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The Role of Multimodality Imaging in Cardiac Sarcoidosis

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AUTHOR'S SUMMARY

Cardiac sarcoidosis (CS) is significantly associated with a poor prognosis due to the associated congestive heart failure, arrhythmias (such as an advanced atrioventricular block), and ventricular tachyarrhythmia. Novel imaging modalities are now available to detect CS lesions secondary to active inflammation, granuloma formation, and fibrotic changes such as 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) and cardiac magnetic resonance imaging (CMR). Systematic review revealed both modalities showed high sensitivity to detect CS, while FDG PET and CMR provide different aspects of the pathophysiology of CS.

ABSTRACT

The etiology and the progression of sarcoidosis remain unknown. However, cardiac sarcoidosis (CS) is significantly associated with a poor prognosis due to the associated congestive heart failure, arrhythmias (such as an advanced atrioventricular block), and ventricular tachyarrhythmia. Novel imaging modalities are now available to detect CS lesions secondary to active inflammation, granuloma formation, and fibrotic changes. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) and cardiac magnetic resonance imaging (CMR) play essential roles in diagnosing and monitoring patients with confirmed or suspected CS. The following focused review will highlight the emerging role of non-invasive cardiac imaging techniques, including FDG PET/CT and CMR.

Keywords: Cardiac sarcoidosis; ^{18}F-FDG PET; Cardiac magnetic resonance imaging

INTRODUCTION

Sarcoidosis is a chronic multi-system inflammatory disorder of unknown etiology characterized pathologically by the formation of non-caseating granulomas in the involved organs or tissues. Essentially, any body tissue may be affected,[1)2)] but the most commonly involved include the lymph nodes, skin, lung, musculoskeletal system, and eyes.

Conflict of Interest

Dr. Noriko Oyama-Manabe has activities as consultant for Canon Medical Systems; also, she got payment for lectures from Daiichi-Sankyo, Philips Medical Systems, Eisai, Bayer Healthcare, GE Healthcare, Nihon Medi-Physics, Co., Ltd. and Canon Medical Systems.

Data Sharing Statement

The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions

Conceptualization: Oyama-Manabe N; Data curation: Oyama-Manabe N, Aikawa T, Tsuneta S; Formal analysis: Oyama-Manabe N, Aikawa T; Funding acquisition: Oyama-Manabe N; Investigation: Oyama-Manabe N, Manabe O; Methodology: Oyama-Manabe N, Manabe O, Aikawa T; Project administration: Oyama-Manabe N, Manabe O, Aikawa T; Resources: Oyama-Manabe N, Manabe O, Aikawa T, Tsuneta S; Software: Manabe O, Aikawa T, Tsuneta S; Supervision: Oyama-Manabe N, Manabe O; Validation: Tsuneta S; Visualization: Aikawa T, Tsuneta S; Writing - original draft: Oyama-Manabe N; Writing - review & editing: Oyama-Manabe N, Manabe O.

Although the overall prognosis of patients with systemic sarcoidosis is generally favorable, cardiac sarcoidosis (CS) is significantly associated with a poor prognosis due to congestive heart failure, arrhythmias (such as an advanced atrioventricular block), and ventricular tachyarrhythmia.[3)4)] Thus, an early and precise diagnosis of CS is essential. Recent studies have demonstrated the usefulness of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and cardiac magnetic resonance imaging (CMR) for assessing CS. In this review, we focus on the pathophysiology and diagnostic aspects of CS with multimodality imaging.

ETIOLOGY

The incidence of sarcoidosis and its cardiac involvement varies among ethnic groups and regions.[5)6)] Symptomatic CS has been reported in up to 10% of the patients with systemic sarcoidosis.[7-10)] An autopsy series from the United States and Japan showed that approximately 27% and 80% of patients with systemic sarcoidosis, respectively, had CS.[11)12)] Recent advances in cardiac imaging tools have enabled the detection of asymptomatic CS.[13)] As such, imaging series have reported higher rates of cardiac involvement in patients with extra-CS, ranging from 19% to 55% for asymptomatic CS.[4)8)13-15)]

PATHOLOGICAL CHARACTERISTICS OF CARDIAC SARCOIDOSIS

The pathological hallmark of CS is the non-caseating epithelioid granuloma with a compact central area of macrophages and scattered lymphocytes.[1)] If there is active inflammation, the granuloma can progress to irreversible fibrosis.[16)] The myocardium of the left ventricular free wall is the most common location of sarcoid involvement, followed by the interventricular septum, papillary muscles, right ventricle, and atria.[17)18)] An endomyocardial biopsy is a valuable tool in the definitive diagnosis of CS,[19)] but it is limited owing to its low sensitivity due to the patchy distribution of granulomas and its complications.

CLINICAL PRESENTATION

CS manifestations can range widely from a clinically asymptomatic form to sudden cardiac death.[20)] Arrhythmic, cardiomyopathic, and pericardial manifestations are common clinical signs and symptoms (**Table 1**).[20-25)]

Table 1. Clinical presentations of cardiac sarcoidosis

Clinical manifestation	Prevalence (%)
Arrythmias	
Atrioventricular block	23–77.4
Bundle branch block	12–66
Atrial tachycardia	0–15
Ventricular tachycardia	2–42
Sudden cardiac death	12–65
Cardiomyopathy	
Heart failure	10–30
Pericardial disease	
Pericardial effusion	2–20
Pericarditis	Rare

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Atrioventricular conduction disease due to the infiltration of sarcoid granulomas is the most common finding in patients with CS.[26] Ventricular and atrial arrhythmias are also frequent manifestations, with the latter being caused by atrial dilation secondary to left ventricular dysfunction and the atrial infiltration of sarcoid granulomas. Both systolic and diastolic ventricular dysfunction can result from granulomatous inflammation and subsequent scarring, subsequently leading to heart failure. Meanwhile, pulmonary infiltration may lead to right ventricular failure. Less commonly, CS may manifest as progressive pericardial diseases, such as pericarditis or tamponade.

