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Intra-cardiac distribution of late gadolinium enhancement in cardiac sarcoidosis and dilated cardiomyopathy

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Abstract

Cardiac involvement of sarcoid lesions is diagnosed by myocardial biopsy which is frequently false-negative, and patients with cardiac sarcoidosis (CS) who have impaired left ventricular (LV) systolic function are sometimes diagnosed with dilated cardiomyopathy (DCM). Late gadolinium enhancement (LE) in magnetic resonance imaging is now a critical finding in diagnosing CS, and the novel Japanese guideline considers myocardial LE to be a major criterion of CS. This article describes the value of LE in patients with CS who have impaired LV systolic function, particularly the diagnostic and clinical significance of LE distribution in comparison with DCM. LE existed at all LV segments and myocardial layers in patients with CS, whereas it was localized predominantly in the midwall of basal to mid septum in those with DCM. Transmural (nodular), circumferential, and subepicardial and subendocardial LE distribution were highly specific in patients with CS, whereas the prevalence of striated midwall LE were high both in patients with CS and with DCM. Since sarcoidosis patients with LE have higher incidences of heart failure symptoms, ventricular tachyarrhythmia and sudden cardiac death, the analyses of extent and distribution of LE are crucial in early diagnosis and therapeutic approach for patients with CS.

Key words: Magnetic resonance imaging; Late gadolinium enhancement; Sarcoidosis; Dilated cardiomyopathy; Diagnosis

Core tip: Late gadolinium enhancement (LE) in magnetic resonance imaging is a critical finding in the diagnosis of cardiac sarcoidosis (CS), but it is also observed in dilated cardiomyopathy (DCM). We review the significance of LE distribution in comparison with DCM. LE distributed into

all ventricular segments and myocardial layers in CS, whereas it was localized predominantly in the midwall of ventricular septum in DCM. Transmural, circumferential, and subepicardial and subendocardial LE were highly specific in CS. Since patients with LE have more adverse cardiac events, the analyses of extent and distribution of LE are crucial for diagnosis and management of CS.

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INTRODUCTION

Sarcoidosis is a multi-organ granulomatous disorder of undetermined aetiology. Cardiac involvement is identified clinically only in few percentage (%) of patients with systemic sarcoidosis, while post-mortem investigations have found myocardial lesions in around 60%[1]. Necropsies exhibited that cardiac involvement was mostly non-transmural and lesions were located predominantly in the basal left ventricle (LV) and subepicardial myocardium[2,3]. Patients with cardiac sarcoidosis (CS) have a poor prognosis due to congestive heart failure with impaired LV function, and sudden cardiac death associated with lethal ventricular tachycardia (VT) or conduction disturbance[4].

Although endomyocardial biopsy has been the gold standard in diagnosing CS, it has limited sensitivity and certain procedural risks[5]. Actually, the results of endomyocardial biopsy were frequently false negative because of the patchy distribution of the lesions. Therefore, patients with cardiac involvement of systemic sarcoidosis (sCS) and with isolated CS (iCS) are not always positive for endomyocardial biopsy. As a result, a certain part of patients may be diagnosed with normal or dilated cardiomyopathy (DCM), and do not receive immunosuppressive therapies. Since a corticosteroid therapy can improve long-term prognosis of CS[6,7], an earlier diagnosis of CS with non-invasive cardiac imaging is clinically significant.

The recent development of various imaging modalities including magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose-positron emission computed tomography (FDG-PET) has enabled more precise diagnosis of CS. The LV wall in most patients with CS has late gadolinium enhancement (LE) in MRI[5,8-10], and the novel guideline of Japanese Ministry of Health and Welfare (JMH) considers the presence of LE to be a major criterion in CS (Table 1)[11]. However, LE is non-specific and frequently observed in other cardiomyopathies including DCM.

We have been investigating the patterns of LE distribution in various cardiomyopathies and trying to confirm the values for differential diagnosis, clinical features, and prognosis[12-18]. Here we describe the value of LE in patients with CS, particularly the diagnostic and clinical significance of LE distribution in comparison with DCM.

