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Value of ^{18}F-FDG Accumulation in Mediastinal and Hilar Lymph Nodes on ^{18}F-FDG PET/CT: Relation to Recurrence of Cardiac Sarcoidosis

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Abstract

Purpose: ^{18}F-fluorodeoxyglucose (^{18}F-FDG) accumulation in the left ventricular (LV) wall detects active myocardial inflammatory lesions in cardiac sarcoidosis (CS), but the significance of ^{18}F-FDG accumulation in mediastinal and hilar lymph nodes (LNs) remains unclear. We investigated the association between CS recurrence and ^{18}FDG accumulation in the mediastinal and hilar LNs, using positron emission tomography/computed tomography (PET/CT)

Materials and Methods: We retrospectively analyzed the records of 68 patients diagnosed with CS, who underwent ^{18}F-FDG PET/CT before beginning treatment. The minimum follow-up period was 24 months. Patients were assigned to the recurrence (n=18) or no recurrence group (n=50) based on follow-up examinations. The ^{18}F-FDG PET/CT maximum standardized uptake value (SUV_{max}) was measured in the LV wall, right ventricular (RV) wall, and mediastinal and hilar LNs. The association of CS recurrence was analyzed using Cox proportional hazards models. Recurrence-free survival (RFS) curves were made using the Kaplan-Meier method.

Results: In univariate analysis, sex, BNP, LVEF, and the SUV_{max} in the LV wall, RV wall, and mediastinal and hilar LNs were significant risk factors for CS recurrence. In multivariate analysis, only the SUVmax in the mediastinal and hilar LNs was a significant risk factor for CS recurrence. RFS rates were significantly higher in patients with an SUVmax<4.1 vs. ≥ 4.1 (log-rank value=36.0, p<0.01).

Conclusion: The mediastinal and hilar LN SUV_{max} was an independent risk factor for CS recurrence after treatment. ^{18}F-FDG accumulation in mediastinal and hilar LNs on ^{18}F-FDG PET before treatment may be a useful biomarker to predict CS recurrence.

Keywords: Cardiac sarcoidosis; ^{18}F-FDG PET; Lymph nodes; Recurrence-free survival

Abbreviations:

CS: Cardiac Sarcoidosis; LV: Left Ventricular; RV: Right Ventricular; LVEF: Left Ventricular Ejection Fraction; ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; ^{18}F-FDG PET: ^{18}F-Fluorodeoxyglucose Positron Emission Tomography; LNs: Lymph Nodes; CT: Computed Tomography; JMHW: Japanese Ministry of Health and Welfare; CRT: Cardiac Resynchronization Therapy; LVAD: Left Ventricular Assist Device; SUV: Standardized Uptake Value; SUVmax: Standardized Uptake Value Maximum; VOI: Volume of Interest; NYHA: New York Heart Association; RFS: Recurrence-Free Survival; SD: Standard Deviation; ROC curve analysis*:* Receiver Operating Characteristic curve analysis

Introduction

Sarcoidosis is a disease of unknown etiology, characterized by the presence of non-caseating granulomas that can affect multiple organs. Cardiac involvement in sarcoidosis is associated with heart failure, ventricular tachyarrhythmias, conduction disturbances, and sudden cardiac death and is one of the leading causes of disease-related death [1-4]. Cardiac sarcoidosis (CS) may impair left ventricular (LV) [5] and right ventricular (RV) [6] function, and a low LV ejection fraction (LVEF) leads to poor prognosis [5]. Corticosteroid therapy is the mainstay of CS treatment [7,8], and its efficacy is about 50% [9,10]. Options for corticosteroid-refractory CS include immunosuppressant therapy and placement of an implantable cardiac defibrillator. However, recurrence of CS after these treatments is not rare and leads to a poor prognosis. Naruse et al. reported that 38% of CS patients experienced recurrent disease [11]. Therefore, it is clinically meaningful to evaluate the risk of recurrence of CS, although the risk factors remain unclear.