CRITERIA FOR THE DIAGNOSIS OF CARDIAC SARCOIDOSIS

CS is conventionally diagnosed by the appropriate combination of clinical and physiological signs and symptoms and multimodal imaging. Several diagnostic criteria have been proposed, and one commonly used is the Japanese Ministry of Health and Welfare criteria,[27][28] modified in 2015 by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (**Table 2**).[25] The Heart Rhythm Society Expert Consensus Statement of the CS was also published in 2014 (**Table 3**).[29] In these 2 criteria, the diagnosis is separated by histological and clinical methods. To confirm the histological diagnosis, the presence of non-caseating epithelioid granulomas from the endomyocardial biopsy sample should be demonstrated. The histological analysis of operative or endomyocardial biopsy specimens could be the gold standard. However, endomyocardial biopsy cannot be performed on all suspected regions and has a lower sensitivity in diagnosing CS.[19] On the contrary, the clinical diagnosis correlates the histological diagnosis of extra-cardiac sarcoidosis with the electrocardiographic and imaging findings, including echocardiography, ^{67}Ga scintigraphy, ^{18}F-FDG PET, and late gadolinium enhancement on CMR.

^{18}F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY

PET is a highly sensitive and non-invasive molecular imaging technique that can visualize and quantify the active processes of physiological function and disease conditions, in contrast

Table 2. Japanese Society of Sarcoidosis and Other Granulomatous Disorders 2015 criteria for cardiac sarcoidosis[25]

1. Histological diagnosis group
Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid cell granulomas with a histological or clinical diagnosis of extra-cardiac sarcoidosis.
2. Clinical diagnosis group
Cardiac sarcoidosis is confirmed when, although endomyocardial biopsy specimens do not demonstrate non-caseating epithelioid cell granulomas, extra-cardiac sarcoidosis is diagnosed histologically or clinically and the following conditions and the following diagnostic criteria are satisfied:
a) Two or more of the 5 major criteria are met
OR
b) One of the 5 major criteria and 2 or more of the 3 minor criteria are met
Major criteria
1) Advanced atrioventricular block or sustained ventricular tachycardia
2) Basal thinning of the interventricular septum or morphological abnormality (aneurysm, wall thinning, or wall thickening)
3) Depressed ejection fraction (<50%) or regional wall motion abnormality
4) Abnormal uptake of ^{67}Ga or ^{18}F-fluorodeoxyglucose in the heart
5) Delayed gadolinium enhancement on cardiac magnetic resonance
Minor criteria
1) Abnormal electrocardiographic findings: ventricular arrhythmias (non-sustained ventricular tachycardia or multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q-waves
2) Perfusion defects on nuclear imaging
3) Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration of moderate grade

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Table 3. Heart Rhythm Society's Expert Consensus Statement for diagnosis of CS[29]

1. Histologic diagnosis
Non-caseating granuloma on endomyocardial biopsy without alternative cause
2. Clinical diagnosis
a) Histologic diagnosis of extra-CS
And
b) One of the following is present
1) Steroid responsive cardiomyopathy or heart block
2) Unexplained LVEF <40%
3) Unexplained sustained VT
4) Advanced heart block
5) Patchy uptake on cardiac PET
6) LGE on CMR
7) Positive ^{67}Ga uptake
And
c) Other causes for the cardiac manifestation(s) have been excluded

CMR = cardiac magnetic resonance imaging; CS = cardiac sarcoidosis; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; PET = positron emission tomography; VT = ventricular tachycardia.

to anatomical approaches. ^{18}F-FDG is a glucose analog widely used to visualize and quantify glucose metabolism in the target region since it is taken up by plasma membrane glucose transporters (GLUT) in living cells and phosphorylated by intracellular hexokinase into ^{18}F-FDG-6-phosphate (^{18}F-FDG-6-P) similar to glucose. ^{18}F-FDG-6-P is retained within the cell without further metabolism along the glycolytic pathway, a phenomenon known as metabolic trapping. Therefore, tissue activity can be directly visualized using ^{18}F-FDG PET.

Cardiac metabolism and preparation to suppress the physiological ^{18}F-fluorodeoxyglucose uptake

Under normal conditions, free fatty acids (FFAs) and glucose are the major energy sources for cardiac metabolism. Since the ^{18}F-FDG is an analog of glucose, its physiological accumulation in the myocardium has a causal influence on the false-positive diagnosis of CS.[30] The fasting state has a significant effect on the physiological uptake. **Figure 1** shows a representative case of various physiological uptakes during follow-up in one patient (non-CS case). Under long fasting conditions, glucose production and glucose oxidation decrease, leading to the release of available FFA from adipose tissue to provide an alternative energy source. The physiological uptake of ^{18}F-FDG in the myocardium can be suppressed with a low-carbohydrate diet and a high-fat diet due to the switch to FFA metabolism. As such, FFA level is an important marker of physiological ^{18}F-FDG uptake suppression.[31]

^{18}F-fluorodeoxyglucose accumulation in sarcoidosis lesion

The significant ^{18}F-FDG accumulation in sarcoidosis lesions is caused by activated inflammatory cells, such as neutrophils, macrophages, and lymphocytes; GLUT1 and GLUT3 in the cell membrane; and hexokinase.[32][33] As ^{18}F-FDG uptake reflects active inflammation, it is therefore useful in detecting CS and guiding immunosuppression management.[34] **Figure 2** shows a representative case of CS before and after steroid therapy.

Myocardial ^{18}F-FDG uptake patterns are conventionally divided into 4 groups: none, diffuse, focal, and focal on diffuse.[35][36] When myocardial ^{18}F-FDG uptake is absent, it is negative for active CS lesions. Definite diffuse ^{18}F-FDG uptake in the entire left ventricular wall is generally a physiological uptake and does not indicate an abnormality. On the contrary, focal and focal on diffuse ^{18}F-FDG uptake in the left ventricular wall are considered positive for

