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RESPIRATORY INFECTIONS

Positron Emission Tomography in the Evaluation of Pulmonary Nodules Among Patients Living in a Coccidioidal Endemic Region

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Abstract
Background Within a coccidioidal endemic region, pulmonary nodules due to coccidioidomycosis are common. Uptake of ^{18}fluorodeoxyglucose (^{18}FDG) by positron emission tomography with computed axial tomography (PET/CT) has been used to assess whether pulmonary nodules are malignant but inflammatory lesions can be positive. The purpose of this study was to compare by PET/CT the ^{18}FDG uptake in pulmonary nodules likely due to coccidioidomycosis to that of nodules shown to be malignant among patients living in a coccidioidal endemic region.
Methods We retrospectively reviewed patients who underwent a PET/CT at the Southern Arizona Veterans Affairs Health Care System between January 2008 and March 2012 who were subsequently found on biopsy to have pulmonary nodules that were coccidioidal or granulomatous or were due to malignancy.
Results Among 245 diagnostic biopsies where the subject had a previous PET/CT, 15 (6.1 %) were either coccidioidal ($n = 12$) or granulomatous without an identified organism ($n = 3$). The median maximum standard unit of uptake (SUV_{max}) on PET/CT of coccidioidal or granulomatous lesions was 2.0 compared to 9.8 for malignant lesions ($P < 0.001$). The maximum diameter of the coccidioidal or granulomatous nodules was 2.1 cm compared to 3.0 cm for the malignant lesions ($P = 0.009$). On multivariable analysis, an elevated SUV_{max} was the only distinguishing feature between the malignant and the granulomatous lesions (OR 1.28, 95 % CI 1.05–1.55; $P = 0.013$).
Conclusions Coccidioidal pulmonary nodules take up significantly less ^{18}FDG than those due to malignancies, but there is considerable overlap between granulomatous and malignant lesions at lower SUV_{max}.

Keywords Positron emission tomography · Computed tomography · Coccidioidomycosis · Granulomata · Malignancy · Pulmonary nodules

Introduction

It is estimated that 150,000 new infections due to coccidioidomycosis occur in the US each year. Most of these are acquired in the coccidioidal endemic regions, which include the southern San Joaquin Valley and other areas of California, much of Arizona, and portions of Nevada, Utah, and Texas [1]. In 40 % of these cases, infection manifests as a focal bronchopneumonia that can be difficult to distinguish from a community-acquired bacterial infection [2, 3]. The vast majority of these coccidioidal pneumonias resolve, but a frequent event is the development of a pulmonary nodule visible on a plain chest radiograph [4]. Coccidioidomycosis has been estimated to be the etiology of up to 25 % of pulmonary nodules encountered in the coccidioidal endemic area [5]. While the diagnosis of a

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pulmonary coccidioidal nodule may be clear when there is an initial diagnosis of acute pulmonary coccidioidomycosis and the radiologic evolution of the nodule has been documented [6], the diagnosis can be more difficult in other cases. Moreover, while there may be clues pointing to a diagnosis of coccidioidomycosis based on clinical, serologic, and radiographic findings [7–9], these cannot be completely relied upon to preclude a malignancy.

Because of this, other modalities have been employed in an attempt to distinguish coccidioidal nodules from malignant etiologies. By detecting the uptake of ^{18}fluorine-labeled deoxyglucose (^{18}FDG), positron emission tomography combined with thoracic computed tomography (PET/CT) has been used to assess for metabolically active lesions, including malignancies [10–14]. While inflammatory processes may be detected by this technique [15], PET/CT has been increasingly used to differentiate malignant from benign infectious nodules [11, 13–15]. We have observed several patients with pulmonary nodules that were due to coccidioidomycosis whose lesions were found to be positive using PET/CT. This led us to hypothesize that PET/CT frequently may be positive for pulmonary nodules due to coccidioidomycosis. To examine this further, we reviewed the results of PET/CT among a group of patients living in a coccidioidal endemic region who had undergone biopsy for a lung nodule that was found to be due to coccidioidomycosis or was granulomatous without an etiology, with the presumption that these were also due to coccidioidomycosis, and compared the results to those of patients in whom the pulmonary nodule was found to be due to a malignancy.

