^{18}F-FDG Positron-Emission Tomography/Computed Tomography Findings of Radiographic Lesions Suggesting Old Healed Tuberculosis

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The presence of radiographic lesions suggesting old healed tuberculosis (TB) is one of the strongest risk factors for the subsequent development of active TB. We elucidated the metabolic activity of radiographic lesions suggesting old healed TB using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). This cross-sectional study included 63 participants with radiographic lesions suggesting old healed TB and with available ^{18}F-FDG PET/CT scans. The maximum standardized uptake value (SUV$_{max}$) measured in the lesions, the clinical characteristics, results of the tuberculin skin test (TST) and interferon-γ release assay (IGRA) were analyzed. The SUV$_{max}$ in old healed TB was 1.5 or higher among nine (14.3%) participants. Age (adjusted odds ratio [aOR], 1.23; 95% CI, 1.03-1.46), history of previous TB (aOR, 60.43; 95% CI, 1.71-2131.65), and extent of the lesions (aOR, 1.34; 95% CI, 1.02-1.75) were associated with higher SUV$_{max}$. The positive rates for the TST and IGRA were not different between groups with and without increased FDG uptake. Increased FDG uptake on ^{18}F-FDG PET/CT was observed in a subset of patients with radiographic lesions suggesting old healed TB. Given that the factors associated with increased FDG uptake are known risk factors for TB development, the possibility exists that participants with old healed TB lesions with higher SUV on ^{18}F-FDG PET/CT scans might be at higher risk for active TB.

Keywords: Positron-Emission Tomography; Tomography, X-Ray Computed; Tuberculosis, Pulmonary; Latent Tuberculosis; Interferon-gamma Release Tests

INTRODUCTION

Old healed tuberculosis (TB) can be defined as radiographic lesions suggesting TB sequelae without clinical or microbiological evidence of active pulmonary TB. Old healed TB usually presents as pulmonary nodules in the hilar area or upper lobes with fibrotic scars and volume loss. Also, bronchiectasis and pleural scarring may be combined (1). Nodules and fibrotic scars from old healed TB may contain slowly multiplying tubercle bacilli with the potential for future progression to active TB. In previous studies, the presence of radiographic lesions consistent with old healed TB was one of the strongest risk factors for the development of active TB (2). However, there is no information on the metabolic states in such lesions.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been widely used for differentiation of malignant from benign pulmonary lesions

because FDG uptake was significantly increased in malignant pulmonary lesions (3). However, FDG accumulates in not only malignant tumors but also inflammatory lesions of both infectious and noninfectious origins, including pulmonary TB, sarcoidosis, histoplasmosis, and others (4-7). The inflammatory cells such as neutrophils and activated macrophages at the site of inflammation or infection may be responsible for the accumulation of FDG (8, 9). Reports have suggested the usefulness of ^{18}F-FDG PET/CT for the evaluation of inflammatory lesions (6, 10).

Because active pulmonary TB in the acute state has intense glucose hypermetabolism (11), strong uptake of FDG was observed in pulmonary TB (3, 12-14) as well as in pulmonary tuberculoma (15-17). Subsequently, ^{18}F-FDG PET/CT was proposed as a tool for determining the activity of pulmonary tuberculomas (16) and for evaluating the therapeutic response of TB (18, 19). However, there are no reports on PET findings in radio-

graphic lesions suggesting old healed TB. In the present study, we elucidated the metabolic activity of old healed TB using ^{18}F-FDG PET/CT and compared the uptake with the results of the tuberculin skin test (TST) and interferon (IFN)-γ release assay (IGRA).

MATERIALS AND METHODS

Participants and study design

This was a cross-sectional study based on a previous prospectively enrolled trial of 193 participants with radiographic lesions suggesting old healed TB at Seoul National University Hospital (Seoul, Republic of Korea), a tertiary referral hospital, between 1 January 2010 and 31 January 2011 (20). From the cohort, 63 participants with radiographic lesions suggesting old healed TB and available ^{18}F-FDG PET/CT scans performed during the staging work up for the newly diagnosed cancers were included in this study. The maximum standardized uptake value (SUV_{max}) was measured in the radiographic lesions suggesting old healed TB; and the demographic data, clinical characteristics, and results of the TST and IGRA were analyzed.