The inflammatory lesions of CS are known to accumulate 18F-fluorodeoxyglucose (^{18}F-FDG), making ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) a useful modality for diagnosis in patients suspected to have this disease. Further, reports indicate its utility for the detection of active myocardial inflammatory lesions [12-14] and the assessment of therapeutic effects following treatment in patients with CS [15]. In addition to the utility of ^{18}F-FDG PET for the prediction of therapeutic effect in CS, its use for the assessment of the risk for adverse events, including sudden death, has also been investigated [12,15,16]. Recent studies indicate that

metabolism-perfusion imaging (rubidium-FDG PET) predicts disease activity in CS [17] and that 18F-FDG accumulation in the LV and RV wall on ^{18}F-FDG PET predicts the clinical impact of CS [6,18,19].

Mediastinal and hilar lymph nodes (LNs) are common sites of involvement in sarcoidosis [1]. However, no reports focus on the clinical significance of ^{18}F-FDG accumulation in mediastinal and hilar LNs in CS. Inflammation in the thoracic cavity is associated with high ^{18}F-FDG accumulation in the mediastinal and hilar LNs. Therefore, we hypothesized that mediastinal and hilar LNs are also affected by the CS disease process. Moreover, there are no well-established risk factors for recurrent CS. The purpose of this study was to investigate the association between the recurrence of CS and ^{18}F-FDG accumulation in the mediastinal and hilar LNs and in the LV and RV walls in patients with CS.

Methods

Patients

This study was approved by our institutional review board and written informed consent from each patient was obtained. We retrospectively evaluated the medical records of 111 consecutive patients that raised suspicion of CS who underwent 8F-FDG PET-computed tomography (CT) between January 2010-December 2014. Patients diagnosed with CS based on the 2006 Japanese Ministry of Health and Welfare (JMHW) guidelines [20,21] were included. Our exclusion criteria were: 1. high blood glucose level (>150 milligrams per deciliter (mg/dL)), and 2. No uptake or diffuse-type uptake of ^{18}F-FDG in the LV myocardium [21].

Following patient selection, 68 patients were available for our analysis and their characteristics are shown in Table 1. All patients were initially treated with prednisolone, 30 mg per day. In 2 of the 68 patients, the steroid was discontinued due to side effects and the immunosuppressives were used instead. The response to treatment was determined by the consensus of two cardiologists. The patients who did not demonstrate a stabilization of clinical symptoms and improvement of cardiac function after steroid therapy were treated with immunosuppressant therapy, cardiac resynchronization therapy (CRT), or an LV assist device (LVAD).

Variables	No recurrence (n=50)	Recurrence (n=18)
Age (years old)	58 ± 11	63 ± 11
Sex		
Men/women	30/20	3/15
NYHA class		
II/III	41/9	13/5
Myocardial histopathological diagnosis		
Positive/negative	14/36	7/11
Follow-up period (month)	36 ± 5	35 ± 8
BNP (pg/mL)	257 ± 320	487 ± 414
Electrocardiographic abnormalities		
Atrioventricular block	31/50 (62%)	8/18 (44%)
Left bundle branch block	7/50 (14%)	3/18 (17%)
Right bundle branch block	17/50 (34%)	5/18 (28%)
Left axis deviation	14/50 (28%)	5/18 (28%)
Premature ventricular contraction	29/50 (58%)	10/18 (56%)
Ventricular tachycardia	3/50 (6%)	4/18 (22%)
Echocardiography abnormalities		
Interventricular septum wall thinning	40/50 (80%)	13/18 (72%)
Regional wall motion abnormality	44/50 (88%)	16/18 (89%)
Ventricular aneurysm	2/50 (4%)	1/18 (6%)
Regional wall thickening	5/50 (10%)	3/18 (17%)
LVEF (%)	50 ± 15	41 ± 11
Treatment characteristics		
Only steroid therapy	45/50 (90%)	1/18 (6%)
Immunosuppressant therapy	2/50 (4%)	17/18 (94%)
CRT	5/50 (10%)	7/18 (39%)
LVAD	0/50 (0%)	3/18 (17%)

Data are mean ± SD or number of patients.

