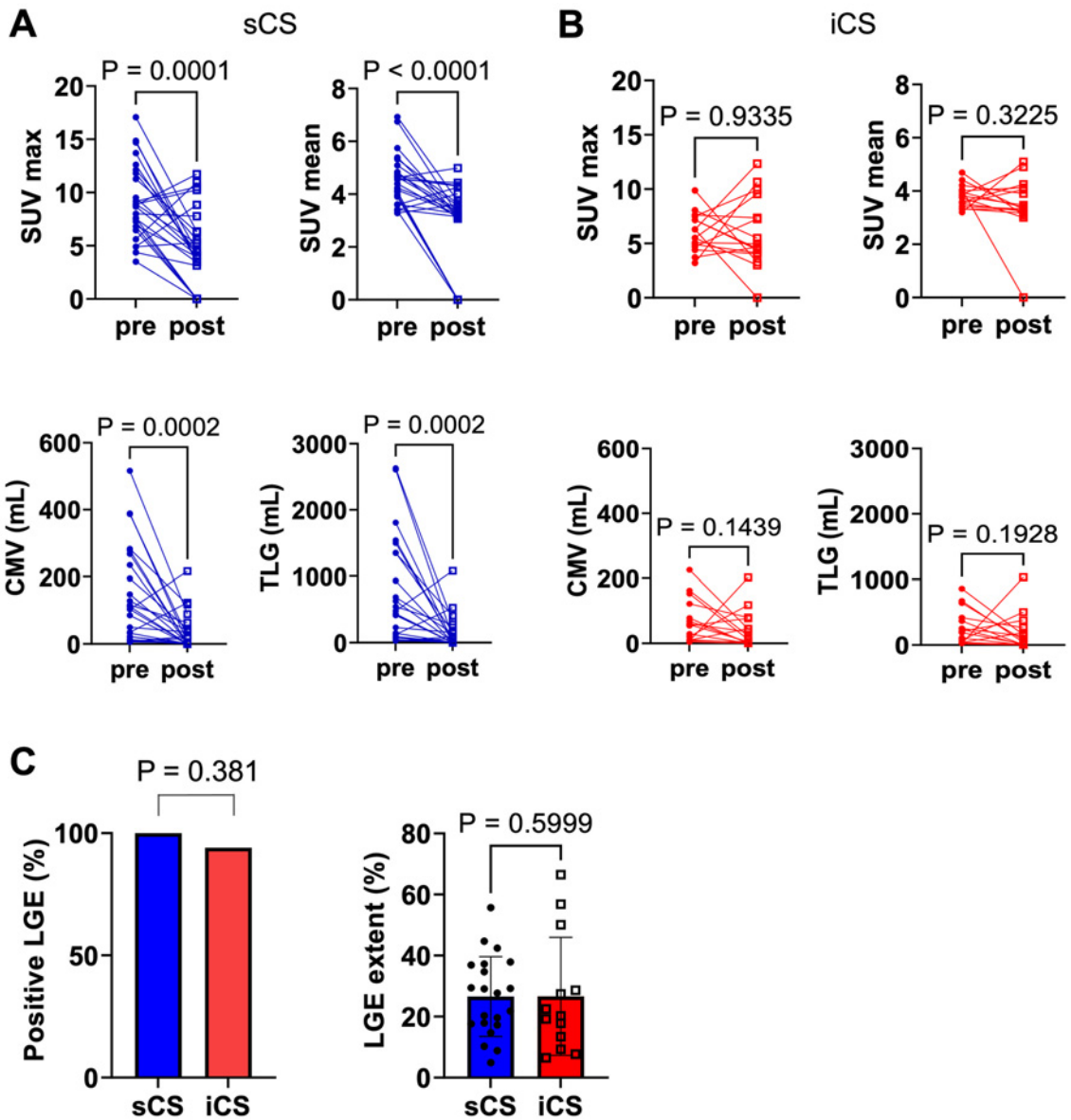

Figure 4. Quantitative measures of FDG-PET and cardiac MRI. **A, B:** Immunosuppressive treatment significantly attenuated all FDG-PET parameters in the patients with sCS (**A**), but did not in the patients with iCS (**B**). The differences of values were analyzed by the paired t-test or Mann-Whitney *U* test (sCS, *n* = 26, and iCS, *n* = 16). **C:** Evaluation of late gadolinium enhancement in cardiac magnetic resonance at first diagnosis. Presence of myocardial LGE is shown (sCS, *n* = 26, and iCS, *n* = 16) (left). Quantitative analysis of myocardial LGE content. The differences among values were analyzed using the Mann-Whitney *U* test (sCS, *n* = 21, and iCS, *n* = 13) (right). CMV indicates cardiac metabolic volume; iCS, isolated cardiac sarcoidosis; LGE, late gadolinium enhancement; sCS, systemic sarcoidosis with cardiac involvement; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; and TLG, total lesion glycolysis.

