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Clinical Application of ^{18}F-fluorodeoxyglucose PET and LGE CMR in Cardiac Sarcoidosis

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Abstract

Sarcoidosis is a multisystem granulomatous disease of unknown etiology that is characterized by the formation of non-caseating granulomas at various sites in the body. Cardiac sarcoidosis (CS) has been underdiagnosed in the past due to a lack of imaging modalities with high sensitivity. CS may cause various symptoms including conduction disturbance, ventricular arrhythmias, cardiac dysfunction and sudden cardiac death, which account for an increased mortality rate in these patients. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) and late gadolinium-enhanced cardiac magnetic resonance imaging (LGE CMR) have played important roles in the recent guidelines for the diagnosis of CS. Each one possesses its own unique abilities and can contribute to early disease detection, assessment of disease activity, response to treatment, and risk stratification. However, further studies are necessary in order to establish the standard methods for clinical application of FDG PET and CMR.

Keywords: ^{18}F-fluorodeoxygluocse, Cardiac magnetic resonance imaging, Cardiac sarcoidosis, Late gadolinium enhancement, Patient monitoring

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Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Non-caseating granulomas are the pathological hallmark of the disease and most often involve lungs and lymph nodes but may affect liver, spleen, skin, eyes, bones, parotid gland and heart as well. The overall prognosis of sarcoidosis is generally favorable; however, patients with cardiac sarcoidosis (CS) have a much worse prognosis than those without CS (1, 2). Unfortunately, CS has been underdiagnosed in the past because of a lack of proper imaging modalities (3, 4). Recent studies have reported the usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) and late gadolinium-enhanced cardiac magnetic resonance imaging (LGE CMR) in the diagnosis of CS (5-10). The present article summarizes the clinical application of FDG PET and CMR in CS.

FDG PET and LGE CMR in the diagnosis of CS

Recent reports have demonstrated the usefulness of FDG PET and LGE CMR for the non-invasive imaging of CS. FDG is an analog of glucose taken by living cells via cell membrane glucose transporters. It is rapidly phosphorylated and trapped within the cell (11). FDG PET under fasting conditions reveals the presence of metabolically active inflammatory cells such as lymphocytes and macrophages. Since the first case report by Takeda et al. (12), a number of case reports and clinical studies have demonstrated the usefulness of FDG PET for the

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detection of active cardiac involvement of sarcoidosis (5-7, 13-18). Focal myocardial FDG uptake indicates the presence of active CS (7, 19). In this respect, the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine (SNM) guideline for FDG PET use in inflammatory and infectious disease indicates sarcoidosis as major indication for FDG PET (20), but the health insurance systems in European countries and North America have not yet approved reimbursement for FDG PET use for sarcoidosis. Fortunately, in April 2012, the Japanese Ministry of Health, Labour and Welfare approved FDG PET study for reimbursement by health insurance plans, including it use for the identification of inflammatory sites in CS (21, 22). There are several pitfalls in the interpretation of FDG PET, given such considerations as physiological myocardial FDG uptake (23) and FDG uptake associated with other cardiac diseases such as pericarditis, myocarditis, ischemic heart disease, or metastasis of neoplastic disease, etc. (24-26).

In contrast, LGE CMR reveals areas of myocardial injury due to necrosis and replacement fibrosis. It is noteworthy that marked edema can also increase the interstitial space, thereby resulting in late gadolinium enhancement (LGE) (27). Many different patterns of LGE can be seen in patients with CS. The most typical patterns include sub-epicardial and mid-wall LGE along the basal septum and/or inferolateral wall (28). The Japanese guidelines for the diagnosis of CS were originally published in 1993 (29), were modified in 2006 (30) by the joint committee of the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Japanese College of Cardiology, and were updated in 2015. In the latest guidelines, positive findings of FDG PET and LGE CMR are included as major criteria based on the results of recent clinical studies. The latest guidelines have not yet been published in English. The Heart Rhythm Society (HRS) 2014 expert consensus recommendation for the diagnosis of CS includes FDG PET and LGE CMR abnormalities (31).

