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Incidence and Prognostic Significance of Myocardial Late Gadolinium Enhancement in Patients With Sarcoidosis Without Cardiac Manifestation

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BACKGROUND: Cardiac death is the leading cause of mortality associated with sarcoidosis in Japan. However, the involvement of sarcoidosis infiltration often remains undetected. Recently, late gadolinium enhancement with cardiovascular MRI (LGE-CMR) imaging has been introduced for the detection of myocardial infiltrative disease, as it enables the detection of even minor myocardial damage. We investigated the incidence and prognostic value of LGE-CMR in patients with extracardiac sarcoidosis without cardiac manifestations.

METHODS: Sixty-one consecutive patients who met the histologic and clinical criteria for sarcoidosis, and who did not have signs or symptoms of cardiovascular involvement, were prospectively recruited. LGE-CMR was performed at the time of enrollment, and patients were classified into positive or negative late gadolinium enhancement groups based on the findings. The study end point was a composite of all-cause death, symptomatic arrhythmia, and heart failure necessitating admission.

RESULTS: Patients were predominantly middle aged (57 ± 15 years) and female (66%), and most had stable disease activity that did not require treatment with immunosuppressants. LGE-CMR detected cardiac involvement in eight patients (13%). Interventricular septal thinning detected by echocardiography was an independent predictor of LGE-CMR-detected cardiac involvement. During the follow-up period of 50 ± 12 months, no significant difference in adverse events was noted between patients in the LGE-CMR-positive and LGE-CMR-negative groups.

CONCLUSIONS: LGE-CMR detected cardiac involvement in 13% of patients with sarcoidosis without cardiac manifestation, but both patients with and without LGE had relatively low event rates.

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ABBREVIATIONS: ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CMR = cardiovascular MRI; CRP = C-reactive protein; IVS = interventricular septum; JMHW = Japanese Ministry of Health and Welfare; LGE = late gadolinium enhancement; LGE-CMR = late gadolinium enhancement with cardiovascular MRI; LVEF = left ventricular ejection fraction; PES = programmed electric stimulation; SSFP = steady-state free precession

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Sarcoidosis is a multiorgan disorder of unknown etiology that is characterized by granulomatous formation.[1] Although the disease is thought to have low mortality and a benign prognosis, cardiac involvement may worsen the prognosis, as it leads to left ventricular dysfunction, congestive heart failure,[2] and life-threatening cardiac arrhythmias.[3] The mortality in patients with sarcoidosis with cardiac manifestation is as high as 25% in Western countries[4] and is even higher in the Japanese population,[5] indicating the need for therapeutic intervention.

Cardiac sarcoidosis is characterized by the presence of cardiac symptoms, particularly impaired systolic left ventricular function, or ECG changes. Frequently, however, the only indicators of cardiac sarcoidosis are minor ECG abnormalities and atypical cardiac symptoms, such as bundle branch and atrioventricular block, and ventricular arrhythmia. Furthermore, cardiac involvement in sarcoidosis is difficult to detect because the infiltration of granulomas into cardiac tissue is often not associated with clinical symptoms.[6,7] Thus, early detection of cardiac involvement in patients with sarcoidosis may improve treatment strategies and mortality.

Noninvasive imaging approaches, such as late gadolinium enhancement (LGE) with cardiovascular MRI (CMR) (LGE-CMR), have enabled detection of cardiac infiltration of sarcoidosis at much earlier phases of the disease.[8,9] LGE distribution varies according to the type of myocardial disease. For example, gadolinium is predominantly distributed in the endocardium of patients with ischemic cardiomyopathy, in the myocardial wall of patients with dilated cardiomyopathy, and in the epicardium of patients with myocarditis.[10,11] Several studies have demonstrated that CMR is able to detect characteristic fibrosis patterns of cardiac sarcoidosis, such as septal thinning, ventricular dilation, and systolic dysfunction.[12,13] LGE-CMR is reported to have high sensitivity and specificity for the detection of cardiac involvement in patients with sarcoidosis, who typically exhibit a nonischemic pattern of LGE.[14,15]

Patel et al[9] reported a retrospective analysis of patients with systemic sarcoidosis. In their study, 19% of patients with systemic sarcoidosis with preserved ejection fraction (left ventricular ejection fraction [LVEF] $>50\%$) showed LGE; some of these patients had cardiac symptoms or an ECG abnormality (37%), and one-quarter (25%) satisfied the Japanese Ministry of Health and Welfare (JMHW) criteria. This study was limited to investigating the characteristics of the LGE-positive and LGE-negative groups and did not include outcome. Patel et al[8] also demonstrated that the prevalence of myocardial damage detected by LGE-CMR in patients with extracardiac sarcoidosis was 26%, and the presence of LGE predicted future adverse events. Their prospective cohort specifically included patients with left ventricular dysfunction, cardiac manifestation (21%), and those who already satisfied the JMHW criteria (10%). Notably, their LGE-positive group had significantly lower LVEF compared with the LGE-negative group; thus, the results were easily understandable.

Therefore, based on these studies, the role of LGE-CMR in less symptomatic patients is still unclear. Detection of myocardial damage by LGE-CMR in patients with extracardiac sarcoidosis without cardiac manifestation is becoming common in daily practice, and the aim of the current study is to clarify the usefulness of LGE-CMR for detecting myocardial damage and future risk stratification in such patients with sarcoidosis.

Materials and Methods

Patient Population

A total of 61 consecutive patients who were histologically and/or clinically diagnosed with extracardiac sarcoidosis, including lung, eye, and skin involvement, were prospectively assessed. Inclusion criteria were the absence of cardiac symptoms suggestive of ischemic or other heart disease; LVEF $\geq 50\%$; no contraindication for LGE-CMR, such as renal impairment or implanted metallic device; and not meeting the diagnostic criteria for cardiac sarcoidosis by tests other than LGE-CMR, as described in the 2006 revised version of the JMHW guidelines.[16,17]

Patients were divided into LGE-CMR-positive and LGE-CMR-negative groups based on the results of CMR imaging performed during an initial evaluation. All subjects provided written informed consent prior to participation in the study. The study was approved by the ethics committee of Keio University Hospital (20-77) and registered under the Japanese UMIN Clinical Trials Registry (UMIN000001549).

Blood Sampling and Testing

Prior to CMR, venous blood samples were collected, and the serum C-reactive protein (CRP) level was then measured by latex photometric immunoassay (Mitsubishi Chemical, Inc). Serum creatinine level was measured enzymatically using the creatinase-sarcosine oxidase-peroxidase method. Angiotensin-converting enzyme (ACE) activity was measured by the Kasahara method.[18]

Echocardiography

Echocardiography was performed prior to CMR. Left ventricular wall-motion abnormality and thinning of the interventricular septum (IVS) were interpreted by two experienced clinicians without knowledge of the patients' background.

CMR Protocol

CMR was performed using a standardized clinical protocol on a 1.5-T magnetic resonance system (Signa TwinSpeed; General Electric Co). All CMR images were ECG-gated and obtained during repeated