there were more patients who received combination therapy that included methotrexate in sCS than iCS. Comparison of outcomes between patients with prednisolone monotherapy versus prednisolone/methotrexate combination therapy using Cox proportional hazards model analysis revealed that the combination therapy was not correlated with major adverse cardiac events (hazard ratio 0.96, 95% CI 0.27-3.41, *P* = 0.95). When sCS and iCS were analyzed separately, combination therapy was not a significant predictor either (HR 1.42, 95% CI 0.26-7.77, *P* = 0.69 for sCS; HR 3.33, 95% CI 0.37-29.95, *P* = 0.28 for iCS). The relapse of sarcoidosis during the tapering of prednisolone was not correlated with major adverse cardiac events (HR1.35, 95% CI 0.51-3.60, *P* = 0.55).

FDG-PET evaluation during immunosuppressive therapy: A total of 42 patients, including 26 with sCS and 16 with iCS, were evaluated by serial FDG-PET during the immunosuppressive therapy. Quantitative measurements of FDG-PET imaging before and after immunosuppressive treatment were compared (Figure 4A and B). The median

duration values from the baseline to follow-up FDG-PET were 211 [IQR, 153-273] and 200 [128, 266] days for sCS and iCS, respectively (P = 0.5039). Interestingly, all parameters including SUVmax, SUVmean, CMV, and TLG significantly decreased after the initiation of immunosuppressive therapy in sCS patients (P = 0.0001, < 0.0001, 0.0002, and 0.0002 for each); whereas those values were unaffected by immunosuppressive therapy in iCS patients (P = 0.9335, 0.3225, 0.1439, and 0.1928 for each). These findings suggest that iCS had poor responsiveness to immunosuppressive therapy despite the lower baseline disease activity compared to that of sCS. As described above, FDG-PET analysis suggested that the baseline disease activity was lower in iCS than sCS (Table I, Figure 4A and B). This may raise the possibility that most patients with iCS were already in the burn-out stage at the time of the first diagnosis, and therefore immunosuppressive therapy failed to attenuate disease activity. However, quantitative analysis of LGE in cardiac MRI did not demonstrate any significant difference in myocardial LGE content between iCS and sCS (Figure 4C). These findings rule out the possibility that the patients with iCS were already in an advanced disease stage at the initial evaluation; rather, they suggest a different underlying pathophysiology between the groups.

Discussion

In the present study, we demonstrated that iCS patients had an inferior cardiac prognosis as evaluated by the composite of all-cause death, hospitalization for heart failure, and fatal ventricular arrhythmia compared to sCS patients despite the immunosuppressive therapy. In addition, the worse cardiac outcome of patients with iCS compared to sCS despite the higher rate of use of antiarrhythmics suggests the lack of an apparent beneficial impact of beta-blockers and antiarrhythmics on cardiac outcome in iCS patients. Multivariate analysis showed that a diagnosis of iCS was an independent predictor of adverse cardiac events in patients with sarcoidosis. No previous study has reported a poorer cardiac prognosis for iCS than sCS, even under immunosuppressive therapy. We also evaluated the disease activity of CS by quantitative measures of FDG-PET imaging using CMV and TLG. These parameters, by quantifying the 3-dimensional distribution volume of the FDG-positive area and integrating it as metabolic activity by multiplying the volume by uptake value, represent disease activity more accurately than classical parameters such as SUV max.[22] Even though the patients with iCS showed smaller lesion distribution and lower lesion metabolic activity than the patients with sCS, immunosuppressive therapy failed to attenuate disease activity in iCS in contrast to sCS.

Previous studies have shown that immunosuppressive therapy with a corticosteroid reduced SUVmax values in CS.[11,23] Indeed SUVmax is an easily obtained indicator of FDG-PET imaging, however, SUVmax is just the highest value of FDG uptake and it represents only 1-dimensional information at 1 point in the myocardium. It does not include information on lesion distribution or total disease activity in the entire heart. Since CMV and TLG include information concerning 3-dimensional lesion distribution, these parameters are thought to be more accurate than SUVmax. In fact, the usefulness of MTV and TLG has been demonstrated in various types of tumors.[24-26] Furthermore, a previous study has shown that the quantitative interpretation of FDG-PET using TLG, or alternatively called cardiac metabolic activity (CMA), reinforced the diagnostic accuracy for evaluating treatment response in cardiac sarcoidosis.[22] We believe that the interpretation of therapeutic response to immunosuppressive therapy in patients with CS using CMV and TLG is more reliable than conventional measure using SUVmax.