Comparison of FDG PET and CMR

Compared to SPECT scans, FDG PET and LGE CMR provide better sensitivity (24). Ohira et al. performed direct comparison of FDG PET and CMR in corticosteroid-naïve patients with conduction system disease and in patients with CS (10). In their patient cohorts, over half of the patients demonstrated positive findings on both modalities. The patients with chronic mild conduction system disease (CSD) (i.e. right bundle branch block and/or axis deviation) were more likely to be positive only on CMR, and the patients with new-onset atrioventricular block (AVB) were more likely to be positive only on FDG PET (FDG PET-positive and CMR-negative) ($p=0.02$). They also investigated the relationship between times from symptoms to scans and results of the imaging studies. Patients who were only positive on FDG PET underwent CMR earlier than did those who were positive on CMR. The results suggest that FDG PET may be more sensitive in patients with new-onset AVB in the very early stage of CS. In patients presenting with new-onset AVB and a negative CMR study, FDG PET may be useful for detecting cardiac involvement due to CS. Note that the time from symptom onset to scan may affect the results of the study. Fig. 1 shows a recent case with FDG PET-positive and LGE CMR-negative. Fig. 2 shows a case with FDG PET-negative and LGE CMR-positive.

Patient monitoring using FDG PET

Visual or quantitative assessment has been used to evaluate disease activity in CS. Takeda et al. showed that the improvement of FDG PET finding predicted recovery of third degree AVB in a CS patient treated with corticosteroids (12). Focal FDG uptake was diminished after steroid therapy. The disease activity was visually evaluated in the study. Blankstein et al. performed rubidium-82 PET and FDG PET to assess resting myocardial perfusion and metabolism (32). They visually classified the results of PET study into 3 groups, namely “Normal perfusion and metabolism”, “abnormal perfusion or metabolism” and “abnormal perfusion and metabolism”. They showed that the presence of abnormal perfusion and FDG on PET showed significant association with adverse events. They also demonstrated that the presence of right ventricular (RV) FDG uptake showed significant association with adverse events. However, visual interpretation of FDG PET for CS diagnosis is sometimes challenging, and reports indicate that there are several factors that may lead to discordant results among readers (33). Ohira et al. demonstrated that having patients follow a strict pre-scan dietary regimen seemed to lead to improved inter-operator agreement. The standardized uptake value (SUV) is commonly used as an index of tracer uptake in tumor imaging. Okumura et al. were the first to identify cardiac sarcoid lesions using this index, noting that the SUV of FDG in patients with CS was significantly elevated compared to that of the non-CS group. However, increased SUV is not specific to patients with CS. It is not uncommon that control subjects and those with other cardiac disease such as dilated cardiomyopathy (DCM) show diffusely increased myocardial FDG uptake (7, 34). A recent study performed by Yokoyama et al. nicely showed that FDG PET/CT with quantification of myocardial SUVmax provides a high sensitivity and specificity for diagnosing CS (16). The difference from the prior studies was that they performed FDG PET/CT with a strict diet restriction (a low-carbohydrate diet) followed by an overnight fast lasting ≥18 h. In a more recent study, Momose et al. demonstrated the SUVmax in the entire myocardium was much higher in

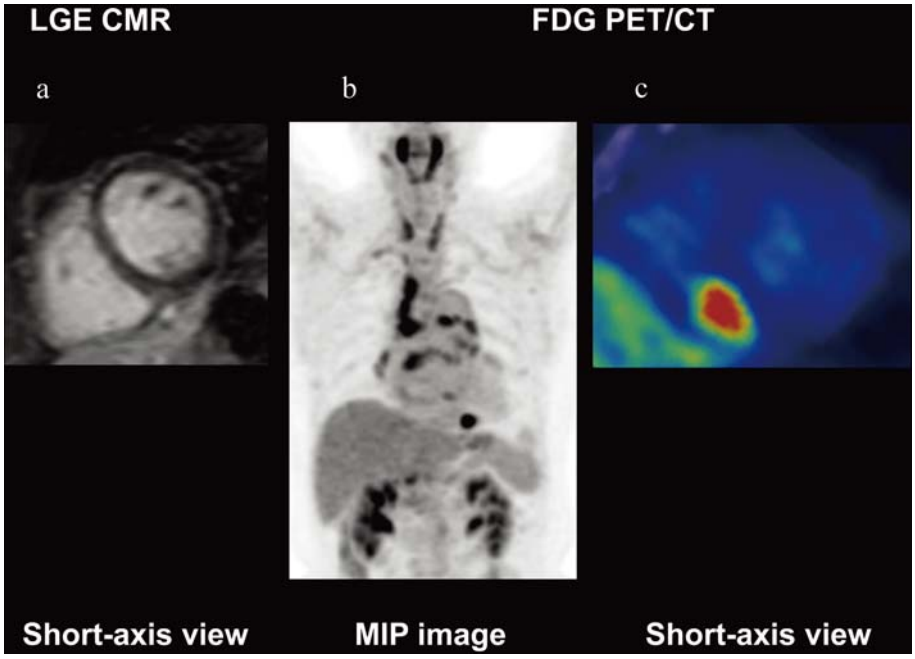

Fig. 1 Representative case of a 70-year-old female with hypertension who developed new-onset third-degree atrioventricular block (AVB). Coronary angiogram showed no significant coronary artery disease.

a: No abnormalities are found on LGE CMR.

b: Maximum intensity projection FDG PET image shows FDG-avid lymphoadenopathy in the mediastinum and bilateral hilar regions.

c: FDG PET image shows focal FDG uptake in the basal septum of the left ventricle (LV). The maximum standardized uptake value (SUVmax) of the LV is 14.6.