Interpretation of computed tomography of the chest

The presence of old healed TB was defined based on criteria proposed by Linh et al. (21) and the Centers for Disease Control and Prevention guidelines (22). The extent of lesions suggesting old healed TB (cm^2) was determined by multiplying the major and minor axes (cm) measured on coronal images of the chest computed tomography (CT), where the major axis was the longest axis.

Whole blood IGRA and TST

For IGRA, the QuantiFERON-TB Gold In-Tube test (QFT-GIT) was performed according to the manufacturer's instructions. Test results were interpreted as negative, indeterminate, or positive (cut off, 0.35 IU/mL) using the manufacturer's software (Cellestis, Carnegie, Australia). TST was performed according to the Mantoux method using a 2-TU dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark). After 48-72 hr, any induration was measured in millimeters using the ballpoint method. A positive TST result was defined as an induration of ≥ 10 mm. QFT-GIT and TST were performed within 1 week of checking ^{18}F-FDG PET/CT.

^{18}F-FDG PET/CT imaging

All patients fasted for at least 6 hr prior to the study. ^{18}F-FDG PET/CT imaging studies were conducted 60 min after intravenous injection of F-18 FDG (5.18 MBq/kg). Patients were examined using dedicated PET/CT scanners (Gemini, Philips; Biograph 40, Siemens). Emission scans were conducted in a three-dimensional mode following a CT scan for attenuation correc-

tion. After scatter and decay correction, PET data were reconstructed iteratively with attenuation correction and were reoriented in axial, sagittal, and coronal slices. PET/CT images were analyzed in three different planes: transverse, coronal, and sagittal.

Two board-certified nuclear medicine physicians, unaware of the demographic/clinical data and laboratory results, interpreted the ^{18}F-FDG PET/CT scans. FDG uptake was measured as the standardized uptake value (SUV) on the emission images, using a vendor-supplied analysis tool package (Syngo.via, Siemens). After visually finding the area of highest FDG uptake in lesions suggesting old healed TB, the region of interest (ROI) was outlined. A SUV normalized for the injected dose and body weight was obtained in each pixel using a standard method: SUV = ROI activity/(injected dose/body weight), where the ROI activity is measured in mCi/mL, the injected dose is measured in mCi, and body weight is measured in g. The maximum pixel value in the ROI was chosen as the maximum SUV (SUV_{max}). We assumed a SUV_{max} of 1.5 as a cut-off value of significant FDG uptake in old healed TB, based on the fact that the SUV of normal lung tissue is usually between 0.4 and 0.5 (23).

Statistical analysis

Data are expressed as median values with minimum and maximum values. Comparisons of demographic characteristics, TST and IGRA results, and radiographic findings between patients with and without meaningful SUV uptake were performed using Pearson's chi-square test or Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables. To elucidate the predictors for meaningful SUV increase, we selected clinical variables through univariate comparison and performed subsequent binary logistic regression. In regression, backward elimination was used to select variables to be maintained in the final model. A P value of 0.10 was the criterion for statistical significance of association. All statistical analyses were performed with PASW software (ver. 17.0; SPSS Inc., Chicago, IL, USA).

Ethics statement

The study protocol was approved by the by the institutional review board of Seoul National University Hospital (IRB No. 1109-037-377).

RESULTS

Baseline characteristics of the participants

The median age of the 63 participants was 65 yr (range, 36-88 yr), and 43 (68.3%) were male. The presence of a BCG scar was confirmed in 22 patients (38.6%), and 30 (47.6%) had a history of TB treatment. In total, 66.7% of participants had a positive TST, and 77.8% had a positive QFT-GIT. The median extent of

the lesions on chest CT was 3.52 cm^2 (range, 0.12–32.86 cm^2) (Table 1).