CS: Cardiac Sarcoidosis; NYHA: New York Heart Association; BNP: Brain Natriuretic Peptide; LVEF: Left Ventricular Ejection Fraction; CRT: Cardiac Resynchronization Therapy; LVAD: Left Ventricle Assist Device.

Table 1: Baseline characteristics of the patients.

^{18}F-FDG PET/CT Imaging

In each patient, a low-carbohydrate and high-fat diet [22] was started 24 hours before 18F-FDG injection and it was continued for 6 hours. After an 18-hour fast, 4 MBq/kg of ^{18}F-FDG was then administered intravenously [23]. Cardiac scanning was started 60 minutes after the injection of ^{18}F-FDG. ^{18}F-FDG PET/CT images were generated using a PET/CT instrument equipped with 24 ring detectors consisting of 560 BGO crystals (4.7 mm × 6.3 mm × 30 mm) (Discovery STE; GE Medical Systems, Milwaukee, WI, US). The acquisition time per bed position in the emission scans was 10 minutes. The PET image matrix size was 128 mm × 128 mm (5.47 mm × 5.47 mm × 3.27 mm). For image reconstruction, the ordered subset expectation maximization method (VUE Point Plus) with 2 iterations and 28 subsets was used. The full-width at half maximum was 5.2 mm. A 16-slice scan (tube voltage, 120 kV; effective tube current, 30 mA to 250 mA) was performed for the purpose of attenuation correction before the PET image scans were started. The CT scan images were 512 × 512 matrices and had a slice thickness of 5 mm. The PET/CT fusion images were obtained using GENIE-Xeleris workstation software (GE Medical Systems, Milwaukee, WI).

Image evaluation

The ^{18}F-FDG PET image standardized uptake value (SUV) maximum (SUV_{max}) was measured in the LV wall, RV wall, and mediastinal and hilar LNs [6,21]. The SUV was obtained from each pixel as pixel activity (injected dose/body weight). A spherical volume

of interest (VOI) corresponding to the LV wall, RV wall, and mediastinal and hilar LNs was manually drawn, and the highest pixel value was determined as the SUV_{max}.

Analysis of CS recurrence

All patients were followed up by cardiologists at our institution at least every 3 months after discharge. The minimum follow-up period was 24 months, and ^{18}F-FDG PET was performed at least every 6 months during this time. Patients in recurrence group had an interim ^{18}F-FDG PET at 3 months to demonstrate resolution. Physicians performed blood tests, ECG, echocardiography, and ^{18}F-FDG PET when they suspected a recurrence of CS. A CS recurrence was judged based on a myocardial focal-type or diffuse-on-focal-type uptake findings on ^{18}F-FDG PET as well as clinical symptoms with New York Heart Association (NYHA) class or more and cardiac dysfunction (EF<50%) [21], and the patients presented with arrhythmia were also defined as a recurrence. The patients were divided into recurrence and no recurrence groups according to their SUVs using the optimal cutoff values and recurrence-free survival (RFS) between the groups.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation (SD). Comparisons of LVEF and the ^{18}F-FDG PET SUV_{max} in the LV wall, RV wall, and mediastinal and hilar LNs pre-treatment between the recurrence and no recurrence groups were analyzed using the Wilcoxon test. The Spearman correlation test was used to assess correlations between two values. The ability of the SUV_{max} in the LV wall, RV wall, and mediastinal/hilar LNs to differentiate the recurrence from the no recurrence group and to predict recurrence after therapy was analyzed by receiver operating characteristic (ROC) curve analysis. In patients with recurrence, comparisons of the SUV_{max} in the LV wall, RV wall, and mediastinal and hilar lymph nodes before treatment and after recurrence were performed using paired t-tests. We applied univariate and multivariate Cox proportional hazard models to analyze the prediction of recurrence of CS. Covariates included age, sex, New York Heart Association (NYHA) class, brain natriuretic peptide (BNP), LVEF, and ^{18}F-FDG PET measurements. Survival curves of patient subgroups were created using the Kaplan-Meier method to clarify the time-dependent, cumulative recurrence-free rate and compared using the log-rank test. The tests were performed using JMP statistical software (version 10.0; SAS Institute, Inc., Cary, NC, USA). A p value of less than 0.05 was considered significant.