Histological diagnosis was confirmed by transbronchial needle aspiration (TBNA) of the mediastinal lymph node, and the patient has been diagnosed to have cardiac sarcoidosis.

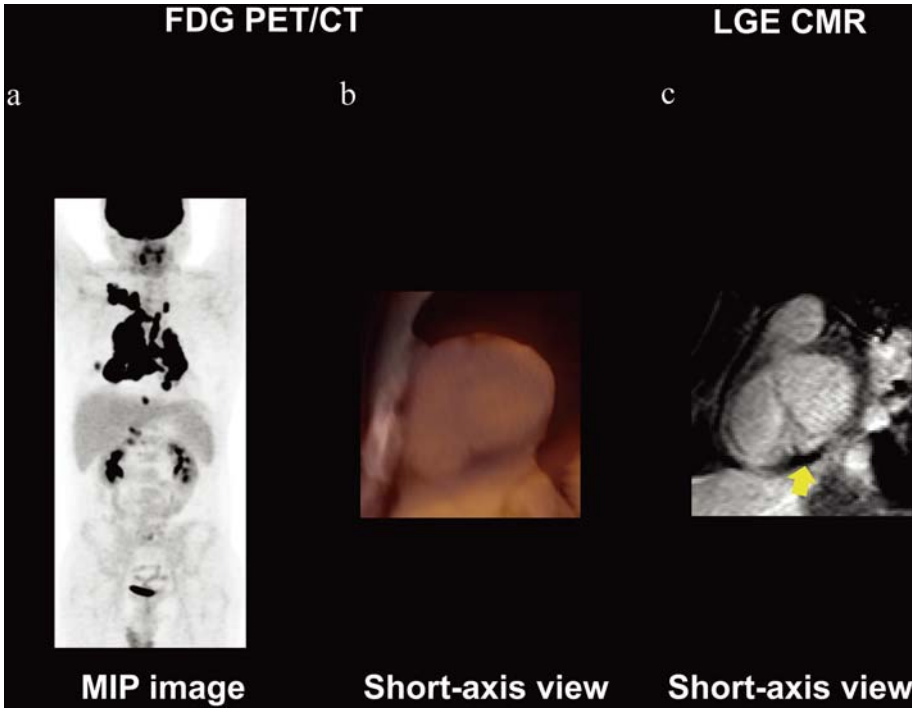

Fig. 2 Representative case of a 27-year-old male patient with known pulmonary sarcoidosis and a new diagnosis of anterior fascicular block.

a: Maximum intensity projection FDG PET image shows significant FDG uptake in the mediastinum, bilateral hilar and subclavian lymph nodes.

b: FDG PET image shows no FDG uptake in the heart.

c: LGE CMR in the short-axis oblique plane shows LGE in the subepicardial wall of the interventricular septum (arrow).

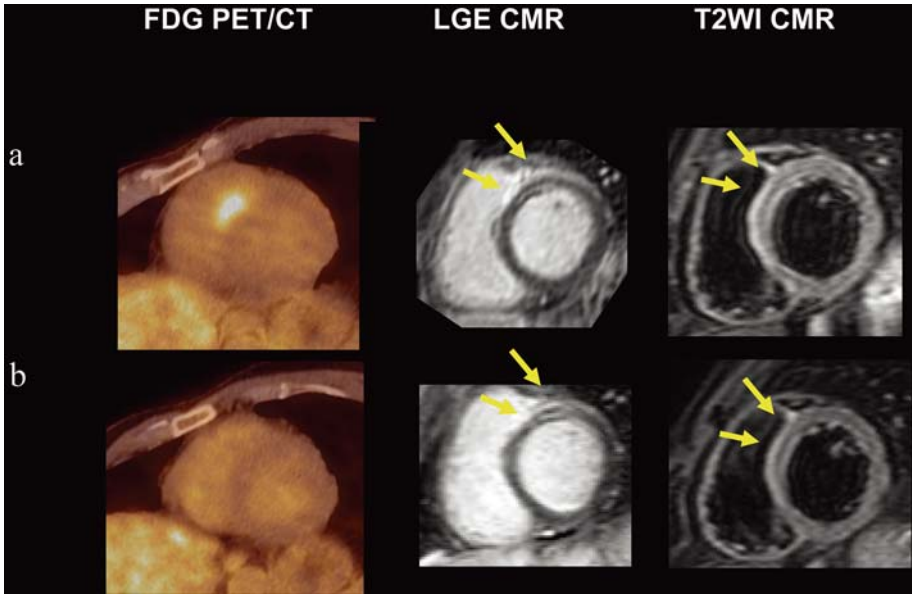

Fig. 3 Baseline and follow-up FDG PET/CT and CMR images from a 35-year-old man with biopsy-proven pulmonary sarcoidosis who developed non-sustained ventricular tachycardia (VT) and mildly reduced left ventricular ejection fraction (LVEF).