Comparison between participants with and without meaningful SUV uptake

In participants, ^{18}F-FDG PET/CT scans were performed for the diagnosis or staging work up of malignant diseases. Fifty-eight (92.1%) of them were diagnosed as having malignant diseases, most commonly lung cancer.

The SUV$_{max}$ was 1.5 or higher in nine (14.3%) participants out of 63 participants. The median age of this group was higher than that of the group without increased FDG uptake (72 vs 63.5 yr, P = 0.03). Body mass index and the presence of a BCG scar were not different between the two groups. In addition, the positive rates of TST and QFT-GIT were not different. However, the extent of the radiographic lesions suggesting old healed TB was larger in the participants with increased SUV$_{max}$ compared with those with lower SUV$_{max}$ (8.33 vs 2.78 cm^2, P = 0.01) (Table 1).

Characteristics associated with higher SUV in old healed TB

In the final model of multiple logistic regression, age, history of previous TB, extent of radiographic lesions, smoking history, TST result, and QFT-GIT result were included. Among them, age (adjusted odds ratio [aOR], 1.23; 95% confidence interval [CI], 1.03-1.46), history of previous TB (aOR, 60.43; 95% CI, 1.71-2131.65), and extent of the lesions (aOR, 1.34; 95% CI, 1.02-1.75) were associated with higher SUV on ^{18}F-FDG PET/CT scans (Table 2).

Subsequent development of active TB

In total, 54 participants were followed for at least 6 months. The median follow-up period was 38.5 (interquartile range, 21.3-42.5) months. During the follow-up period, no one had clinical

Table 1. Demographic, clinical, and radiographic characteristics of 63 participants with old healed TB

Characteristic	Total (n = 63)	FDG uptake ≥ 1.5 SUV$_{max}$ (n = 9)	FDG uptake < 1.5 SUV$_{max}$ (n = 54)	P value
Age (yr)	65 (36-88)	72 (48-79)	63.5 (36-88)	0.03
Male	43 (68.3)	8 (88.9)	35 (64.8)	0.25
Body mass index (kg/m^2)	22.2 (17.6-28.3)	24.0 (17.6-25.8)	22.1 (17.8-28.3)	0.24
Presence of BCG scar	22* (38.6)	1 (12.5)	21 (42.9)	0.13
History of TB treatment	30 (47.6)	7 (77.8)	23 (42.6)	0.07
Ex or current smoker	38 (60.3)	8 (88.9)	30 (55.6)	0.08
Comorbidities				
Diabetes	5 (7.9)	0	5 (9.3)	1.00
Chronic liver disease	3 (4.8)	0	3 (5.6)	1.00
Chronic renal failure	0	0	0	
Malignancy	58 (92.1)	9 (100)	49 (90.7)	1.00
Positive TST (> 10 mm)	38† (66.7)	5 (62.5)	33 (67.3)	1.00
Diameter of induration (mm)	12.0 (0-24)	13.0 (0-24)	11.0 (0-18)	0.50
Positive IGRA	49 (77.8)	8 (88.9)	41 (75.9)	0.67
Titer of TB antigen-nil (IU/mL)	1.12 (0.06-10.0)	1.1 (0.32-7.8)	1.14 (0.06-10.0)	0.73
Chest CT findings				
Extent (cm^2)	3.52 (0.12-32.86)	8.33 (2.90-32.86)	2.78 (0.12-21.93)	0.01
Fibrotic scar	54 (85.7)	8 (88.9)	46 (85.2)	1.00
Calcified nodule	44 (69.8)	8 (88.9)	36 (66.7)	0.26
Non-calcified nodule	22 (34.9)	3 (33.3)	19 (35.2)	1.00
Fibrotic scar with volume loss	5 (7.9)	2 (22.2)	3 (5.6)	0.15
Nodules with volume loss	1 (1.6)	1 (11.1)	0	0.14
Upper lobe bronchiectasis	12 (19.0)	3 (33.3)	9 (16.7)	0.35
Pleural thickening & calcification	51 (81.0)	8 (88.9)	43 (79.6)	1.00

Results are presented as number (percentage) or median (range). *The presence of BCG scar could be evaluated in 58 patients; †The result of the TST could be assessed in 57 patients.

