Acta Med Kinki Univ Vol. 39, No. 1 21–28, 2014

Relationship between clinical manifestations and CMR findings in cardiac sarcoidosis

Masakazu Yasuda, Yoshitaka Iwanaga, Takashi Nakamura, Hanako Morooka and Shunichi Miyazaki

Division of Cardiology, Department of Internal Medicine, Kinki University school of Medicine, Osakasayama, Osaka 589-8511, Japan

Abstract

Background: Different cardiac manifestations/events have been reported in patients with sarcoidosis; however, factors related to the onset of manifestations in cardiac sarcoidosis (CS) remain unclear. Late gadolinium-enhancement cardiac magnetic resonance (LGE-CMR) has been used to detect myocardial damage/fibrosis. Therefore, we examined the characteristics of clinical manifestations in CS patients using LGE-CMR.

Methods: Thirty-three consecutive CS patients underwent CMR. According to the mural location of LGE; mid-wall, epicardial, or transmural, the LGE pattern was classified into three groups: A: LGE existing at one location only, B: LGE at any two locations, C: LGE at all locations. CMR findings were also analyzed in relation to each clinical manifestation.

Results: Myocardial damage was detected by LGE imaging in 91% of the patients and was most frequently observed in the basal septal myocardium. %LGE area was negatively correlated with LV ejection fraction (EF) ($P<0.01$). Significantly decreased LV EF and increased %LGE area were observed in Group B and C. In addition, all patients in group C exhibited a clinical manifestation. The patients with high-grade atrioventricular block showed the increased %LGE area ($P<0.01$). Although occurrence of ventricular tachycardia was not associated with any changes in LV EF, mass, and %LGE area, hospitalization for heart failure was associated with reduced LV EF, and increased mass and %LGE area ($P<0.05$ for all).

Conclusions: Different clinical manifestations in CS have been associated with the development of myocardial fibrosis/damage and resultant myocardial dysfunction shown by CMR. CMR may be useful for characterizing the pathophysiology of respective clinical manifestations/events.

Key words: cardiac sarcoidosis, magnetic resonance imaging, heart failure, ventricular tachycardia, atrioventricular block

Background

Cardiac involvement has been closely associated with prognosis in patients with sarcoidosis and various adverse cardiac events have been reported, including severe arrhythmias and heart failure (HF) [1–3] Autopsy results revealed cardiac involvement in 20-30% of patients with sarcoidosis.[4,5] A previous study reported sudden cardiac death in two-thirds of patients with histological evidence of cardiac sarcoidosis (CS) at autopsy.[6] The 5-year mortality rate in patients with CS when structural deformation or functional abnormality is present, according to the Japanese Ministry of Health and Welfare (JMHW) diagnostic criteria, was shown to be 40%, with the cause of death being the progression of HF or cardiac arrest[7]. Therefore, cardiac involvement in patients with sarcoidosis may often be clinically unrecognized and is a primary

Received October 28, 2013; Accepted November 14, 2013

cause of death. However, risk stratification and clinical management are difficult in these patients and factors affecting the onset of clinical manifestations/events in CS also remain unclear.

Late gadolinium-enhancement cardiac magnetic resonance (LGE-CMR) has been used to detect myocardial damage/fibrosis, and recent findings have suggested that LGE-CMR is more sensitive than clinical diagnostic criteria for detecting CS.[8–10] The utility of LGE-CMR has been extensively studied in patients with sarcoidosis who are asymptomatic or at low risk for cardiac involvement. However, the utility of LGE in patients with sarcoidosis who present with high-grade cardiovascular symptoms has not yet been established. A previous study demonstrated that LGE-CMR-positive patients had a higher rate of adverse events, including cardiac death during follow-up, than that of LGE-CMR-negative patients.[11] However, the cohort consisted of patients with sarcoidosis (not CS), and few events were observed (10% in 36 months). A detailed analysis of the relationship between CMR findings and each cardiac event has also not yet been conducted. Therefore, we analyzed cardiac damage and function in detail in advanced patients with CS using CMR. We assumed that the LGE pattern may progress in conjunction with the development of the pathophysiology in CS. We then attempted to explore the relationship between clinical manifestations and cardiac characteristics using CMR.