Table 1 Clinical cardiac findings in Diagnostic Standard and Guideline for Sarcoidosis-2015-Japanese Society of Sarcoidosis and Other Granulomatous Disorders

(1) More than two of five major findings are satisfied
(2) One of five major findings and more than two of three minor findings are satisfied
Major findings
Advanced atrioventricular block (including complete atrioventricular block) or sustained ventricular tachycardia
Basal thinning of the interventricular septum or morphological ventricular abnormality (ventricular aneurysm, wall thinning of other ventricular region, wall thickening)
Impaired left ventricular contraction (LVEF < 50%) or regionally abnormal wall motion
Abnormal cardiac uptake in gallium-67 citrate scintigraphy or fluorine-18 fluorodeoxyglucose PET
Late myocardial enhancement in gadolinium enhanced magnetic resonance imaging
Minor findings
Non-sustained ventricular tachycardia, multifocal or frequent premature ventricular contractions, bundle branch block, axis deviation, or abnormal Q wave in electrocardiography
Defect on myocardial perfusion scintigraphy
Endomyocardial biopsy: Interstitial fibrosis or monocyte infiltration over moderate grade

LVEF: Left ventricular ejection fraction; PET: Positron emission tomography.

LE DISTRIBUTION IN CS AND DIFFERENTIAL DIAGNOSIS FROM DCM

Patient characteristics

We initially enrolled 21 patients with CS who had LE in the myocardium between 2003 and 2015. Among them, the intra-cardiac and intra-mural distribution of LE were analyzed in 14 (67%) patients (13 sCS and 1 iCS) who showed reduced LV ejection fraction (LVEF: < 50%). The clinical characteristics and LE features were compared with 30 patients with DCM who were diagnosed by the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies[19]. The present study was performed in accordance with the Declaration of Helsinki and the protocol was approved by an institutional review board. All study participants provided informed consent.

Patients with CS included more female patients and were younger, but there were no differences in symptoms, ECG findings and medications excluding corticosteroids (Table 2). Patients with CS had less decreased LVEF and smaller LV end-systolic volume index, while LV end-diastolic volume index and LV mass index did not differ from those in DCM. The LV segment number with LE was also greater in patients with CS. Figure 1 shows LE-MRI images (left) and corresponding

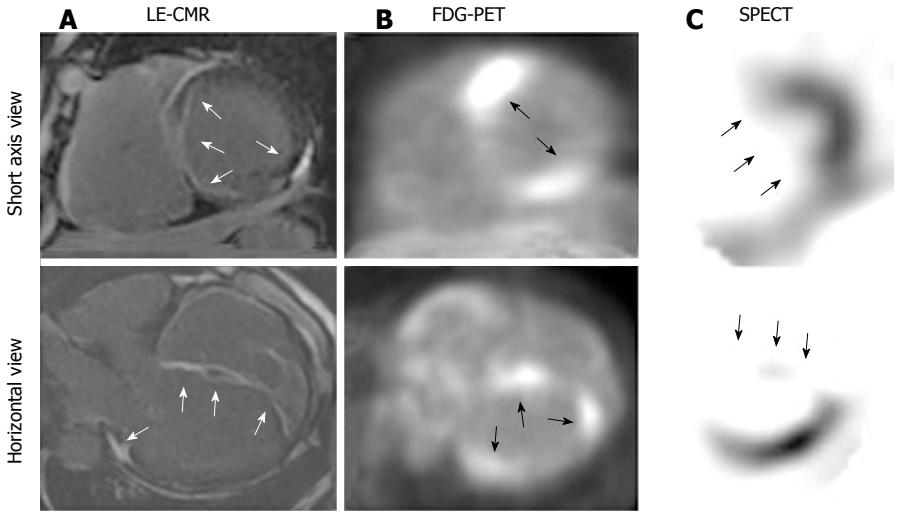

Figure 1 Non-invasive cardiac imaging in a 61-year-old male patient with cardiac involvement of systemic sarcoidosis. LE-CMR (A) shows diffuse LE in the subepicardium (RV side) and subendocardium (LV side) of basal to apical ventricular septum and patchy LE in the midwall of posterior LV (white arrows); Corresponding FDG-PET (B) demonstrates focal uptake in basal and apical ventricular septum and posterior LV wall (black arrows); ^{99m}Tc-sestamibi SPECT (C) exhibits a defect only in ventricular septum (black arrows). CMR: Cardiac magnetic resonance; FDG-PET: ^{18}F-fluorodeoxyglucose-positron emission computed tomography; LE: Late gadolinium enhancement; LV/RV: Left and right ventricles; SPECT: Single photon emission computed tomography.