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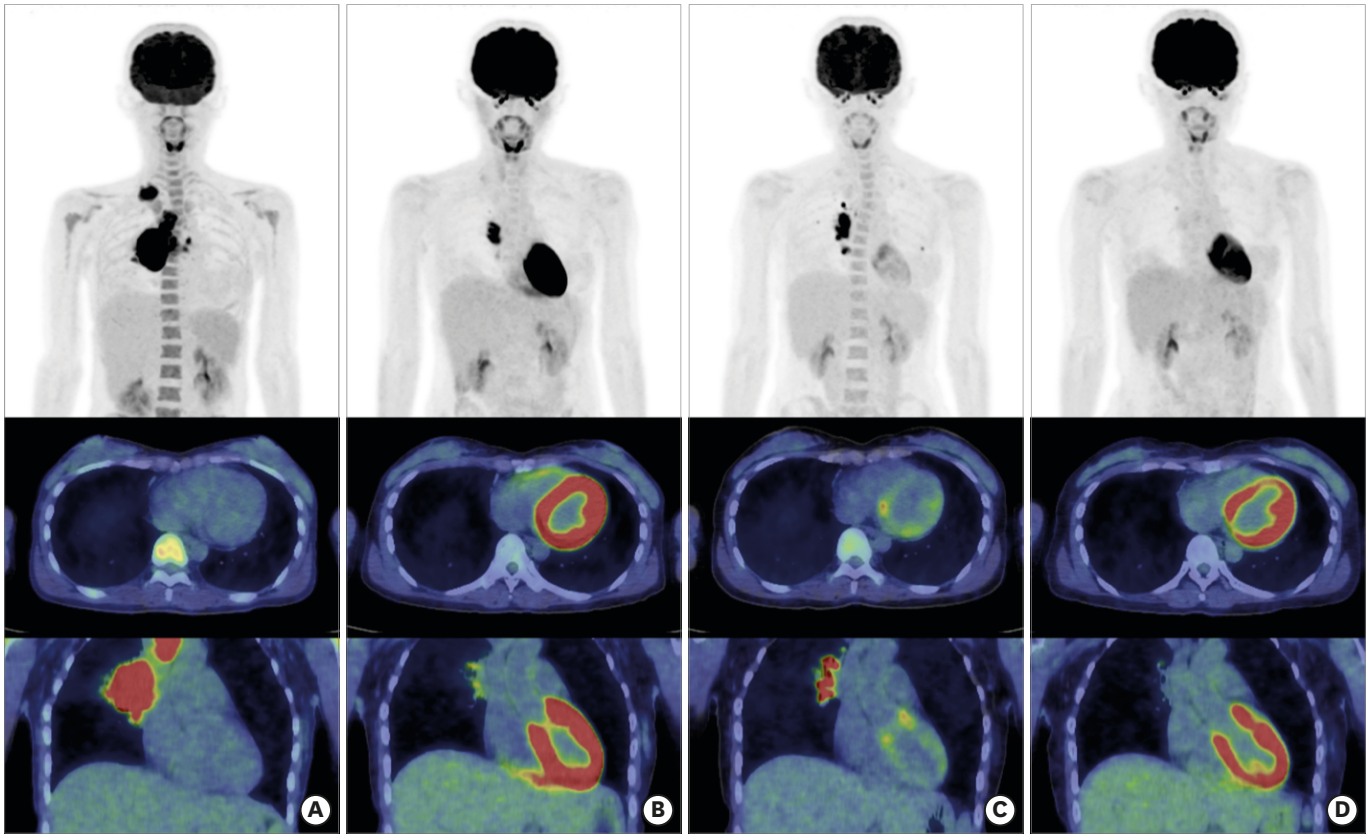

Figure 1. A representative case of various physiological myocardial uptake patterns during follow-up in one patient.
A patient with malignant lymphoma underwent serial ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scans for follow-up after chemotherapy. Focus on the left ventricular uptake, no uptake (A), diffuse strong uptake with left ventricular uptake (B), predominant regional uptake in the base of the myocardium (C), and diffuse uptake (D) is pointed out.

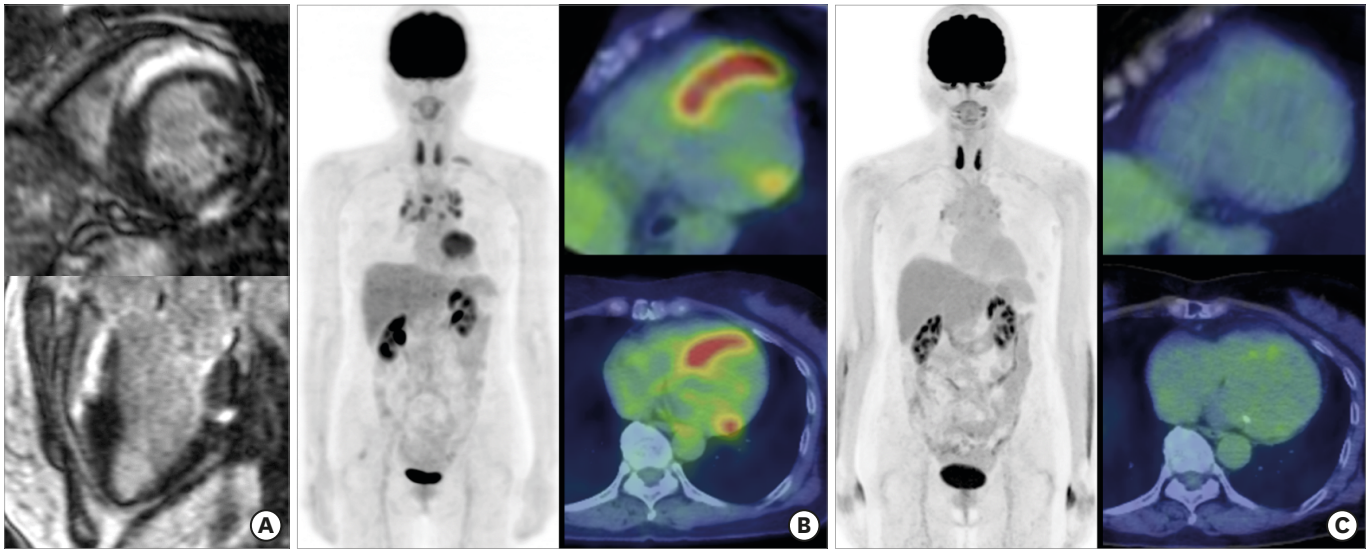

Figure 2. A representative case of a woman in her 60s with complete right bundle branch block before and after steroid therapy. Cardiac magnetic resonance shows subepicardial gadolinium enhancement at the basal septum and lateral wall (A). Focal myocardial fluorodeoxyglucose uptake at the septum and multiple uptake at the mediastinal lymph nodes are consistent with cardiac sarcoidosis (B). After administration of steroid therapy, myocardial and mediastinal uptake are diminished (C).