Methods

Study Protocol

A total of 33 consecutive CS patients referred for CMR were enrolled between February 2008 and May 2013 at Kinki University Hospital, Osakasayama. Patients were enrolled if they fulfilled the following criteria : 1) JMHW criteria group : CS diagnosed by the 2006 revised JMHW criteria[12] ; or 2) Clinical group : strongly suspected CS due to characteristic manifestations and positive findings on echocardiography, 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET), or CMR with or without extra-cardiac sarcoidosis after the exclusion of other known cardiac diseases.[13] The characteristic positive findings of CMR were based on previous reports.[8,14,15] The work-up at the initial diagnosis included an electrocardiogram (ECG), echocardiography, coronary angiography, left ventriculography, 24-h Holter ECG, FDG-PET and CMR imaging. Clinical manifestations/events were defined as syncope, cardiac device implantation (implantable cardioverter defibrillator, pacemaker, or cardiac resynchronization therapy), HF hospitalization, and severe arrhythmias such as high-grade atrioventricular block (AVB), non-sustained/sustained ventricular tachycardia (VT), and ventricular fibrillation (VF). This study was approved by the Institutional Review Boards.

CMR Image Acquisition

CMR was performed using a 1.5-T scanner (Intera 1.5T ; Philips Medical Systems, Netherlands) and a standardized protocol. Cine images were acquired with a steady-state free-precession breath-hold sequence in 3 long-axis planes and contiguous short-axis slices (10-mm no gap) from the atrioventricular ring to the apex. Myocardial edema was Visualized using a T2-weighted triple inversion recovery breath-hold pulse sequence. LGE images were obtained 5-10 min after intravenous administration of 0.2 mmol•kg-1 gadolinium-DTPA (Magnevist ; Bayer Schering Pharma, Germany), using an inversion recovery gradient echo sequence with 5 mm slice thickness at the same position as the long- and short-axis cines in end-diastole. The inversion time was adjusted per patient to optimally null the signal from the normal myocardium, typically between 250 and 350 ms.

Image Analysis

On CMR, left ventricular (LV) functional and geometric parameters such as LV end-diastolic volume index (EDVI), LV end-systolic volume index (ESVI), LV ejection fraction (EF), LV mass index was measured. Distribution of LGE and high T2-weighted image areas, %LGE area, and LGE pattern were also evaluated. LV volume, LV mass, and wall thickness were calculated with commercially available workstations (View Forum ; Philips Medical System. Netherlands ; or Aze Virtual Place : Aze Ltd., Japan). To calculate LV mass, the endocardial and epicardial borders of the LV myocardium were manually planimetered on successive short-axis cine images at end-diastole. Particular care was taken to avoid including papillary muscles in the LV mass calculation. LV mass was derived from the summation of the discs method and multiplying myocardial muscle volume by 1.05 g/cm^3. To assess LGE, all short-axis slices from the base to the apex were inspected visually to identify the

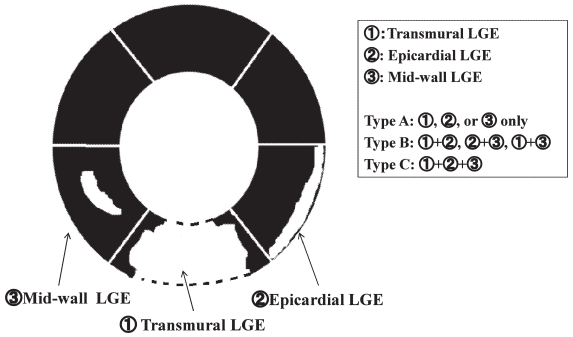

Fig. 1 Classification of LGE patterns by CMR analysis. LGE, late gadolinium enhancement.

areas of a normal (completely nulled) myocardium. Mean signal intensity (and standard deviation [SD]) was derived and a threshold of 6 SD exceeding the mean was used to define areas of LGE.[16–18] Summing the planimetered areas of LGE in all short-axis slices yielded % LGE area, which was also expressed as a proportion of total LV myocardium. LV fibrosis mass (g) was calculated by multiplying %LGE area. Local wall thickness, and the distribution/pattern in LGE and T2-weighted images were also analyzed based on the AHA 17-segment model.[19] According to the mural location of LGE, mid-wall, epicardial, or transmural, the LGE pattern was classified into three groups; A: LGE existing at one location only, B: LGE at any two locations, C: LGE at all locations (Figure 1). All analyses were performed by one experienced reader and were reviewed and confirmed by a second expert reader, with both of the independent observers being blinded to patient identities and clinical profiles. Any discrepancy in analysis between the two readers was then adjudicated by a senior observer.