FDG-PET (middle) and ^{99m}Tc-sestamibi single photon emission computed tomography (SPECT: right) in a 61-year-old patient with sCS. LE-MRI exhibits diffuse LE in the subepicardium (RV side) and subendocardium (LV side) of basal to apical ventricular septum and patchy LE in the midwall of posterior LV (white arrows). FDG-PET demonstrates focal uptake in basal and apical ventricular septum and posterior LV wall (black arrows). ^{99m}Tc-sestamibi SPECT shows a defect only in ventricular septum (black arrows).

Intra-LV and intra-mural LE distribution

The intra-LV LE distribution was analyzed using the 17-segments model[16]. Next, we visually divided the intra-mural LE distribution into subepicardial, midwall and subendocardial distribution. Then, the extent of LE in each segment was determined with a five-point scoring system (0 = no LE, 1 = 1%-25%, 2 = 26%-50%, 3 = 51%-75%, 4 = 76%-100% of transmural extent of LE). The segment with score 4 was defined as "transmural" distribution[16]. LE in patients with CS existed predominantly in the basal and mid septum, but also distributed throughout LV segments. While in patients with DCM, LE was localized mostly in the basal and mid septum[13,16]. In addition, LE distributed across all the myocardial layers in patients with CS, but was predominantly localized at the midwall in those with DCM (Figure 2). The averaged LE score in each LV segment was significantly higher in CS than that in DCM [0.95 ± 0.67 *vs* 0.42 ± 0.43, mean ± standard deviation (SD), $P < 0.05$].

Typical LE distribution profiles

Previous reports have also shown that transmural (nodular) distribution, circumferential subepicardial distribution, and subepicardial and subendocardial distribution (with spared midwall) are highly charac-

Table 2 Clinical features and magnetic resonance imaging parameters in patients with cardiac sarcoidosis and with dilated cardiomyopathy

	CS	DCM	*P* values
Number	14	30	
Sex (M/F)	M4/F10	M23/F7	0.001
Age (yr)	59.8 ± 13.5	69.2 ± 12.6	0.03
Syncope *n* (%)	2 (14.3)	6 (20.0)	0.65
Palpitation *n* (%)	7 (50.0)	17 (56.7)	0.74
NYHA	8/5/1/0	8/11/6/5	0.08
(I/II/III/IV)	(57.1%/35.7%/ 7.1%/0%)	(26.7%/36.7%/ 20%/16.7%)	
ECG findings			
PQ duration	188.4 ± 26.0	188.1 ± 40.9	0.91
1st/2nd AVB	7/1 (50.0%/7.1%)	7/0 (23.3%/0%)	0.14
QRS duration	118.6 ± 22.9	128.4 ± 36.3	0.18
Abnormal Q waves *n* (%)	6 (42.9)	3 (10.0)	0.09
RBBB/LBBB	3/5 (21.4%/35.7%)	2/15 (6.7%/50%)	0.57
VTs *n* (%)	7 (50.0)	15 (50.0)	0.74
Medications *n* (%)			
Corticosteroids	7 (50.0)	0 (0)	< 0.001
ACEI/ARB	9 (64.3)	20 (66.7)	0.73
β blockers	7 (50.0)	23 (76.7)	0.07
AADs	4 (28.6)	14 (46.7)	0.51
Diuretics	7 (50.0)	18 (60.0)	0.32
MRI			
LVEDVI (mL/m^2)	107.0 ± 45.8	135.5 ± 43.4	0.08
LVESVI (mL/m^2)	74.2 ± 44.5	106.3 ± 42.1	0.04
LVMI (g/m^2)	60.1 ± 24.9	67.1 ± 28.9	0.34
LVEF (%)	33.9 ± 11.0	22.8 ± 10.0	0.003
LE segment number	8.6 ± 4.6	5.3 ± 3.1	0.04

