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. 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

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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.

Sano M, Satoh H, Suwa K, Saotome M, Urushida T, Katoh H, Hayashi H, Saitoh T. Intra-cardiac distribution of late gadolinium enhancement in cardiac sarcoidosis and dilated cardiomyopathy. World J Cardiol 2016; 8(9): 496-503 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i9/496.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i9.496

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-postin 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.

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

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

| Diagnostic Criteria | sCS | iCS |
|--------------------|-----|-----|
| (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.
FDG-PET (middle) and ⁹⁹mTc-sestamibi single photon emission computed tomography (SPECT: right) in a 61-year-old patient with scCS. 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). Corresponding FDG-PET (B) demonstrates focal uptake in basal and apical ventricular septum and posterior LV wall (black arrows). ⁹⁹mTc-sestamibi SPECT (C) exhibits 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-

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**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        | M25/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%/ | (26.7%/36.7%/|          |
|               | 7.1%/0%)      | 20%/16.7%)    |          |
| ECG findings  |               |               |          |
| PQ duration   | 188.4 ± 26.0  | 188.1 ± 40.9  | 0.91     |
| 1°/2° AVB     | 7/1 (50.0% / | 7/0 (23.3% / | 0.14     |
|               | 71.7%)        | 0%)           |          |
| QRS duration  | 118.6 ± 22.9  | 128.4 ± 36.3  | 0.18     |
| Abnormal Q    | 6 (42.9)      | 3 (10.0)      | 0.09     |
| waves n (%)   |               |               |          |
| 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/m²) | 107.0 ± 45.8  | 135.5 ± 43.4  | 0.08     |
| LVEF (mL/m²)  | 74.2 ± 44.5   | 106.3 ± 42.1  | 0.04     |
| LVMI (g/m²)   | 60.1 ± 24.9   | 67.1 ± 28.9   | 0.34     |
| LV EF (%)     | 33.9 ± 11.0   | 22.8 ± 10.0   | 0.003    |
| LE segment    | 8.6 ± 4.6     | 5.3 ± 3.1     | 0.04     |

The categorical variables were expressed as number and percentage (%) and compared by χ² 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.
of hot spots in CS\textsuperscript{[20-22]}. While LE and defects in SPECT reflect irreversible fibro-granulomatous replacement, the hot spots in T2-weighted black-blood imaging (T2WBB), \textsuperscript{\textit{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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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...
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 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.

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In sarcoidosis, previous reports showed that patients

### 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    |
| Sub-epi + sub-end | 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 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\[38] mentioned that the clinical features and prognosis did not differ between patients with sCS and iCS, whereas Kandolin et al\[39] 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\[21,29].

### 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 there is a risk of nephrogenic systemic fibrosis. 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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