Methods

Patient Population

We retrospectively reviewed the records of all patients who had a diagnostic pulmonary biopsy of a pulmonary nodule at the Southern Arizona Veterans Affairs Health Care System (SAVAHCS) between January 2008 and March 2012 and identified those patients whose biopsies were either diagnostic for coccidioidomycosis, based on the identification of spherules, or were granulomatous but without a specific etiology. These biopsies were compared to those with a diagnosis of malignancy. A chart review was done with further identification of those individuals who had PET/CT as part of their diagnostic workup prior to performing the biopsy. The project was approved by the Human Subjects Protection Program of the Research and Development Committee of SAVAHCS (#13-3014). Informed consent was waived for the study.

Biopsy Assessment

All biopsied samples were subjected to standard laboratory specimen-handling processes in concordance with the College of American Pathologists and Joint Commission for Accreditation of HealthCare Organizations. For histopathological and cytopathological analyses, the biopsy materials and stained slides were examined by an experienced pathologist (MAR). The diagnosis of coccidioidomycosis was based on observing spherules in the biopsy specimen or growing Coccidioides from the specimen.

PET/CT Acquisition and Interpretation

PET/CT was performed on a Siemens Biograph 64 scanner. The CT scan was performed for attenuation correction as well as anatomic localization of radiotracer abnormalities. Patients were asked to fast for a minimum of 6 h; they were subsequently intravenously injected with 370 MBq (10 mCi) of ^{18}FDG, followed within 60 min by PET/CT. Images were obtained from the orbits to mid-thigh level. Results were reported as positive or negative based on maximum standard uptake values that are based on body weight (SUV_{max}). All PET/CT scans were reviewed by an experienced nuclear medicine physician (TKW). A nodule or other area was considered positive if there was increased uptake of ^{18}FDG compared to the blood pool [16].

Data Analysis

Data were analyzed using Stata® 13 (StataCorp, College Station, TX). Continuous variables were compared using the Mann-Whitney rank sum test while the χ^2 test was used for discrete variables. A P value of < 0.05 was considered significant. Multivariable analysis was performed using factors with a P value < 0.10 on univariate analysis and an odds ratio (OR) with 95 % confidence interval (CI) was calculated from this. The nonparametric Kruskal-Wallis test was used in an analysis of variance to ascertain if there were differences among the various malignancies with regard to SUV_{max} or size.

Results

Demographics and Clinical Description of the Cohorts

A total of 351 cases had a diagnostic pulmonary nodule biopsy performed at SAVAHCS between January 1, 2008 and March 31, 2012. Among these, 51 (14.5 %) were either coccidioidal (n = 39) or granulomatous without a diagnosis (n = 12). The other 300 nodules were due to malignancy. Two patients had separate biopsies for different

pulmonary lesions. The median age of those with coccidioidomycosis or a granulomatous process was 63 years compared to 69 years for those with cancer ($P < 0.001$). Two of the 51 with coccidioidomycosis or a granulomatous process were female compared to 11 of 300 with cancer ($P = 0.929$). Eight of the 51 subjects who were found to have either coccidioidomycosis or a granulomatous process on biopsy smoked tobacco compared to 24 with a cancer found on biopsy ($P = 0.078$). A coccidioidal serology was performed in 37 (72.5 %) of the 51 patients with a granulomatous process compared to 153 (51.0 %) of the 300 patients with malignancy ($P < 0.001$). A positive coccidioidal serology was found in 9 (24 %) of the 37 with a granulomatous process who had serology performed compared to 3 (2.0 %) of those with malignancies ($P < 0.001$).