Table 2. Predictors of increased FDG uptake among patients with radiographic lesions suggesting old healed TB

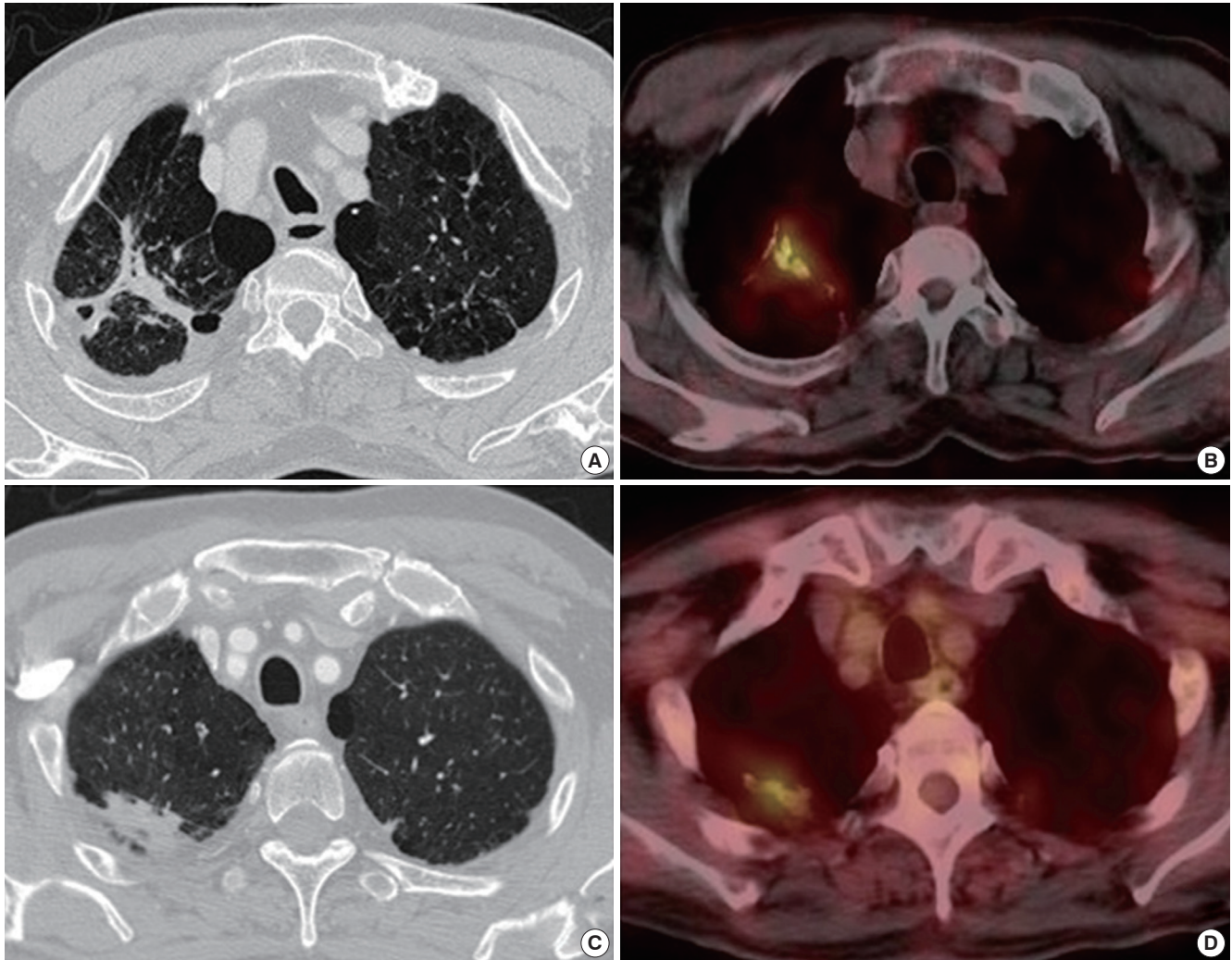| Factor	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age*	1.07 (0.99-1.16)	0.74	1.23 (1.03-1.46)	0.02
History of TB treatment	4.72 (0.90-24.85)	0.07	60.43 (1.71-2131.65)	0.02
Extent of lesions on CT	1.18 (1.04-1.33)	0.01	1.34 (1.02-1.75)	0.03
Presence of smoking history	6.40 (0.75-54.78)	0.09	2.09 (0.15-29.12)	0.59
Positive TST	0.81 (0.17-3.81)	0.79	3.35 (0.24-47.82)	0.37
Positive IGRA	2.54 (0.29-22.23)	0.40	1.21 (0.06-23.41)	0.90