The categorical variables were expressed as number and percentage (%) and compared by χ^2 test. The continuous variables were expressed as means ± SD and examined by unpaired *t* test. CS: Cardiac sarcoidosis; DCM: Dilated cardiomyopathy; M/F: Male/female; NYHA: New York Heart Association; ARB: Angiotensin receptor blockers; ACEI: Angiotensin converting enzyme inhibitors; AVB: Atrioventricular block; AAD: Anti-arrhythmic drugs; MRI: Magnetic resonance imaging; LVEDVI and LVESVI: Left ventricular end-diastolic and end-systolic volume indices; LVEF: LV ejection fraction; LE: Late gadolinium enhancement; L/RBBB: Left/right bundle branch blocks; LVMI: LV mass index; VT: Ventricular tachycardia.

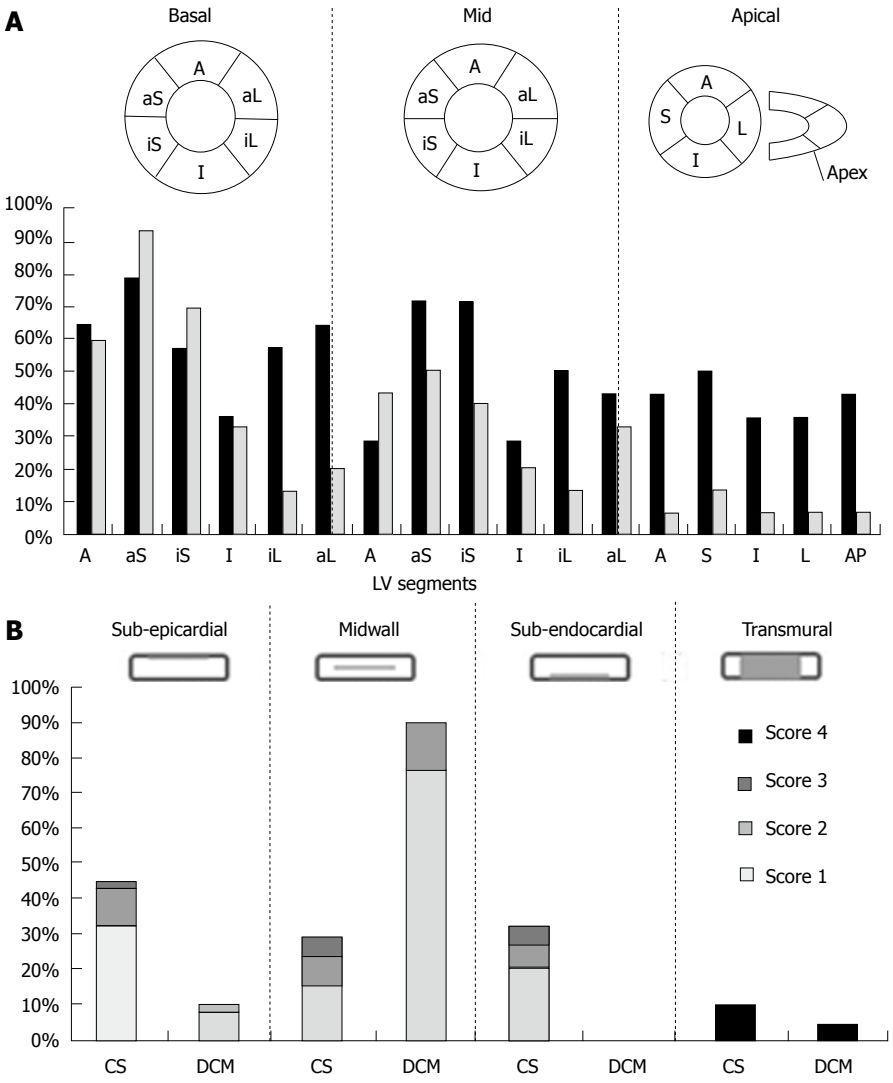

Figure 2 Intra-left ventricles (A) and intra-mural (B) late gadolinium enhancement distribution in patients with cardiac sarcoidosis and with dilated cardiomyopathy. A: Columns indicate prevalence of LE at each LV segment in patients with CS (black) and with DCM (gray). A: Anterior; aL: Antero-lateral; aS: Anterior septal; I: Inferior; iL: Infero-lateral wall in basal, mid and apical LV; AP: LV apex; B: Columns consist of prevalence of LE with scores 1 to 3 at different intra-mural distribution in patients with CS and with DCM. Score 4 indicates the transmural distribution. CS: Cardiac sarcoidosis; DCM: Dilated cardiomyopathy; LV: Left ventricles.