Statistical analysis

Groups were compared using the χ^2 test for proportions and unpaired t-test or analysis of variance for continuous variables, as appropriate. The linearity of the relationship between two variables was assessed by linear regression analysis and Pearson's correlation coefficient was calculated using JMP version 10.0. $P<0.05$ was considered significant. Results are expressed as the mean±SD.

Results

Baseline characteristics

We enrolled 33 consecutive patients who underwent CMR (Table 1). Among them, 16 patients were classed as the JMHW criteria group (CS based on the 2006 revised JMHW criteria) and the remaining 17 patients were classed as the clinical group (strongly suspected CS). The mean age of patients was 63.5±11.1 years and 66.7% were female. The BNP level was increased (212.3±289.1 pg/ml) and LV EF was reduced (46.7±14.0%). Twelve patients were receiving corticosteroid therapy and 19 patients exhibited clinical manifestations such as syncope, high-grade AVB, VT/VF, and HF. No significant differences in baseline characteristics, including CMR parameters and the prevalence of clinical manifestations, were observed between the JMHW criteria group and clinical group, except for the presence of extra-cardiac involvements, ACE levels and corticosteroid therapy.

CMR analysis

LGE images from three representative cases are shown in Figure 2; one patient in the JMHW criteria group had no clinical manifestation (LGE pattern A), one in the clinical group had VT (LGE pattern B), and one in the JMHW criteria group had HF (LGE pattern C).

Myocardial damage was detected by LGE imaging in 91% of patients and was most frequently observed in the basal septal myocardium (Figure 3). T2-weighted high - intensity areas were also frequently observed in the basal septum. As shown in Figure 4, %LGE area (% fibrosis area) was negatively correlated with LV EF ($R=0.55$, $P<0.01$) and positively with the LV EDVI ($R=0.35$, $P=0.046$), but was not associated with LV mass ($P=0.359$). When LGE patterns were analyzed (Figure 1 and Table 2), a decrease in LV EF and increase in LV fibrosis were observed in conjunction with progression of the LGE pattern. In addition, more clinical manifestations were observed in Group B and C, and all patients in group C had some manifestation/event. Hospitalization for HF, high-grade AVB and device implantation was significantly correlated with progression of the LGE pattern.

CMR findings and clinical manifestations/events

LV EF was significantly lower, and LV mass, and % LVG and fibrosis mass were significantly higher in CS patients with some clinical manifestation ($n=19$) than in those without manifestations ($n=14$). High-grade AVB ($n=7$) was correlated with an increase in %LGE area only ($P<0.01$). VT/VF ($n=8$) was not associated with any changes in LV EF, LV mass index and

Table 1 Patient characteristics

	All Patients (n=33)	JMHW criteria (n=16)	Clinical (n=17)	p value
Age, years	63.5±11.1	63.6±10.4	63.5±12.0	0.99
Female	22(66.7)	13(81.3)	9(52.9)	0.08
Extra-cardiac sarcoidosis	18(54.5)	16(100)	2(11.7)	<0.01
NYHA class≥II	12(36.4)	8(50.0)	4(23.5)	0.11
HT	17(51.5)	8(50.0)	9(52.9)	0.87
ACE, IU/L	19.5±11.6	25.0±13.0	14.3±7.1	<0.01
BNP, pg/mL	212.3±289.1	219.8±373.1	205.7±202.2	0.89
ECG abnormality	23(69.7)	11(68.8)	12(70.6)	0.91
LV morphological abnormality				0.42
Thinning	12(36.3)	5(31.3)	7(41.2)	
Aneurysmal	5(15.2)	3(18.8)	2(11.8)	
Others	7(21.2)	5(31.3)	2(11.8)	
Medication				
ACEI or ARB	16(48.5)	9(56.3)	6(35.3)	0.23
β-blocker	9(27.3)	4(25.0)	5(29.4)	0.78
Corticosteroids	12(36.4)	10(62.5)	2(11.8)	<0.01
CMR parameters				
LV EDVI, ml/m^2	97.6±38.8	101.6±36.9	93.9±41.4	0.58
LV ESVI, mlv/m^2	55.3±32.2	57.0±36.8	53.7±28.4	0.77
LV EF, %	46.7±14.0	47.6±16.3	46.0±11.9	0.75
LV mass index, g/m^2	75.8±13.2	74.4±11.8	77.1±14.7	0.57
%LGE area, %	19.6±14.0	18.0±13.0	21.1±15.2	0.54
Fibrosis mass index, g/m^2	14.1±10.7	13.5±10.3	14.8±11.5	0.74
Clinical manifestations/events				
Syncope	8(24.2)	3(18.8)	5(29.4)	0.22
Cardiac device Implantation	11(33.3)	3(18.8)	8(47.1)	0.08
High-grade AVB	8(24.2)	3(18.8)	5(29.4)	0.35
VT/VF	8(24.2)	3(18.8)	5(29.4)	0.22
Hospitalization for HF	7(21.2)	3(18.8)	4(23.5)	0.35