Evaluation with PET/CT

A total of 245 (69.8 %) of the 351 who had a diagnostic biopsy had a prior PET/CT performed, including 15 (6.1 %) with a coccidioidal ($n = 12$) or a granulomatous process ($n = 3$) and 230 (93.9 %) with cancer. Comparison of these two groups is shown in Table 1. As can be seen, there was a trend toward a younger age in those with a granulomatous process and both the SUV_{max} and the nodule diameter were significantly lower in those with a granulomatous process compared to those with a malignancy (for both, $P < 0.01$). Coccidioidal serology was positive in 1 (8.3 %) of 12 with a granulomatous process compared with 2 (1.7 %) of 117 with malignancy ($P = 0.147$). The cohorts were overwhelmingly male and most of the subjects in both groups used tobacco products ($P = 0.359$). Uptake of ^{18}FDG by lymph nodes in the mediastinum and hila was also assessed. Two (13.3 %) of the 15 subjects with granulomatous nodules had ^{18}FDG uptake in these areas compared with 108 (47.0 %) of 122 with malignancies ($P = 0.011$). Multivariable analysis of age, nodule diameter, whether there was ^{18}FDG uptake in the mediastinum or hila, and pulmonary nodule SUV_{max} revealed that only pulmonary nodule SUV_{max} was significantly different between those with malignancies and those with granulomatous lesions (OR 1.28, 95 % CI 1.05–1.55; $P = 0.013$).

The pulmonary nodule SUV_{max} for the 15 subjects with granulomatous lesions ranged from 0 in four subjects to a maximum of 5.9 for one subject. For malignancies, the SUV_{max} ranged from 0 in seven subjects to a value of 30. Figure 1 demonstrates the distribution of SUV_{max} among the subjects with granulomatous lesions and those with malignancies. While there is overlap at the lower SUV_{max} values, all nodules with $SUV_{max} > 5.9$ were due to malignancies. The sensitivity for distinguishing a malignant from a granulomatous coccidioidal process based on an SUV_{max} of >2.5, a value noted by Sim et al. [17] to be associated with malignancy, was 93 % and the specificity was 47 %. The positive predictive value was 96 % and the negative predictive value was 29 %. Using an SUV_{max} of >5.9, the highest value for a granulomatous coccidioidal

Table 1 Comparison of 15 patients with a PET/CT scan and diagnostic biopsy of granulomatous pulmonary nodules to 230 with a biopsy diagnosis of malignancy

Characteristic	Granuloma	Cancer	*P* value
Number	15	230	
Age (years)			
Median	65	69	0
Range	56–76	43–90	
Sex			
Male	15	219	0
Female	0	11	
Smoker			
No	2	16	0
Yes	13	214	
Serology result			
Negative	11	115	0
Positive	1	2	
Nodule diameter (cm)			
Median	2	3.0	0
Range	1.4–3.2	0.7–20	
Lymph node ^{18}FDG uptake			
No	13	122	0
Yes	2	108	
Nodule SUV_{max}			
Median	2.0	10	<0.001
Range	0–5.9	0–30	

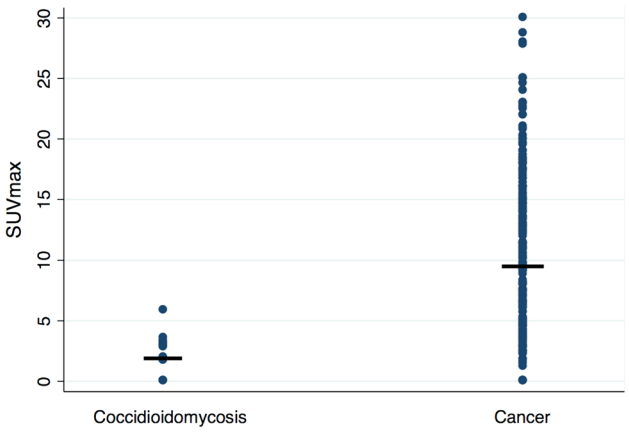

Fig. 1 *Vertical dot* plot of the pulmonary nodule SUV_{max} of the 15 subjects with a coccidioidal or granulomatous etiology (Coccidioidomycosis) and that of the 230 subjects with malignancies (Cancer). *Horizontal bars* indicate median SUV_{max} for each group

Table 2 Comparison of pulmonary nodule SUV_{max} and size among the 230 malignancies

Type of carcinoma	SUV_{max}	Nodule size (cm)
Adenocarcinoma		
Median	8.0	2.7
Range	0–30	0.7–9.5
N	88	88
Squamous cell		
Median	11.7	3.2
Range	0–28	1.0–20.3
N	84	82
Undifferentiated		
Median	7.6	2.7
Range	0–24	1.1–9.1
N	25	25
Small cell carcinoma		
Median	11.5	4.1
Range	0–25	1.6–8.0
N	19	19
Other[a]		
Median	8.9	3.2
Range	0–16	1.5–7.5
N	14	14

[a] Renal cell (6), lymphoma (2), melanoma (2), bronchoalveolar (2), carcinoid (1)

lesion in this study, the sensitivity was 69 %, the specificity was 100 %, the positive predictive value was 100 %, and the negative predictive value was 17 %.