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CS. In addition, the diffuse at base uptake pattern is known to be associated with inadequate physiologic suppression.[37]

The combination of ^{18}F-FDG and perfusion findings has led to improvements in the accurate diagnoses and prognostication.[3]

With its high diagnostic value and high inter-rater reproducibility, ^{18}F-FDG PET texture analysis can also be used to diagnose CS, focusing on its heterogeneous distribution.[38] Texture analysis can differentiate abnormal and physiological CS uptake.

CARDIAC MAGNETIC RESONANCE IMAGING

Late gadolinium enhancement

CMR offers both functional and structural information to help detect the acute and chronic inflammatory phases of CS. In contrast, it does not require specific preparation such as long fasting before examination as required for ^{18}F-FDG PET; however, it is contraindicated in patients with MR unsafe or some MR conditional implantable devices.

CMR with late gadolinium enhancement (LGE) is an emerging tool for evaluating CS. Mid-wall or subepicardial LGE in the basal ventricular wall, lateral wall, and septum (**Figure 2**) is the most common pattern seen in CS,[4] recently confirmed in a meta-analysis of studies with histological confirmation.[39]

Myocardial enhancement on LGE-CMR images adds an independent prognostic value for the risk stratification sarcoidosis patients.[40][41] Greulich et al.[8] also reported that the presence of LGE was the best independent predictor of death and other adverse events in CS. However, it is difficult to differentiate active inflammation from chronic fibrosis using LGE alone.

T1/T2 mapping

CMR mapping techniques such as T1, T2, and extracellular volume can provide additional quantitative information regarding interstitial changes. In combination with LGE, CMR mapping can significantly improve the diagnosis of subclinical CS.[42] Greulich et al.[43] compared 61 patients with sarcoidosis and 26 healthy patients and found that the former had significantly higher native T1, T2, and extracellular volume. The weighted mean T1 value at 1.5 T of 994 ms (range, 975–1,039 ms) in the patients with sarcoidosis was significantly higher than the controls (960 ms; range, 942–986 ms), independent of the presence of LGE. Meanwhile, the patients with sarcoidosis had a weighted mean T2 value at 1.5 T of 52.3 ± 3.8 ms, higher than the 49.0 ± 1.6 ms in the controls. At 3 T, the values were 54.0 ± 12.2 ms and 45.0 ± 10.8 ms, respectively.[44] **Figure 3** shows active CS with LGE-CMR and T2 mapping, which correlate with positive ^{18}F-FDG PET findings. T2 mapping provides an absolute and objective parameter for active inflammation. Native T1 and T2 mapping could be used for disease monitoring and differentiating sarcoid patients from healthy controls without the use of gadolinium.[45]

Strain imaging

Myocardial strain analysis has been developed to objectively evaluate the regional myocardial function, including longitudinal, circumferential, radial, and rotational myocardial strains.[46] Among these, left ventricular global longitudinal strain (GLS) has been receiving the most

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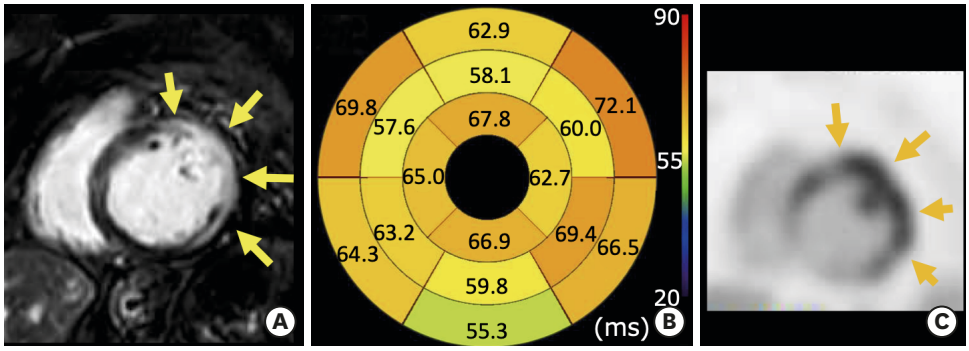

Figure 3. A woman in her 60s was admitted to the hospital with acute heart failure. Cardiac magnetic resonance imaging shows abnormal gadolinium enhancement with transmural and epicardium distribution of left ventricle (A, arrows). Through T2 mapping, the diffuse prolongation of T2 values is observed, suggesting myocardial edema or inflammation due to active cardiac sarcoidosis (B, normal range was under 54 ms). ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography reveals correlated focal uptake, confirming active cardiac sarcoidosis (C, arrows).

attention because subendocardial fibers originate longitudinally and thus, may be sensitive in detecting early changes in various cardiomyopathies. Two-dimensional speckle tracking echocardiography has been used to evaluate CS. GLS and global circumferential strain were significantly lower in extra-cardiac sarcoidosis patients despite not exhibiting any cardiac symptoms.[47] Impaired GLS is associated with major cardiac events in patients with CS.[47] Due to its association with cardiac events in patients with sarcoidosis, a recent study also reported that biventricular strain deterioration can be used as an early marker of cardiac involvement.[48]

Similar to speckle tracking echocardiography, CMR techniques for assessing myocardial strain, such as tagging,[49] strain-encoded (SENC) magnetic resonance imaging (MRI),[50][51] and myocardial feature-tracking deformation imaging (FTI),[52] have the potential to detect a wide range of myocardial diseases early, accurately, and without the need for contrast agent injection. A small study using SENC for CS has been reported.[53] Specifically, FTI is also useful for evaluating regional and global strains, well correlated with SENC MRI.[54] This method requires only cine images without specific extra scanning. Dabir et al.[55] reported that GLS assessed with FTI was reduced in patients with a negative outcome, possibly serving as a marker for early cardiac involvement in sarcoidosis. **Figure 4** shows a case of positive LGE and ^{18}F-FDG PET with FTI evaluation. In this case, regional deformation due to aneurysmal formation was visualized well with FTI.

An autopsy study reported that aneurysm formation was present in 8% of patients with cardiac sarcoidosis,[18] the combination of CMR and ^{18}F-FDG PET could help differentiate left ventricular aneurysm due to CS from myocardial infarction.