Values are the mean±SD or number (%).

ACE, angiotensin-converting enzyme; ACEI; ACE inhibitor; ARB, angiotensin receptor blocker; AVB, atrioventricular block; BMI, body mass index; BNP, B-type natriuretic peptide; CS, cardiac sarcoidosis; EDVI, end-diastolic volume index; EF; ejection fraction; ESVI, end-systolic volume index; HF, heart failure; HT, hypertension; LGE, late gadolinium enhancement; LV, left ventricular; VT, ventricular tachycardia; VF, ventricular fibrillation.

%LGE area (P=0.194, P=0.072, and P=0.175, respectively) (Figure 5). In patients with NYHA class ≥II (n=12), reduced EF, and increased LV mass index and %LGE area were all observed (P=0.011, P=0.012, P=0.024, respectively). Similar correlations were also observed in those with HF hospitalization (n=7). BNP levels were significantly increased in patients with VT/VF and HF (P=0.008 and P=0.002, respectively).

Discussion

Three major findings were obtained when the myocardium in 33 CS patients was analyzed using CMR in the present study: first, 51.5% of patients did not fulfill the JMHW diagnostic criteria. Almost all the patients had isolated CS (i.e. the absence of extra-cardiac sarcoidosis) and were administered an attenuated corticosteroid treatment. Second, cardiac dysfunction and different clinical manifestations/events, such as syncope, high-grade AVB, VT/VF, and HF, were reported in patients with CS in conjunction with progression of the LGE pattern, i.e. the development of myocardial damage/fibrosis. Lastly, distinct characteristics were observed in each clinical manifestation by CMR analysis,

which suggests that CMR may be a useful tool for characterizing the pathophysiology of respective clinical manifestations/events in CS patients.

Diagnosis and CMR in CS

The diagnosis of CS, especially isolated CS, is challenging because its clinical manifestations are non-specific and no gold standard diagnostic test has yet been established. The JMHW criteria were revised in 2006 and the positive findings of LGE by CMR were added to these criteria because they may improve the sensitivity of diagnosis.[8,13] The CMR features of CS may include focal myocardial thickening with wall motion abnormalities and increased T2-weighted signals in the acute stage, and scarring and focal areas of myocardial thinning with a variable and non-vascular pattern of LGE in the chronic stage.[20] Previous studies have shown that LGE-CMR is more sensitive than electrocardiography, echocardiography, or the JMHW criteria for diagnosing CS.[9,21] In addition, Kandolin et al. reported that LGE was observed in 94% of 33 patients with cardiac biopsy-proven CS,[22] which is similar to the findings obtained in our cohort (LGE-positive in 91% of patients). Almost all patients (87.5%) were also positive for LGE on CMR in the JMHW criteria group in the present study. Myocardial biopsy is necessary to diagnose isolated CS; however, its sensitivity is known to be low.[7,23] Although the clinical characteristics, including clinical manifestations of the clinical group (strongly suspected isolated CS) in our cohort, were similar to CS with extracardiac involvement, only corticosteroid treatment was attenuated. This has been attributed to the difficulty associated with establishing a clinical diagnosis of isolated CS.[24] Valuable diagnostic tools are required to differentiate this diagnosis from other cardiomyopathies such as idiopathic dilated cardiomyopathy. The detailed identification of CMR characteristics in