Results

Comparison of 18F-FDG PET measurements between the recurrence and no recurrence groups

CS recurrence occurred in 18 patients. The 18 CS patients with recurrence were followed for 25 to 49 months (median follow-up, 36 months) and the 50 CS patients without recurrence were followed for 24 months to 52 months (median follow-up, 34 months). The SUVmax results in the LV and RV walls and mediastinal and hilar LNs pre-treatment were significantly higher in the recurrence group than in the no recurrence group (8.6 ± 3.8 vs. 5.1 ± 2.7, p<0.0001, 3.8 ± 3.2 vs. 1.8 ± 1.0; p=0.01, 8.6 ± 4.6 vs. 2.8 ± 1.1; p<0.0001, respectively) (Table 2).

Variables	No recurrence (n=50)	Recurrence (n=18)
SUVmax		
LV wall	5.1 ± 2.7	8.6 ± 3.8**
RV wall	1.8 ± 1.0	3.8 ± 3.2*
Mediastinal/hilar LNs	2.8 ± 1.1	8.6 ± 4.6**

^{18}FDG-PET=^{18}F-fluorodeoxyglucose positron emission tomography; SUVmax=maximum of standardized uptake value.

*p<0.05 vs. patients without recurrence; **p<0.0001 vs. patients without recurrence

Table 2: The difference in 18FDG-PET measurements between patients with and without recurrence of CS.

Correlations between ^{18}F-FDG accumulation in mediastinal/hilar LNs and myocardium

There was a significant positive linear correlation between the SUVmax in the mediastinal and hilar LNs and the LV wall (r=0.70, p<0.0001) and between the SUVmax in the mediastinal and hilar LNs and the RV wall (r=0.71, p<0.0001).

Correlations between LVEF and ^{18}F-FDG PET parameters

There was a significant inverse linear correlation between the LVEF and SUV_{max} in the LV wall (r=0.38, p=0.001) and between the LVEF and the SUV_{max} in the RV wall (r=0.25, p=0.04). However, there was no significant correlation between the LVEF and the SUV_{max} in the mediastinal and hilar LNs (r=0.21, p=0.09).

Predictability of recurrence after treatment in patients with CS with ^{18}F-FDG PET parameters

ROC curve analysis revealed that the optimal SUV_{max} thresholds for predicting recurrence of CS in the LV wall, RV wall, and mediastinal and hilar LNs were 6.4, 2.4, and 4.1, with an AUC of 0.82, 0.69 and 0.93, accuracy of 76% (52/68), 81% (55/68) and 91% (62/68), sensitivity of 83% (15/18), 56% (10/18) and 94% (17/18), and specificity of 74% (37/50), 90% (45/50) and 90% (45/50), respectively (Figure 1).

RFS analysis with Cox proportional hazards model

In univariate analysis, the χ^2 and the hazard ratio to predict recurrence of CS were 1.96 and 0.69 for age, 5.90 and 0.54 for sex, 0.82 and 0.75 for the NYHA class, 11.0 and 0.43 for BNP, 7.31 and 0.50 for

LVEF, 10.3 and 0.41 for the LV wall SUV_{max}, 5.54 and 0.43 for the RV wall SUV_{max}, and 20.6 and 0.24 for the mediastinal and hilar LN SUV_{max}, respectively. In multivariate analysis, the χ^2 and the hazard ratio to predict recurrence of CS were 0.20 and 0.87 for age, 2.56 and 0.64 for sex, 0.89 and 0.64 for the NYHA class, 2.36 and 0.56 for BNP, 3.60 and 0.50 for the LVEF, 0.014 and 0.95 for the LV wall SUV_{max}, 0.31 and 0.78 for the RV wall, and 7.69 and 0.34 for the mediastinal and hilar LN SUV_{max}, respectively (Table 3).