teristic in CS, whereas striated distribution in midwall is typical in DCM (Figure 3A)[5,10]. In our analysis, transmural (nodular), circumferential, and subepicardial and subendocardial LE distribution were highly specific in patients with CS, although the prevalence of those distribution patterns was low. In contrast, the prevalence of striated midwall LE distribution was high in both groups, but the specificity was low (Figure 3B and Table 3).

DISCUSSION

We initially demonstrated typical findings of various cardiac imaging in a patient with CS. Many reports have exhibited the correlations among LE-MRI, SPECT and FDG-PET in the evaluation of CS. The intra-mural extent of LE was quite concordant with perfusion defects in ^{201}Tl- or ^{99m}Tc-sestamibi-SPECT[9,13]. On the other hand, FDG-PET exhibits focal or focal on diffuse type of hot spots in CS[20-22]. While LE and defects in SPECT reflect irreversible fibro-granulomatous replacement, the hot spots in T2-weighted black-blood imaging (T2WBB), ^{67}Ga-SPECT and FDG-PET express active inflammatory change. The hot spots can be targeted for an endomyocardial biopsy if tissue diagnosis is required, and be adopted for an evaluation of corticosteroid therapy[21,23]. Since FDG-PET can give higher sensitivity and specificity than SPECT, we recommend the combination of LE-MRI and FDG-PET for assessing CS[20,21]. LE sometimes overlaps with hot spots in FDG-PET or T2WBB according to the disease progression or recurrence. Thus, it is important to carefully interpret findings in LE-MRI and other imaging modalities[24].

LE distributions in CS

Managing patients with reduced LV contraction who are suspected CS without histologic manifestation is a critical issue, since these cases may be diagnosed