DIAGNOSTIC ABILITY

Systematic reviews about the diagnostic ability of ^{18}F-FDG PET and CMR are summarized in **Tables 4-6**.[56-111] The sensitivity of ^{18}F-FDG PET in the diagnosis of CS ranges from 27% to 100%, depending on disease activity since it can only detect active lesions. CMR has a similar sensitivity in detecting CS (range, 28%–100%). Importantly, ^{18}F-FDG PET and CMR provide different aspects of the pathophysiology of CS.[108] Therefore, both modalities are

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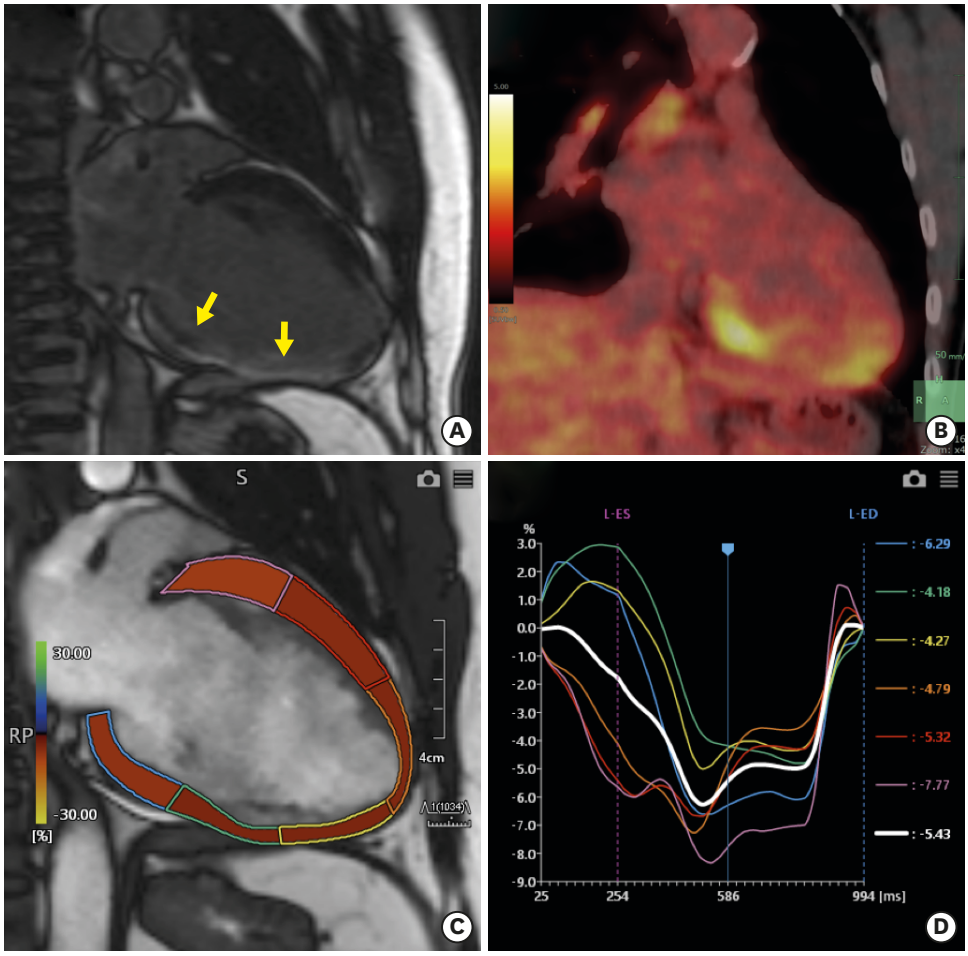

Figure 4. A man in his 40s was diagnosed as systemic sarcoidosis by transbronchial lung biopsy.
Due to complete right bundle branch block and diffuse left ventricular dysfunction, he was referred for CMR. Left ventricular 2-chamber view of the late gadolinium enhanced CMR shows hyperenhancement at the inferior wall (A, yellow arrows). After a long fast with a low-carbohydrate diet, the ^{18}F-FDG positron emission tomography/computed tomography reveals abnormal FDG uptake at the inferior wall, indicating active cardiac sarcoidosis (B). (C and D) Feature-tracking using cine magnetic resonance imaging for longitudinal strain clearly depicts regional wall motion abnormality with aneurysmal deformation of the mid-inferior wall (green strain curve).
CMR = cardiac magnetic resonance imaging; FDG = fluorodeoxyglucose.

recommended for patients who meet the following criteria: (1) equivocal or negative CMR findings in the setting of high clinical suspicion; (2) CMR findings with highly probable CS. In such cases, ^{18}F-FDG PET may identify inflammation/potential role for immunosuppressive therapies. The suggested algorithm for diagnosis is CMR. If LGE is negative, the patient's prognosis would be excellent. However, if LGE is positive or inconclusive, the disease activity should be evaluated using ^{18}F-FDG PET for immunosuppressive therapy.

COMPUTED TOMOGRAPHY

The disadvantage of MRI is that it is contraindicated for patients with MR unsafe implantable devices or implantable devices. In patients with non-ischemic cardiomyopathy unable to undergo CMR, cardiac computed tomography (CT) can also be used to perform delayed enhancement imaging.[112] CT may be advantageous due to its comprehensive systemic

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Table 4. Diagnostic performance of ^{18}F-FDG PET and ^{18}F-FDG PET/CT to detect cardiac involvement in patients with sarcoidosis