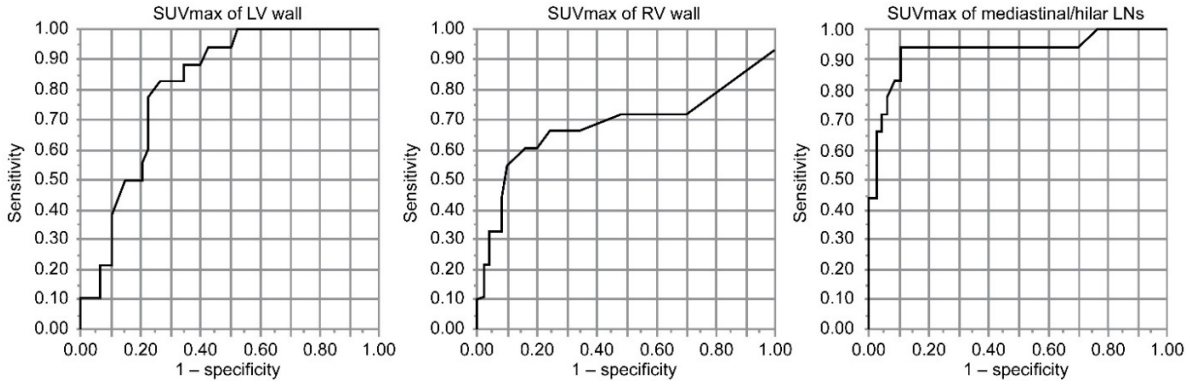

Figure 1: Predictability of risk for cardiac sarcoidosis (CS) recurrence after treatment, using receiver operating characteristic (ROC) curve analysis. ROC curves demonstrating the ability of the maximum standardized uptake value (SUVmax) to predict CS recurrence are shown for the left ventricular (LV) wall (left), right ventricular (RV) wall (center), and mediastinal and hilar lymph nodes (LNs) (right). The areas under the curve for SUVmax in the LV wall, RV wall, and mediastinal and hilar LNs were 0.82, 0.69, and 0.93, respectively.

Characteristics	Variables	Univariate analysis			Multivariate analysis			
		χ2	Hazard ratio	*p*	χ2	Hazard ratio	95% CI	*p*
Age (years old)	≥ 54 vs.<54	1.96	0.69	0.17	0.2	0.87	0.46- 1.65	0.66
Sex	Men vs. women	5.9	0.54	0.02	2.56	0.64	0.36-1.11	0.11
NYHA class	III vs. II	0.82	0.75	0.37	0.89	0.64	0.26-1.62	0.35
BNP (pg/mL)	≥ 133 vs.<133	11	0.43	0.0009	2.36	0.56	0.26-1.18	0.13
LVEF (%)	<45 vs. ≥ 45	7.31	0.5	0.007	3.6	0.5	0.25-1.06	0.07
^{18}F-FDG PET measurement								
SUVmax of LV wall	≥ 6.4 vs.<6.4	10.3	0.41	0.0013	0.014	0.95	0.44-2.12	0.91
SUVmax of RV wall	≥ 2.4 vs.<2.4	5.54	0.43	0.019	0.31	0.78	0.32-1.89	0.58
SUVmax of mediastinal/hilar LNs	≥ 4.1 vs.<4.1	20.6	0.24	<0.0001	7.69	0.34	0.16-0.73	0.0058

NYHA: New York Heart Association; BNP: Brain Natriuretic Peptide; LVEF: Ejection Fraction in Left Ventricle; ^{18}F-FDG PET: ^{18}F-Fluorodeoxyglucose Positron Emission Tomography; Suvmax: Maximum Standardized Uptake Value; RV: Right Ventricle; LN: Lymph Nodes

Table 3: Recurrence relation factor after treatment of CS.