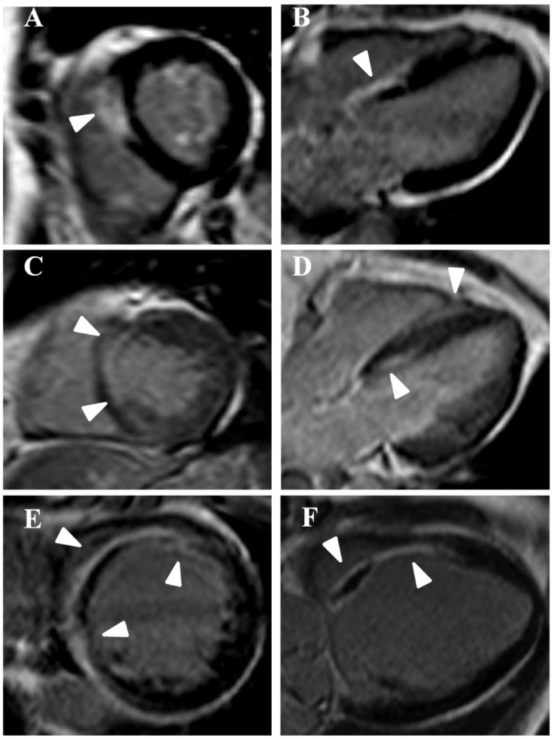

Fig. 2 LGE images in three representative cases; (A) (B) one patient in the JMHW criteria group had no clinical events (LGE pattern A), (C) (D) one in the clinical group had VT (LGE pattern B), and (E) (F) one in the JMHW criteria group had HF (LGE pattern C). Arrowheads show the lesions of LGE in the myocardium. HF, heart failure; LGE, late gadolinium enhancement; VT, ventricular tachycardia.

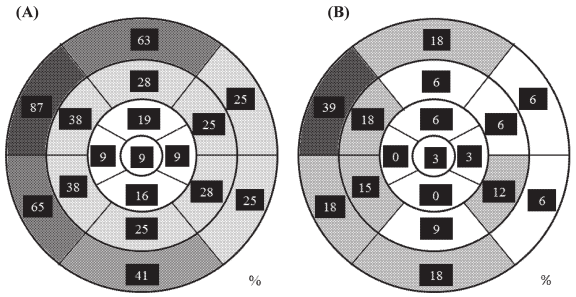

Fig. 3 Distribution of (A) LGE-positive and (B) T2-weighted high intensity areas according to the AHA 17-segment model. Percentage (%) of positive lesions in each AHA segment is shown. LGE; late gadolinium enhancement.

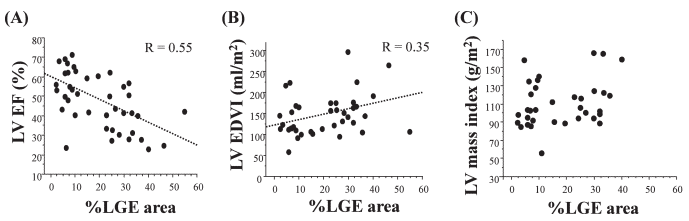

Fig. 4 Relationship of %LGE (fibrosis) area with LV EF (A), LV EDVI (B), and LV mass (C). EDVI, end-diastolic volume index; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular.

Table 2 LGE patterns, CMR parameters, and clinical manifestations/events

	Type A (n=13)	Type B (n=11)	Type C (n=8)	p value
Age, years	65.3±10.9	63.3±13.0	63.1±8.5	0.87
Female	10(76.9)	7(63.6)	4(50.0)	0.44
ACE, IU/L	26.8±13.5	14.9±7.4	14.1±7.5	0.01
BNP, pg/mL	122.0±216.3	147.0±175.2	416.7±419.8	0.06
NYHA≥II	3(23.1)	4(36.4)	5(62.5)	0.19
LV EDVI, ml/m²	87.4±29.9	95.4±41.1	109.5±44.9	0.44
LV EF, %	55.1±12.7	44.8±12.6	35.6±10.7	<0.01
LV mass index, g/m²	73.2±13.3	74.9±13.5	79.5±12.8	0.06
%LGE area, %	7.4±4.0	21.7±9.3	36.4±10.4	<0.01
Fibrosis mass index, g/m²	5.3±2.6	16.3±7.9	27.2±9.1	<0.01
Clinical manifestations/events	3(23.1)	7(63.6)	8(100)	<0.01
Syncope	2(15.4)	2(18.2)	3(37.5)	0.46
Cardiac device implantation	1(7.7)	5(45.5)	4(50.0)	0.04
High-grade AVB	0(0)	3(27.3)	4(50.0)	0.02
VT/VF	1(7.7)	4(36.4)	3(37.5)	0.17
Hospitalization for HF	1(7.7)	1(9.1)	5(62.5)	<0.01

Values are the mean±SD or number (%).