*x+1 yr vs x yr.

Fig. 1. Chest computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT findings of two participants with old healed tuberculosis (TB), showing increased FDG uptake. (**A**, **B**) Fibrotic scar and calcified nodules suggesting old healed TB in the right upper lobe was observed on the chest CT of a 76-yr-old man without a history of TB. The SUV$_{max}$ of the lesions was measured as 4.0 by ^{18}F-FDG PET/CT. Both the TST and IGRA were negative. (**C**, **D**) Fibrotic scar and nodules in the right upper lobe were observed on the chest CT of a 71-yr-old man. He had been treated for pulmonary TB 25 yr earlier. The SUV$_{max}$ of the lesions was measured as 2.2 by ^{18}F-FDG PET/CT. Both the TST and IGRA were positive.

or radiological evidence of the development of active TB.

DISCUSSION

In this study, we demonstrated increased FDG uptake in radiographic lesions suggesting old healed TB in a subset of patients. Increased FDG uptake was more frequent among older patients, in patients with a history of treatment for TB, or in patients with more extensive radiographic lesions.

Latent TB infection is not simply a state of bacterial stasis, but rather a state of dynamic bacterial and immunological equilibrium (24). It has been observed in mouse models that a subpopulation of bacteria continues to replicate, although the size of the bacterial population remains stable (25). In addition, a recent study using a non-human primate model showed that

Mycobacterium tuberculosis accumulated mutations during latency (26). Given that at least a subset of old healed TB includes *M. tuberculosis* in dormancy, the increased FDG uptake in old healed TB in our study may represent active immunological and metabolic processes.

In the present study, age, history of previous TB, and the extent of lesions were associated with higher SUV on ^{18}F-FDG PET/CT scans. The incidence of TB is higher in the older population than in the younger population partly because of the reactivation of dormant *M. tuberculosis* (27) due to age-related waning of anti-mycobacterial host immunity (28). In addition, the incidence of TB among patients with a history of past TB treatment is higher compared with those without a history of TB (29-31). Furthermore, the higher incidence of active TB among patients with a larger extent of old healed TB lesions has been reported

previously (32). Given that the factors associated with increased FDG uptake are known risk factors for TB development, the possibility exists that participants with old healed TB lesions with higher SUV on ^{18}F-FDG PET/CT scans might be at higher risk for active TB. Long-term close monitoring for clinical or radiological evidence of the development of active TB among participants would reveal the clinical meaning of the increased FDG uptake on radiographic lesions suggesting old healed TB.

Interestingly, there was no correlation between increased FDG uptake and positive TST or IGRA results in our study. This observation can be explained by the limited predictive value of TST and IGRA for the progression to active TB (33, 34) when increased FDG uptake in old healed TB could represent the risk for subsequent TB development. Otherwise, the role of increased FDG uptake, TST, and IGRA in predicting active TB may be complementary.

In conclusion, some of the lesions suggesting old healed TB showed increased FDG uptake on ^{18}F-FDG PET scans. FDG uptake within lesions suggesting old healed TB may imply the presence of active metabolic activity in the lesions. The possibility that ^{18}F-FDG PET/CT imaging of old healed TB lesions could be exploited as a biomarker for the development of active TB should be tested in a future study.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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