RFS rates were significantly higher in patients with a mediastinal and hilar LN SUV_{max}<4.1 than in those with an SUV_{max} ≥ 4.1 (log-rank value=27.9, p<0.0001) (Figure 2).

Comparison of the SUV_{max} in the LV wall, RV wall, and mediastinal/hilar LNs before and after treatment in CS patients with recurrence

^{18}F-FDG PET was performed at the time that recurrence was diagnosed in all 18 cases. There was no significant difference in the SUV_{max} in the LV wall (8.6 ± 3.9 vs. 6.7 ± 2.7, p=0.06) or the RV wall (3.8 ± 3.3 vs. 2.5 ± 1.8, p=0.08) between the pretreatment and disease recurrence examinations. In contrast, the SUV_{max} in the mediastinal and hilar LNs was significantly lower before-treatment than after recurrence (8.5 ± 4.6 vs. 4.0 ± 2.0, p<0.01) (Table 4).

Representative ^{18}F-FDG PET images before treatment and at the time recurrence was diagnosed are presented in Figure 3.

Discussion

Our results demonstrate that the SUVmax in the LV wall, RV wall and mediastinal and hilar LNs before treatment in the recurrence group were significantly higher than the corresponding SUVmax results in the no recurrence group. Additionally, our multivariate

analysis indicates that the high SUVmax in mediastinal and hilar LNs was a significant risk factor for recurrence of CS after treatment. Significant correlations in the SUVmax between the mediastinal and hilar LNs and the LV and RV walls were observed, whereas there was no significant correlation between the SUVmax in the mediastinal and hilar LNs and the LVEF. The disease progression of sarcoidosis leads to decreased mediastinal involvement and increased parenchymal involvement. Aysun Yakar et al. reported that in sarcoidosis without cardiac involvement, mediastinal LN^{18}F-FDG accumulation decreases as the disease progresses [24]. We hypothesize that cardiac sarcoidosis with highly remaining^{18}F-FDG accumulation in mediastinal and hilar LNs implies a high degree of sarcoidosis activity.^{18}F-FDG accumulation in the mediastinal and hilar LNs may be associated with the degree to which CS is refractory and not directly reflect cardiac dysfunction.

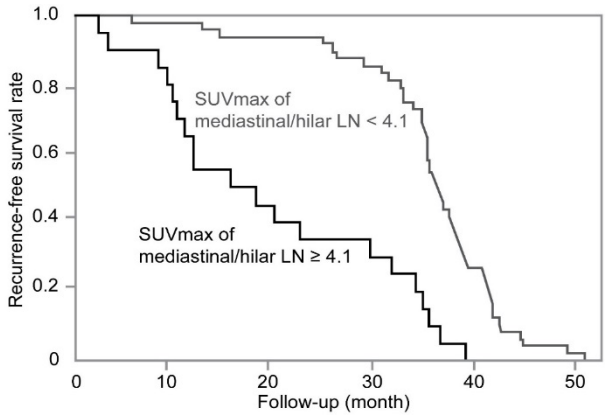

Figure 2: Recurrence-free survival (RFS) curves of two groups classified by a cutoff value of 4.1 for the maximum standardized uptake value (SUVmax) in the mediastinal and hilar lymph nodes. RFS rates were significantly different between patients with SUVmax<4.1 (red) vs. ≥ 4.1 (blue).