Several studies have reported a poor prognosis for iCS, however, there was a difference in the rate of corticosteroid use between iCS and sCS.[10,12] Kaneko and colleagues reported no significant difference in the treatment responses and major adverse cardiac events between iCS and sCS patients receiving immunosuppressive therapy.[27] This discrepancy could be ascribed to the backgrounds of the patients, treatment duration, and definition of treatment response. The histological positive rate was extremely low at 6% in the sCS and 0% in iCS groups (18% and 35% in the present study), and the treatment response was defined as complete resolution of FDG-uptake in their study. The reason why iCS showed a worse cardiac prognosis than sCS even under immunosuppressive treatment in the present study can be attributed to several factors. First, the lack of extracardiac sarcoidosis lesions tends to result in the delay of diagnosis.[10] In our cohort, however, there was no significant difference between the groups in the rate of patients who were asymptomatic at the initial diagnosis. Rather, the percentage of asymptomatic patients was smaller in sCS than in iCS, although the difference was not statistically significant (Table I and Supplemental Table I). Even when analyzed only with patients who were clinically symptomatic at the initial diagnosis, the results showed the same tendency (Supplemental Figure 2). Furthermore, quantitative analysis of myocardial LGE content did not support the possibility that the patients with iCS were in an already advanced stage at the initial diagnosis of sarcoidosis (Figure 4C). Second, there is a possibility that the clinical diagnosis group of iCS might include cardiomyopathies other than cardiac sarcoidosis, such as inflammatory cardiomyopathy and chronic myocarditis. However, histopathology did not demonstrate any inflammatory cell infiltration in the myocardium of our biopsy-negative clinically-diagnosed iCS patients. Furthermore, the clinical diagnosis of iCS is justifiable considering the comparable clinical outcome between biopsy-proven iCS and clinically diagnosed iCS.[10,28] Among iCS patients with negative myocardial biopsy findings in our cohort, 31% experienced fatal ventricular arrhythmia and 23% died of cardiac cause; whereas a previous study reported that 5.8% of those diagnosed with inflammatory cardiomyopathy suffered from fatal ventricular arrhythmia and their cardiac mortality was 3%.[29] Such striking differences in the clinical features do not convincingly support the criticism that our iCS cohort mainly comprised inflammatory cardiomyopathy. Third, iCS might have a different underlying pathophysiological condition from sCS. In fact, a poorer prognosis was ob-

served in the patients with iCS despite their lower baseline disease activity than sCS in the present study.

Because of the lack of consensus on the optimal treatment for iCS, the patients with iCS were treated with conventional corticosteroid-based regimens, as were the sCS patients, in our cohort.[10,30] Further prospective studies are warranted to confirm whether the same immunosuppressive treatment that is used for sCS is also effective in patients with iCS.

This study has several limitations. First, it was a retrospective and observational study with a small sample size from a single center. Our cohort included only Japanese patients, and thus the present results might not always be globally observed. Future assessment of more patients from a multicenter registry is needed. Second, an immunosuppressive therapy protocol for CS has not been established by validation through randomized clinical trials. We adopted a standard protocol with an initial dose of 30 mg of prednisolone followed by tapering every 4 weeks. It is possible that other therapeutic regimens might have changed the results. Third, we performed genetic testing for cardiomyopathy in only a very limited number of patients. A recent report suggested that genetic testing might help identify genetic cardiomyopathies in patients diagnosed as iCS.[31] Finally, it is difficult to definitely exclude the possibility that patients with clinically diagnosed iCS might have inflammatory cardiomyopathy or chronic myocarditis. While endomyocardial biopsy did not demonstrate inflammatory cell infiltration in the myocardium in those patients, there can be false negatives due to sampling error. However, false negatives can also occur for iCS. Our observation might imply a dilemma in diagnosing iCS based on clinical diagnosis criteria that do not include positive biopsy findings, considering the nonspecific nature of MRI and FDG-PET findings. That is, the clinical diagnosis criteria avoids delayed diagnosis, but overdiagnosis can occur to some extent. Further investigations to clearly distinguish inflammatory cardiomyopathy from isolated cardiac sarcoidosis are needed.

In conclusion, iCS showed a poorer response to immunosuppression treatment and worse prognosis than sCS. Conventional immunosuppressive therapy for sCS might be inadequate for patients with iCS. Further investigations are required in order to establish optimal treatment for iCS.

Disclosure

Conflicts of interest: Tomomi Ide received research funding from Johnson & Johnson K.K, SBI Pharmaceuticals, MEDINET Co. Ltd, and Pfizer Japan Co., Ltd. The other authors hereby state there are no other conflicts of interest to declare.

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Supplemental Files

Supplemental Tables I-V

Supplemental Figures 1, 2

Please see supplemental files; https://doi.org/10.1536/ihj.24-166