ACE, angiotensin-converting enzyme; AVB, atrioventricular block; BNP, B-type natriuretic peptide; EDVI, end-diastolic volume index; EF, ejection fraction; HF, heart failure; HT, hypertension; LGE, late gadolinium enhancement; LV, left ventricular; NYHA, New York Heart Association functional class; VT, ventricular tachycardia; VF, ventricular fibrillation.

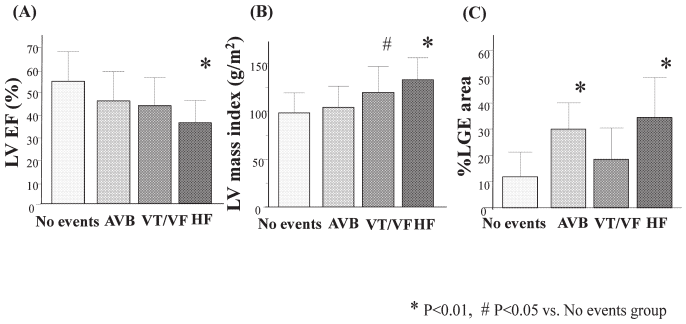

Fig. 5 Relationship between each clinical manifestation/event and CMR findings; LV EF (A), LV mass (B), and %LGE area (C). AVB, high-grade atrioventricular block; EF, ejection fraction; HF, heart failure hospitalization; LGE, late gadolinium enhancement; LV, left ventricular; VT, ventricular tachycardia; VF, ventricular fibrillation.

isolated CS may be helpful.

Clinical Manifestations in CS

Patients with CS are complicated by various clinical manifestations. A necropsy study by Roberts et al. reported the following electrocardiogram (ECG) abnormalities: complete heart block (22%); complete bundle branch block (2%); VT (17%); premature ventricular contractions (PVCs) (29%); and atrial arrhythmias (16%).[6] Thus, the clinical manifestations of CS may depend on the location and extent of granulomatous infiltration and resultant fibrosis. Our correlation analysis clearly showed the characteristics of respective cardiac manifestations on CMR in CS patients (Figure 5). High-grade AVB was correlated with an increase in %fibrosis area only. In contrast, the occurrence of VT/VF was not associated with decreased LV EF and increased % LGE area. Recent CMR studies of non-ischemic cardiomyopathy suggest that a more extensive scar predicts the inducibility of VT/VF.[25] Such a result may be obtained if fibrosis is analyzed in a broad range of patients with sarcoidosis. However, the localization, distribution, or inhomogeneous pattern rather than the extent of fibrosis may be an important determinant in CS patients.[26] In addition, LV fibrosis mass index was extensively increased in patients with HF hospitalization (27.0±12.8 g/m² vs. 9.3±7.1 g/m² in non-event group; P<0.001). It also showed a close negative relationship with LV EF (R=0.661, P<0.001) in CS

patients. Extensive myocardial fibrosis after granulomatous infiltration and the resultant reduced LV function may be a basic pathological mechanism of HF in patients with CS.

Several groups determined that CMR using LGE may be promising for predicting future adverse events, including cardiac death in CS, in addition to improving the detection of CS. The presence of LGE among similar patients in a recent prospective study yielded a Cox hazard ratio of 31.6 for death, aborted sudden cardiac death, and appropriate ICD discharge, and of 33.9 for events including death and VTs during a follow-up of 3.4 years.[27] Analyses were performed in these studies based on the presence or absence of LGE, and the studied cohort consisted of a broad range of patients with systemic sarcoidosis. However, as shown in the present study, the LGE pattern, spacial distribution, and extent varied and may be associated with clinical manifestations differently in patients with CS. Therefore, the detailed analysis performed in our study may be more useful in predicting future adverse events in patients with CS. CMR in CS may yield detailed prognostic information above that of traditional risk models and further prospective studies are necessary to elucidate this.