Variables	SUVmax at diagnosis	SUVmax at recurrence
LV wall	8.6 ± 3.8	6.7 ± 2.7
RV wall	3.8 ± 3.2	2.5 ± 1.7
mediastinal/hilar LNs	8.5 ± 4.6	4.0 ± 2.0*

^{18}FDG-PET=^{18}F-fluorodeoxyglucose positron emission tomography; SUVmax=maximum of standardized uptake value; LV: Left Ventricle; RV: Right Ventricle

*p<0.05 vs. SUVmax at diagnosis

Table 4: The difference in ^{18}FDG-PET measurement in patients with recurrence, between diagnosis and after recurrence.

Interestingly, the SUV_{max} in mediastinal and hilar LNs at recurrence was significantly lower than before treatment, while there was no significant difference in the LV or RV wall SUVmax between the two examinations. In the CS recurrence group, a decreased SUVmax in mediastinal and hilar LNs was not a sign of treatment response. There might be a difference in the treatment response between the myocardium and LNs.

LV and RV wall SUV_{max} values were not independent risk factors for CS recurrence. A possible explanation on ^{18}F-FDG accumulation in the LV wall is the passage from the active inflammatory phase to the chronic phase. CS in chronic phase does not necessarily show as high ^{18}F-FDG accumulation in LV wall as in active inflammatory phase because of fibrosis of myocardium. Thus, it might to be difficult to evaluate disease progression of CS only by mean of SUV_{max} values of ^{18}F-FDG accumulation in LV wall. With respect to ^{18}F-FDG accumulation in RV wall, a recent study reported that increased RV ^{18}F-FDG accumulation reflects RV pressure overload or pulmonary hypertension [25].

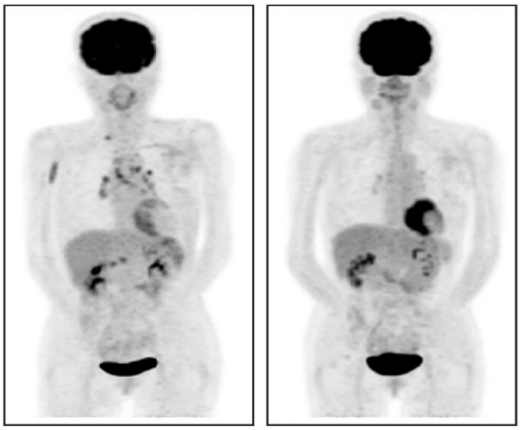

Figure 3: A 65-year-old female patient with recurrence 6 months after steroid therapy for cardiac sarcoidosis. Maximum intensity 18F-fluorodeoxyglucose positron emission tomography projection images before steroid therapy (left) and 6 months after steroid therapy (lower right) are presented. The left ventricular ejection fraction and maximum standardized uptake value (SUVmax) in the left ventricular (LV) wall, right ventricular (RV) wall, and the mediastinal and hilar lymph nodes (LNs) before treatment were 25%, 4.4, 1.6, and 5.5, respectively. The SUVmax in the LV wall, RV wall, and the mediastinal and hilar LNs at recurrence were 8.7, 1.8, and 2.5, respectively.

All patients were maintained on a low-carbohydrate and high-fat diet for a period of 6 hours, followed by fasting for 18 hours before ^{18}F-FDG injection. As this protocol is known to inhibit physiological myocardial uptake [22,23], we believe that our evaluation of myocardial ^{18}F-FDG uptake here has sufficient validity.

The present study has several limitations. First, the median follow-up period was 31 months, so it lacks long-term follow-up data to confirm the outcomes of patients who responded to steroid therapy and showed no recurrence during this period. Second, the patients with CS who were analyzed were relatively few and recruited from a single center. Further studies are needed to confirm our hypotheses by evaluating the outcomes of patients with CS in multicenter studies with longer follow-up periods.

Conclusion

In conclusion, the ^{18}F-FDG PET SUV_{max} in mediastinal and hilar LNs was a significant risk factor for recurrence of CS. ^{18}F-FDG accumulation in mediastinal and hilar LNs may be a useful biomarker

to predict CS recurrence and facilitate the clinical management of patients with CS.

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