Analysis of the SUV_{max} among different types of malignancies was performed and is shown in Table 2. As can be seen, there is great overlap between both the SUV_{max} and the size of the nodules for the different groups of cancers. Nonparametric analysis of variance demonstrated no significant differences between these cancers with regard to either parameter (for both, $P > 0.600$).

Discussion

The noninvasive diagnosis of pulmonary nodules remains challenging [14, 15, 18] and no single method has proven to be entirely satisfactory. Several studies have suggested specificity for malignancy based on the detection of the uptake of ^{18}FDG by PET either in the lesion or in the mediastinum. However, none of these studies was done in a coccidioidal endemic region. In the current study, we chose to study patients with pulmonary nodules that were biopsy-confirmed to be due to a granulomatous process likely to be coccidioidomycosis and compare them to subjects who were ultimately found to have a malignancy on biopsy. In the present study, all patients underwent pulmonary biopsy because of a presumed high risk of malignancy based on clinical parameters. None had evidence of clinically active coccidioidomycosis at the time of study.

Nearly 15 % of all the biopsies of pulmonary nodules in this study were diagnosed as granulomatous and 11 % were definitively coccidioidal. This percentage dropped in those who underwent PET/CT and is lower than noted in previous studies [5, 19–21]. These results still indicate that pulmonary nodules are not uncommonly found to be granulomatous in the coccidioidal endemic region. There have been two prior case reports of positive PET/CT associated with pulmonary coccidioidomycosis [22, 23]. Their findings of ^{18}FDG uptake are similar to ours and indicate that our data are not anomalous.

We found several potentially distinguishing characteristics in subjects with pulmonary nodules due to a granulomatous process compared to malignancies, including older age, nodule size, uptake of ^{18}FDG in the mediastinum or hila, and the SUV_{max} of the nodule. However, the only significant distinguishing characteristic was the SUV_{max}.

Weaknesses of this study include the relatively small number of subjects and possible bias given its retrospective, nonrandomized design. Unlike Gupta et al. [11], we did not assess the uptake of ^{18}FDG over time nor were isotropic volume data generated on CT, as reported by Ohno et al. [24]. We were not able to ascertain the SUV_{max} at two separate time points, as reported by Kim et al. [25]. These methods may have further distinguished granulomatous from malignant lesions, particularly for lesions with low SUV_{max}. Despite this, the results indicate that pulmonary nodules due to coccidioidomycosis are frequently positive by PET/CT, but that a high SUV_{max} appears to distinguish a pulmonary nodule due to a malignancy from one due to coccidioidomycosis. These results are bolstered by three recent studies comparing PET results from pathologically benign and malignant pulmonary lesions [17, 26, 27]. In all three studies, inflammatory lesions, none of which were coccidioidal, had significantly lower SUV_{max} than those due to pulmonary malignancies, with values in both groups similar to what was observed here. In our study, all nodules with a $SUV_{max} > 5.9$ were malignant. However, given the small numbers, it is possible that some coccidioidal nodules could have a value exceeding this number. Moreover, most malignancies in this study had $SUV_{max} > 2.5$.

Several factors, such as age, smoking history, and whether the patient has a positive coccidioidal serologic test, should be considered when determining whether a pulmonary nodule in a patient living in a coccidioidal endemic region should undergo immediate biopsy or be followed clinically. The results of this study suggest that if PET/CT is performed, the results are most useful when the

SUV_{max} is elevated above 5.9, suggesting that the lesion is malignant.

Conflict of interest The authors have no conflicts of interest to disclose.

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