Author	Year	Countries	No.	Fasting time (hr)	Preparation	Quantitative PET interpretation	Diagnostic criteria (years)	TP (n)	FP (n)	FN (n)	TN (n)	Sensitivity (%)	Specificity (%)
FDG PET													
Yamagishi et al.[56]	2003	Japan	17	≥5	None	Yes	JMHW (1993)	14	0	3	0	82	-
Okumura et al.[57]	2004	Japan	22	≥12	None	Yes	JMHW (1993)	11	1	0	10	100	91
Ishimaru et al.[36]	2005	Japan	32	≥6	UFH	No	JMHW (1993)	5	5	0	22	100	81
Matoh et al.[58]	2008	Japan	3	≥5	None	No	JMHW (1993)	0	2	0	1	-	33
Ohira et al.[59]	2008	Japan	21	≥6	UFH	No	JMHW (1993)	7	13	1	5	88	28
Tahara et al.[60]	2010	Japan	24	≥12	None	Yes	Modified JMHW (2006)	12	1	0	11	100	92
Manabe et al.[26]	2013	Japan	50	≥6	UFH	No	JMHW (1993)	23	10	1	16	96	62
Manabe et al.[61]	2014	Japan	59	≥6	UFH	Yes	JMHW (1993)	25	10	2	22	93	69
FDG PET/CT													
Langah et al.[62]	2009	USA	30	>18	None	Yes	JMHW (1993)	17	1	3	9	85	90
Youssef et al.[63]	2012	Canada	24	≥12	None	Yes	Modified JMHW (2006)	11	3	3	7	79	70
Ambrosini et al.[64]	2013	Italy	43	>12	HFLC	No	JMHW (1993)	0	2	3	38	-	95
Mc Ardle et al.[65]	2013	Canada	27	≥12	HFLC	No	Modified JMHW (2006)	26	0	1	0	96	-
Soussan et al.[66]	2013	France	58	≥4	HFLC	No	JMHW (1993)	10	10	2	36	83	78
Blankstein et al.[3]	2014	USA	112	≥3	HFLC	No	JMHW (1993)	16	15	22	59	42	80
Ito et al.[37]	2014	Japan	19	>12	UFH	No	Modified JMHW (2006)	9	0	10	0	47	-
Kobayashi et al.[67]	2015	Japan	31	≥18	None	No	Modified JMHW (2006)	17	0	14	0	55	-
Momose et al.[68]	2015	Japan	52	≥12	LC+UFH	No	Modified JMHW (2006)	15	19	0	18	100	49
Orii et al.[69]	2015	Japan	32	≥18	LC+UFH	No	Modified JMHW (2006)	26	0	6	0	81	-
Simonen et al.[70]	2015	Finland	68	≥12	None	No	Own criteria	62	0	6	0	91	-
Yokoyama et al.[71]	2015	Japan	92	≥18	LC	Yes	Modified JMHW (2006)	36	9	1	46	97	84
Gormsen et al.[72]	2016	Denmark	19	NA	None	No	JMHW (1993)	1	2	2	14	33	88
Ohira et al.[73]	2016	Canada, Japan	30	≥12	HFLC	No	Modified JMHW (2006)	24	0	6	0	80	-
Ahmadian et al.[74]	2017	USA	17	≥12	HFLC	Yes	Modified JMHW (2006)	17	0	0	0	100	-
Lee et al.[75]	2017	USA	16	>8	HFLC	Yes	JMHW (1993)	16	0	0	0	100	-
Norikane et al.[76]	2017	Japan	20	>18	None	No	JSSOG (2015)	11	0	2	7	85	100
Yalagudri et al.[77]	2017	India	18	NA	NA	No	HRS (2014)	14	0	4	0	78	-
Furuya et al.[78]	2018	Japan	38	≥18	LC	Yes	JSSOG (2015) or HRS (2014)	38	0	0	0	100	-
Lebasnier et al.[79]	2018	France	30	≥12	HFLC	Yes	Modified JMHW (2006)	5	4	1	20	83	83
Varghese et al.[80]	2018	USA	154	NA	HFLC	Yes	Modified JMHW (2006) or HRS (2014)	19	33	16	86	54	72
Muser et al.[81]	2018	USA	29	≥18	HFLC+UFH	Yes	HRS (2014)	14	0	15	0	48	-
Schildt et al.[82]	2018	Finland	231	≥12	None	Yes	HRS (2014)	23	40	24	141	50	78
Divakaran et al.[83]	2019	USA	18	≥4	HFLC	No	Explanted heart histology	9	5	0	4	100	44
Furuya et al.[84]	2019	Japan	10	≥18	LC	No	JSSOG (2015)	9	0	0	1	100	100
Manabe et al.[38]	2019	Japan	89	≥18	LC	Yes	JSSOG (2015)	35	10	2	42	95	81
Ning et al.[34]	2019	USA	34	≥12	LC	No	Own criteria	27	0	7	0	79	-
Sgard et al.[85]	2019	France	80	NA	HFLC	No	Modified JMHW (2006)	6	5	16	53	27	91
							HRS (2014)	11	0	29	40	28	100
Togo et al.[86]	2019	Japan	85	≥18	LC	Yes	JSSOG (2015)	26	5	7	47	79	90
Zipse et al.[87]	2019	USA	72	NA	NA	No	HRS (2014)	49	0	8	15	86	100
Higashi et al.[88]	2020	Japan	36	>18	LC	No	Modified JMHW (2006)	10	4	0	22	100	85
Kawai et al.[89]	2020	Japan	94	≥18	LC	No	JSSOG (2015)	31	11	3	49	91	82
							HRS (2014)	16	26	6	46	73	64
Miller et al.[90]	2020	USA	69	≥8	HFLC	Yes	Modified JMHW (2006)	24	2	5	38	83	95
Okune et al.[91]	2020	Japan	74	≥18	LC	Yes	JSSOG (2015)	29	9	11	25	73	74
FDG PET/MR (PET alone)													
Wicks et al.[92]	2018	UK	51	≥12	HFLC	No	Modified JMHW (2006)	20	8	13	10	61	56

CT = computed tomography; FDG = fluorodeoxyglucose; FN = false negative; FP = false-positive; HFLC = high-fat/low-carbohydrate diet; HRS = Heart Rhythm Society; JMHW = Japanese Ministry of Health and Welfare; JSSOG = Japanese Society of Sarcoidosis and Other Granulomatous Disorders; LC = low-carbohydrate; MR = magnetic resonance; NA = not available; PET = positron emission tomography; TN = true negative; TP = true positive; UFH = unfractionated heparin injection.