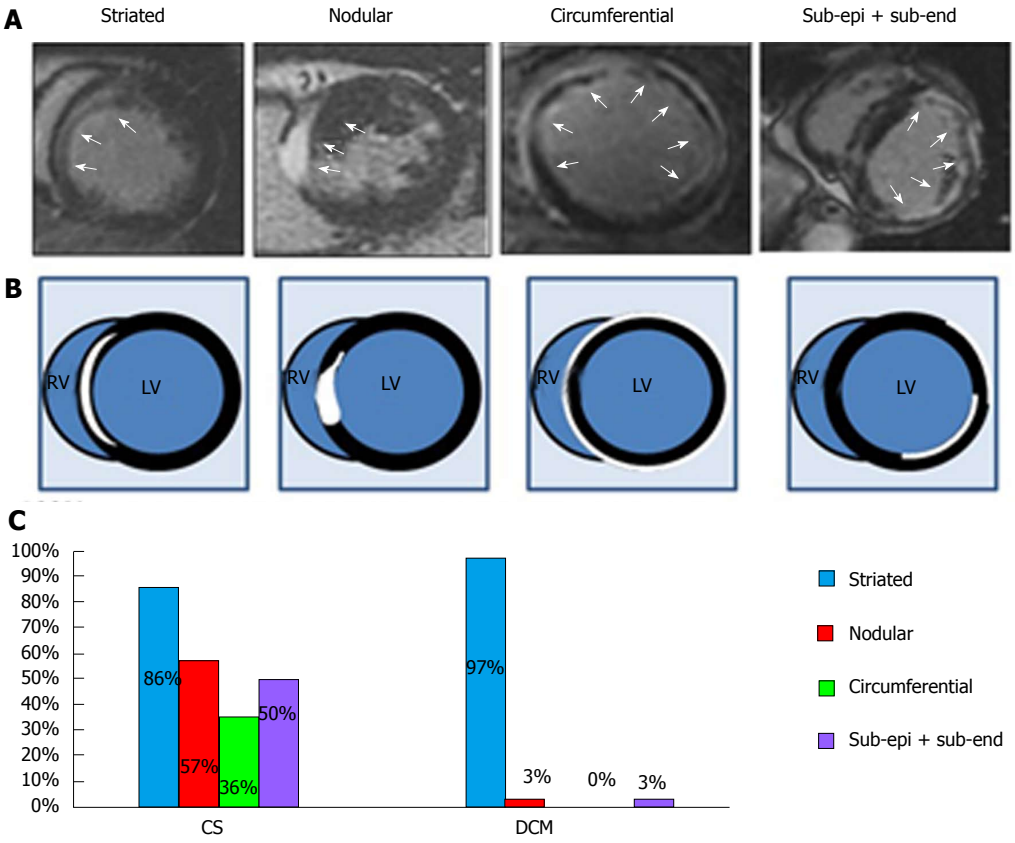

Figure 3 Typical late gadolinium enhancement distribution profiles. Characteristic patterns of LE distribution in LE-MRI (A) and the cartoons (B). Striated: Striated LE distribution in midwall; Nodular: Nodular (transmural) LE distribution; Circumferential: Subepicardial LE distribution in > 50% circumferential LV wall; Sub-epi + sub-end: Subepicardial and subendocardial LE distribution with spared midwall (white arrows); C: The prevalence of characteristic patterns of LE distribution in patients with CS and with DCM. CS: Cardiac sarcoidosis; DCM: Dilated cardiomyopathy; LE: Late gadolinium enhancement; LV/RV: Left and right ventricles; MRI: Magnetic resonance imaging.

Table 3 Diagnostic value of characteristic late gadolinium enhancement distribution patterns to differentially diagnose cardiac sarcoidosis from dilated cardiomyopathy

LE patterns	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Striated	85.7	3.3	29.3	33.3
Nodular	57.1	96.7	88.9	82.9
Circumferential	35.7	96.7	83.3	76.3
Subepi + subend	50.0	96.7	87.5	80.6

PPV and NPV: Positive and negative predictive values; Sub-epi + sub-end: Subepicardial and subendocardial distribution with spared midwall; LE: Late gadolinium enhancement.

with DCM, and do not receive corticosteroid therapy[25]. Oppositely, the inclusion of the presence of LE in the novel JMH guideline (Table 1) may cause an increase in false positive patients. Although FDG-PET can be an additional tool for diagnosing CS, it is not always available in all hospitals and patients. Therefore, more detailed analyses of LE-MRI are required to differentiate CS from DCM.

Many previous studies have clarified the characteristic LE distribution in CS (Table 4). In general, LE in CS is polymorphic and heterogeneous; a classic pattern of midwall or subepicardial LE can be seen, but subendocardial or transmural LE as in patients with ischemic cardiomyopathy is also possible. LE may correspond to the location of wall thinning, wall motion abnormalities and myocardial edema[5,8,10,13,25-30]. Tezuka *et al*[25] reported that there was no difference in LE distribution between sCS and iCS.

In our analysis, transmural (nodular), circumferential, and subepicardial and subendocardial LE distribution were highly specific in patients with CS, although the prevalence of those distribution patterns was low. In contrast, the prevalence of striated midwall LE distribution was high in both groups, but the specificity was low. Although the mechanisms of these types of LE distribution remain unknown, more aggressive examination for CS such as serological tests, ^{67}Ga-SPECT and FDG-PET should be considered, when patients with reduced LVEF showed diffuse and characteristic features of LE distribution.

Clinical implications of LE

In general, LE in patients with cardiomyopathies correlates with all-cause mortality, heart failure hospitalization, and sudden cardiac death. Thus, detection of LE by LE-MRI has excellent prognostic significance and may help guide risk stratification and management in patients with various cardiomyopathies[17,31].