a: Baseline study: FDG PET/CT image shows focal FDG uptake in the interventricular septum of the left ventricle (arrows) (SUVmax 7.1). LGE CMR image in the short-axis oblique plane shows LGE in the subepicardial wall of the interventricular septum (arrows). T2 weighted image (T2WI) in the short-axis oblique plane shows high-intensity area in the corresponding area of LGE CMR.

b: Follow-up study (4 weeks after steroid therapy): There is significant reduction in myocardial FDG uptake on FDG PET/CT (SUVmax 1.7).
In contrast, it is difficult to find the changes in cardiac MR with LGE and T2WI.

patients with than those without CS (17). They also performed FDG PET/CT with a low-carbohydrate diet and 12-h fast.

Tahara et al. reported that the coefficient of variation (COV) representing heterogeneous myocardial FDG uptake may be a useful diagnostic marker for CS. They also showed that COV may be a useful marker for monitoring disease activity in CS. Serial FDG PET after corticosteroid therapy revealed a complete resolution of the heterogeneity of myocardial FDG uptake, whereas more heterogeneous myocardial FDG uptake was seen in an untreated patient after 1 year. In oncologic FDG PET studies, measurement of the volume and volume-intensity of abnormal FDG uptake is commonly referred to as “metabolic tumor volume” and “total lesion glycolysis”. Ahmadian et al. applied this method for CS, and reported that cardiac metabolic activity in CS correlates with lower left ventricular ejection fraction (LVEF), clinical events, and immunosuppression treatment (35). More recently, Ahmadian et al. showed that quantitative interpretation of FDG PET/CT in CS can detect changes in FDG uptake in response to immunosuppression (36).

Patient monitoring using CMR

Greulich et al. investigated whether the presence of LGE is a predictor of death and other adverse events in patients with suspected CS (37). Multivariable Cox regression analysis including the presence of LGE, the initial LVEF, the initial left ventricular end-diastolic volume (LVEDV), and initial presentation as heart failure (HF) revealed LGE as the best independent predictor of potential lethal events. For patients experiencing any event (death, sudden cardiac death, implantable cardioverter defibrillator (ICD) discharge, or ventricular tachycardia), LGE was the best independent predictor. But initial LVEF and LVEDV were also significant. Shimada et al. reported the usefulness of gadolinium CMR for monitoring disease activity. High-intensity areas were markedly diminished in size and intensity after steroid therapy (38). LGE can be observed in all pathological stages of CS from the active inflammatory phase, including necrosis and/or edema, to the chronic fibrotic phase. If LGE consists mainly of edema associated with inflammation and infiltration from granuloma, the size and intensity of LGE can be diminished through effective treatment. However, if LGE represents fibrosis in a patient with “burn-out” CS, no significant change is expected after steroid therapy. T2-weighted (T2WI) CMR can detect active inflammation with edema; however, the image quality of T2WI is still limited. An incomplete dark-blood preparation sometimes leaves a bright rim blood artifact adjacent to the endocardium, which makes it difficult to differentiate subendocardial edema from intracavitary blood. Crouser et al. showed improved detection of CS using CMR

with myocardial T2 mapping (39). Compared to healthy control subjects, patients with CS had considerably higher myocardial T2. Crouser et al. suggested that myocardial T2 is quantitatively abnormal in patients with CS and that the inclusion of abnormal T2 complements LGE abnormality for the detection of CS. Fig. 3 shows a representative case of a patient who underwent serial FDG PET/CT and CMR before and after steroid therapy.

Conclusions

The increased accuracy of advanced imaging, FDG PET and LGE CMR add to diagnostic capabilities and include the latest diagnostic guidelines. FDG PET and LGE CMR play complementary roles in the diagnosis of CS. In addition to the diagnostic value of these tests, FDG PET and LGE CMR are also useful for identifying patients with higher risk of adverse events. Further studies are needed to establish standard methods for assessing response to immunosuppressive therapy using FDG PET and CMR.

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Conflicts of interest

No conflicts of interest.

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