Study limitations & clinical implications

Several limitations should be considered when interpreting our results. First, the study population was relatively small. Therefore, any negative findings were caused by low statistical power. However, the size of our cohort was average relative to that of other studies using CMR in CS, and our study uniquely addressed the relationship between CMR findings and clinical manifestations in patients with CS. Second, the present study was retrospective and cross-sectional; thus, it had several inherent limitations, including selection and referral biases. Third, the study population consisted of CS patients who could undergo CMR; patients who could not tolerate the procedure or would be at high risk were excluded. In particular, patients with previously implanted devices, were excluded. Therefore, the applicability of our results to patients with more severe forms of arrhythmia remains uncertain.

Funding: S.M. received research support from Daiichi-Sankyo Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Sanofi-Aventis K.K.; however, these companies played no role in the conception, conduct, or analysis of this study.

Conflicts of interest: none to declare.

References

1. Segikuchi M, Yazaki Y, Isobe M, Hiroe M (1996) Cardiac sarcoidosis: diagnostic prognostic and therapeutic considerations. Cardiovasc Drugs Ther 10: 495–510
2. Kim JS, et al. (2009) Cardiac sarcoidosis. Am Heart J 157: 9–21
3. Doughan AR, Williams BR (2006) Cardiac sarcoidosis. Heart 92: 282–288
4. K.J. Silverman, G.M. Hutchins, B.H. Bulkley (1978) Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation 58: 1204–1211
5. Longcope WT, Freiman DG (1952) A study of sarcoidosis; based on a combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. Medicine (Baltimore) 31: 1–132
6. Roberts WC, McAllister HA Jr., Ferrans VJ (1977) Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). Am J Med 63: 86–108
7. Yazaki Y, et al. Central Japan Heart Study Group (2001) Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol 88: 1006–1010
8. Smedema JP, et al. (2005) Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol 45: 1683–1690
9. Mehta D, et al. (2008) Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. Chest 133: 1426–1435
10. Ohira H, et al. (2008) Myocardial imaging with 18-F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. Eur J Nucl Med Mol Imaging 35: 933–941
11. Patel MR, et al. (2009) Detection of myocardial damage in patients with sarcoidosis. Circulation 120: 1969–1977
12. Tahara N, et al. (2010) Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. JACC Cardiovasc Imaging 3: 1219–1228
13. Youssef G, Beanlands RS, Birnie DH, Nery PB (2011) Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. Heart 97: 2078–2087
14. Tadamura E, et al. (2005) Effectiveness of delayed enhanced MRI for identification of cardiac sarcoidosis: comparison with radionuclide imaging. AJR Am J Roentgenol 185: 110–115
15. Vignaux O (2005) Cardiac sarcoidosis: spectrum of MRI features. AJR Am J Roentgenol 184: 249–254
16. Bondarenko O, et al. (2005) Standardizing the definition of hyperenhancement in the quantitative assess-

ment of infarct size and myocardial viability using delayed contrast-enhanced CMR. J Cardiovasc Magn Reson 72 : 481–485
17. Flett AS, et al. (2011) Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovasc Imaging 4 : 150–156
18. Spiewak M, et al. (2010) Comparison of different quantification methods of late gadolinium enhancement in patients with hypertrophic cardiomyopathy. Eur J Radiol 74 : e149–153
19. Cerqueira MD, et al. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging (2002) Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. J Nucl Cardiol 9 : 240–245
20. Habersberger J, Manins V, Taylor AJ (2008) Cardiac sarcoidosis. Intern Med J 38 : 270–277
21. Patel AR, et al. (2011) Myocardial damage in patients with sarcoidosis and preserved left ventricular systolic function : an observational study. Eur J Heart Fail 13 : 1231–1237
22. Kandolin R, et al. (2011) Diagnosing isolated cardiac sarcoidosis. J Intern Med 270 : 461–468
23. Uemura A, et al. (1999) Histologic diagnostic rate of cardiac sarcoidosis : evaluation of endomyocardial biopsies. Am Heart J 138 : 299–302
24. Hamzeh NY, Wamboldt FS, Weinberger HD (2012) Management of cardiac sarcoidosis in the United States : a Delphi study. Chest 141 : 154–162
25. Gulati A, et al. (2013) Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA 309 : 896–908
26. Tavora F, et al. (2009) Comparison of necropsy Findings in Patients with Sarcoidosis Dying Suddenly from Cardiac Sarcoidosis Versus dying Suddenly from Other Causes. Am J Cardiol 104 : 571–577
27. Greulich S, et al. (2013) CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. JACC Cardiovasc Imaging 6 : 501–511