In sarcoidosis, previous reports showed that patients

Table 4 Reports for patterns of late gadolinium enhancement distribution and clinical relevance of late gadolinium enhancement in cardiac sarcoidosis

Ref.	Patients	LE distribution		Clinical relevance
		Intra-cardiac	Intra-mural	
Smedema *et al*[8]	12 CS	Mostly basal and lateral LV wall	Any	Diagnostic
Matoh *et al*[13]	5 sCS	Mid ventricular septum	Midwall to subepicardial	Correlations between LE area and LVEDV, LVESV and LVEF
Ichinose *et al*[10]	10 CS	Any, but mostly basal LV wall	Any, but mainly subepicardial	Correlations between sum of LE score and BNP, LVEF, LVEDV
Manis *et al*[26]	11 CS	Ventricular septum	Patchy	Diagnostic
Patel *et al*[5]	21sCS	Any, but mainly basal ventricular septum, rarely RV wall	CAD; subendo-cardial non-CAD; mid wall, subepi-cardial, patchy	Higher rate of adverse events and cardiac death
Watanabe *et al*[27]	19 CS	NA	Subepicardial, transmural	Correlations between total LE segments, and reduced LV function and duration of extra-cardiac lesions
Greulich *et al*[28]	39 sCS	Any, but mainly ventricular septum (RV side)	Patchy, intramural to transmural	Higher Hazard ratio for MACE than other clinical parameters
Yang *et al*[29]	6 sCS	Ventricular septum, LV free wall, papillary muscle	Patchy	Decreased T2 (inactive phase)
Pöyjönen *et al*[30]	8 CS	Basal ventricular septum	Multifocal	Diagnostic
Tezuka *et al*[25]	9 sCS and 4 iCS	Any, but mainly anterior ventricular septum	Any, but mainly subepicardial	No difference between sCS and iCS in LE distribution and clinical features

BNP: Serum brain natriuretic peptide level; CAD: Coronary arterial disease type; CS: Cardiac sarcoidosis; iCS: Isolated CS; LV/RV: Left/right ventricles; LVEDV/ESV: LV end-diastolic/systolic volume; LVEF: LV ejection fractionl; MACE: Major adverse cardiac events; NA: Not available; sCS: Cardiac involvement of systemic sarcoidosis.

with LE in myocardium had high prevalence of heart failure symptoms, ECG abnormalities and lethal arrhythmias[5,28]. There are significant correlations between LE burden, and LV volume and function[5,8,10,27]. Regions of granulomatous infiltration evolving into scar tissue serve as substrates for re-entrant tachyarrhythmia[32,33]. Murtagh *et al*[34] exhibited that increased LE burden and right ventricular dysfunction can identify patients at highest risk of sudden cardiac death and VT. The efficacies of implantable cardioverter defibrillator (ICD) and catheter ablation were also reported for preventing sudden cardiac death and VT storm[35,36]. Therefore, not only the presence of LE, but also the LE burden and distribution should be considered for the risk stratification and therapeutic approach for CS. Although the smaller LE burden or non-specific scarring may be associated with a benign outcome[37], patients with LE should be carefully followed up, even when they had preserved LV function because of certain risks for sudden cardiac death and VT.

Tezuka *et al*[25] mentioned that the clinical features and prognosis did not differ between patients with sCS and iCS, whereas Kandolin *et al*[38] showed poorer outcomes in patients with iCS. The total segments with LE may correlate with the duration of extra-CS[27]. LE in CS mostly reflects irreversible myocardial scarring, and previous reports failed to show a decrease in LE volume after corticosteroid therapy[5,8,29]. The serial FDG-PET imaging is valuable to evaluate the effect of corticosteroid therapy for cardiac and systemic sarcoid lesions[21,39].

Limitations

Initially, MRI is not always available in all hospitals and patients, and has a problem of cost. Patients with pulmonary congestion cannot tolerate long data acquisition time of MRI. MRI has been prohibited in patients who have had device implantation. Therefore, patients who required urgent pacemaker or ICD implantation because of atrioventricular blocks or VT were excluded from the analyses of MRI. MR conditional pacemakers can be implanted in patients who may need MRI after device implantation[40,41]. Gadolinium cannot be injected to patients with chronic renal failure, because there is a risk of nephrogenic systemic fibrosis. Finally, different determination thresholds (> 2 SD to > 5 SD) and difficult quantification of LE are also limitations.

CONCLUSION

Although LE in myocardium has become a major criterion in the novel JMH guideline for CS, the present article suggests that more diffuse and characteristic patterns of LE distribution (in combination with abnormal wall motion and morphology) may be helpful for differentiating CS from DCM in patients with reduced LVEF. Future large and longitudinal follow-up studies are necessary to define characteristic patterns of LE distribution in CS as well as those prognostic values.

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