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Table 5. Diagnostic performance of CMR to detect cardiac involvement in patients with sarcoidosis

Author	Year	Countries	No.	Scanner	CMR protocol	T1/T2 maps	Diagnostic criteria (years)	TP (n)	FP (n)	FN (n)	TN (n)	Sensitivity (%)	Specificity (%)
Smedema et al.[93]	2005	The Netherlands	88	1.5T	Cine, T2WI, LGE	None	JMHW (1993)	12	12	2	62	86	84
Smedema et al.[94]	2005	The Netherlands	58	1.5T	Cine, T2WI, LGE	None	JMHW (1993)	12	10	0	36	100	78
Tadamura et al.[95]	2005	Japan	10	1.5T	Cine, LGE	None	JMHW (1993)	10	0	0	0	100	-
Ichinose et al.[96]	2008	Japan	30	1.5T	Cine, LGE	None	JMHW (1993)	10	0	1	29	91	100
Matoh et al.[58]	2008	Japan	12	1.5T	Cine, LGE	None	JMHW (1993)	2	3	0	7	100	70
Ohira et al.[59]	2008	Japan	21	1.5T	Cine, LGE, T2WI	None	JMHW (1993)	6	3	2	10	75	77
Manins et al.[97]	2009	Australia	20	1.5T	Cine, LGE, T2WI	None	JMHW (1993)	8	3	0	9	100	75
Patel et al.[4]	2009	USA	81	1.5T	Cine, LGE	None	JMHW (1993)	8	13	2	58	80	82
Patel et al.[14]	2011	USA	152	1.5T	Cine, LGE	None	JMHW (1993)	14	13	21	102	40	89
Mc Ardle et al.[65]	2013	Canada	13	NA	LGE	None	Modified JMHW (2006)	8	0	5	0	62	-
Soussan et al.[66]	2013	France	35	1.5T	Cine, LGE, T2WI	None	JMHW (1993)	10	7	0	18	100	72
Watanabe et al.[98]	2013	Japan	19	1.5T	Cine, LGE	None	Modified JMHW (2006)	17	0	2	0	89	-
Matsumoto et al.[99]	2015	Japan	17	NA	LGE	NA	Modified JMHW (2006)	7	0	0	10	100	100
Momose et al.[68]	2015	Japan	27	1.5T or 3.0T	Cine, LGE	NA	Modified JMHW (2006)	6	21	0	0	100	-
Orii et al.[69]	2015	Japan	32	1.5T	Cine, LGE, T2WI	None	Modified JMHW (2006)	32	0	0	0	100	-
Simonen et al.[70]	2015	Finland	43	NA	Cine, LGE	None	Own criteria	33	0	10	0	77	-
Tezuka et al.[100]	2015	Japan	24	1.5T	Cine, LGE, T2WI	None	Modified JMHW (2006)	15	6	0	3	100	33
Yokoyama et al.[71]	2015	Japan	69	NA	LGE	None	Modified JMHW (2006)	24	28	2	15	92	35
Komada et al.[101]	2016	Japan	9	1.5T	Cine, LGE	None	JMHW (1993)	9	0	0	0	100	-
Ohira et al.[73]	2016	Canada, Japan	30	1.5T	Cine, LGE	None	Modified JMHW (2006)	26	0	4	0	87	-
Aikawa et al.[102]	2017	Japan	14	1.5T or 3.0T	Cine, LGE	None	JSSOG (2015)	10	3	0	1	100	25
Kataoka et al.[103]	2017	Japan	16	1.5T or 3.0T	Cine, LGE	None	Modified JMHW (2006)	7	9	0	0	100	-
Stanton et al.[104]	2017	Australia	46	1.5T	Cine, LGE, T2WI	None	Modified JMHW (2006)	2	8	0	36	100	82
Smedema et al.[105]	2017	The Netherlands	40	1.5T	Cine, LGE	None	JMHW (1993)	29	0	1	10	97	100
Kouranos et al.[106]	2017	Greece	321	1.5T or 3.0T	Cine, LGE	None	HRS (2014)	93	0	3	225	97	100
Yalagudri et al.[77]	2017	India	11	NA	LGE	None	HRS (2014)	11	0	0	0	100	-
Ghanizada et al.[107]	2018	Denmark	9	NA	Cine, LGE, T2WI	None	JMHW (1993)	9	0	0	0	100	-
Muser et al.[81]	2018	USA	29	1.5T	Cine, LGE	None	HRS (2014)	26	0	3	0	90	-
Vita et al.[108]	2018	USA	107	3.0T	Cine, LGE	None	HRS (2014)	51	40	6	10	89	20
Wicks et al.[92]	2018	UK	51	PET/MR3.0T	Cine, LGE	None	Modified JMHW (2006)	26	6	7	12	79	67
Darlington et al.[109]	2019	Sweden	42	1.5T	Cine, LGE	None	HRS (2014)	12	0	0	30	100	100
Divakaran et al.[83]	2019	USA	31	3.0T	Cine, LGE	None	Explanted heart histology	1	7	0	23	100	77
Russo et al.[110]	2019	Canada	25	NA	Cine, LGE	None	HRS (2014)	10	7	1	7	91	50
							Modified JMHW (2006)	8	7	3	7	73	50
Sgard et al.[85]	2019	France	80	1.5T	Cine, LGE, T2WI	None	Modified JMHW (2006)	18	16	4	42	82	72
							HRS (2014)	34	0	6	40	85	100
Zipse et al.[87]	2019	USA	104	NA	LGE	None	HRS (2014)	36	0	25	43	59	100
Kawai et al.[89]	2020	Japan	52	NA	LGE	None	JSSOG (2015)	16	16	3	17	84	52
							HRS (2014)	9	23	3	17	75	43
Miller et al.[90]	2020	USA	69	NA	LGE	None	Modified JMHW (2006)	8	14	21	26	28	65
Okune et al.[91]	2020	Japan	74	1.5T	Cine, LGE	None	JSSOG (2015)	39	24	1	10	98	29
Orii et al.[111]	2020	Japan	50	1.5T	Cine	None	HRS (2014)	3	1	5	41	38	98
					T2WI			6	2	2	40	75	95
					LGE			8	10	0	32	100	76

CMR = cardiac magnetic resonance imaging; FN = false negative; FP = false-positive; HRS = Heart Rhythm Society; JMHW = Japanese Ministry of Health and Welfare; JSSOG = Japanese Society of Sarcoidosis and Other Granulomatous Disorders; LGE = late gadolinium enhancement; MR = magnetic resonance; NA = not available; PET = positron emission tomography; T2WI = T2-weighted imaging; TN = true negative; TP = true positive.

evaluation of sarcoidosis. After whole-body scanning, a delayed cardiac scan could be consequently performed even in patients with implantable devices. We reported that the image quality of delayed iodine contrast-enhanced CT (DE-CT) sufficiently allows for the assessment of hyper-enhanced myocardium in patients with or without implantable devices.[102][113] DE-CT can also delineate the extent of CS with an accuracy comparable to that of LGE-CMR.[102]

Figure 5 shows a representative case before and after implantation of a cardioverter-defibrillator following DE-CT. Since the contrast noise ratio of DE-CT was relatively lower

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Table 6. Diagnostic performance CMR in combination with FDG PET to detect cardiac involvement in patients with sarcoidosis

Author	Year	Countries	No.	Fasting time	CMR scanner	CMR protocol	Diagnostic criteria (years)	TP (n)	FP (n)	FN (n)	TN (n)	Sensitivity (%)	Specificity (%)
Matoh et al.[58]	2008	Japan	3	≥5	1.5T	Cine, LGE	JMHW (1993)	2	0	0	1	100	100
Ohira et al.[59]	2008	Japan	21	≥6	1.5T	Cine, LGE, T2WI	JMHW (1993)	8	8	0	5	100	38
Soussan et al.[66]	2013	France	35	≥4	1.5T	Cine, LGE, T2WI	JMHW (1993)	10	10	0	15	100	60
Yokoyama et al.[71]	2015	Japan	26	≥18	NA	LGE	Modified JMHW (2006)	26	0	0	0	100	-
Yalagudri et al.[77]	2017	India	11	NA	NA	LGE	HRS (2014)	11	0	0	0	100	-
Wicks et al.[92]	2018	UK	51	≥12	Hybrid PET/MR 3.0T	Cine, LGE	Modified JMHW (2006)	30	13	3	5	91	28
Divakaran et al.[83]	2019	USA	7	≥4	3.0T	Cine, LGE	Explanted heart histology	1	3	0	3	100	5
Sgard et al.[85]	2019	France	80	NA	1.5T	Cine, LGE, T2WI	Modified JMHW (2006)	18	18	4	40	82	69
							HRS (2014)	36	0	4	40	90	100
Okune et al.[91]	2020	Japan	74	≥18	1.5T	Cine, LGE	JSSOG (2015)	39	26	1	8	98	24
Orii et al.[111]	2020	Japan	50	1.5T	1.5T	Cine, T2WI, LGE	HRS (2014)	8	10	0	32	100	76

CMR = cardiac magnetic resonance imaging; FDG = fluorodeoxyglucose; FN = false negative; FP = false-positive; HRS = Heart Rhythm Society; JMHW = Japanese Ministry of Health and Welfare; JSSOG = Japanese Society of Sarcoidosis and Other Granulomatous Disorders; LGE = late gadolinium enhancement; MR = magnetic resonance; NA = not available; PET = positron emission tomography; T2WI = T2-weighted imaging; TN = true negative; TP = true positive.

than CMR, reader experience is required to visually assess the DE-CT results. As observed in ^{18}F-FDG PET,[38] objective texture analysis of myocardial DE-CT showed a similar diagnostic value and higher reproducibility for differentiating between CS and non-CS patients compared to visual assessment.[114]

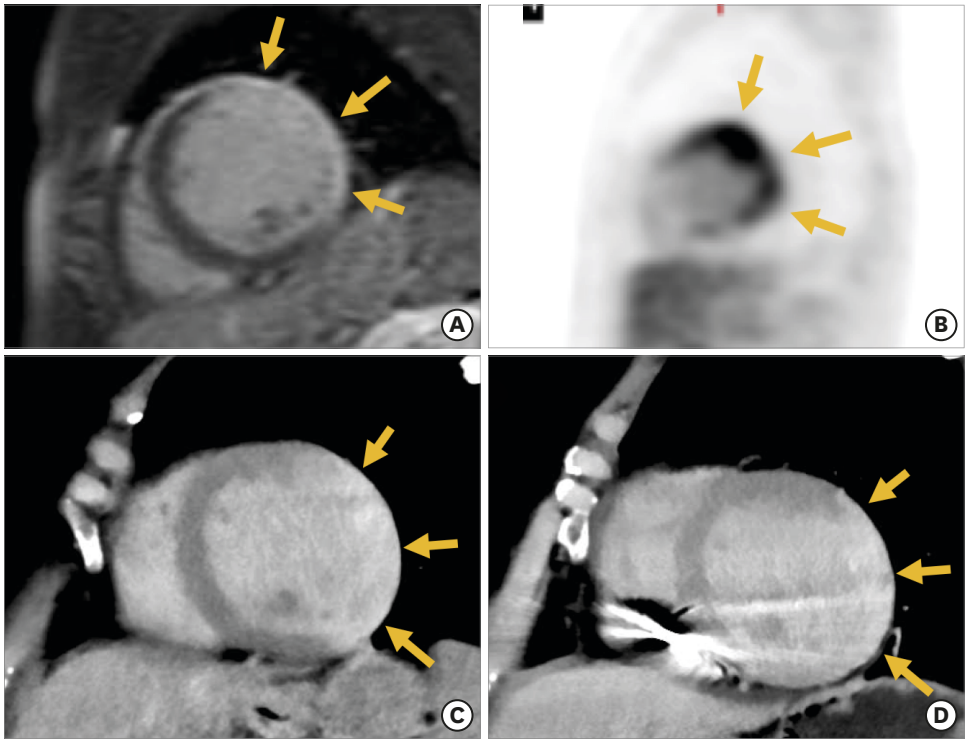

Figure 5. Arrhythmia was detected in a woman in her 50s. Abnormal enhancement and uptake are shown in the left ventricular lateral wall with late gadolinium enhancement of CMR and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (A and B, arrows). DE-CT also highlights the abnormal enhancement in the lateral wall, seen in the CMR (C, arrows). The patient was diagnosed with active cardiac sarcoidosis and was implanted with an ICD to prevent ventricular tachycardia. DE-CT after ICD implantation reveals abnormal enhancement in the lateral wall, as seen previously (D, arrows). Although there were metal artifacts mainly at the septum due to the ICD leads, we were able to compare the 2 images and confirm that the lesion was not worsening over time.
CMR = cardiac magnetic resonance imaging; DE-CT = delayed iodine contrast-enhanced computed tomography; ICD = implantable cardioverter-defibrillator.

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CONCLUSION

CS remains a morbid and potentially fatal manifestation of sarcoidosis. Though the diagnosis of CS is still challenging, ^{18}F-FDG PET and CMR are promising tools that may help us improve the diagnosis and understanding of the pathophysiology of CS.

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