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Original Article

The flip-flop fungus sign: an FDG PET/CT sign of benignity

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Abstract: Benign granulomatous processes such as fungal infection may mimic metastatic lung cancer on FDG PET/CT. We found that these processes often have draining lymph node(s) with equal or greater FDG activity than associated lung nodule(s), a "flip-flop" of what is commonly seen in lung cancer. The aim of this study was to examine the utility of this "flip-flop fungus" (FFF) sign for diagnosing benign pulmonary disease. FDG PET/CT scans performed between 9/09-3/13 for the indications of pulmonary nodule or mass were reviewed. Scans with at least one hilar or mediastinal FDG avid draining node were included. Patients with a history of cancer, lack of pathologic confirmation, or without at least two years of imaging follow-up were excluded. A total of 209 FDG PET/CT exams were included and reviewed in a blinded fashion. A positive FFF sign had a sensitivity of 60.0% (95% CI: 47.6-71.5%) and specificity of 84.9% (95% CI: 77.8-90.4%) (P<0.0001) for benign disease. With additional strict imaging criteria applied, the FFF sign had a specificity of 98.6% (95% CI: 94.9-99.8%) (P<0.0001) and a positive predictive value of 90.0% (95% CI: 68.3-98.5%). A positive FFF sign was predominately due to granulomatous disease (91%), mostly histoplasmosis (73%). A positive FFF sign combined with positive fungal serology (n=16) had a specificity of 100% for benign disease. The FFF sign predicts benign disease in patients with a lung nodule(s) and an FDG avid draining lymph node(s) that would otherwise be considered worrisome for cancer.

Keywords: Histoplasmosis, positron emission tomography, lung nodule, granulomatous, lung cancer

Introduction

The first FDA-approved use of PET for cancer was for further characterization of indeterminate solitary pulmonary nodules as benign or malignant. Since that time, many studies have shown the clinical value of FDG PET/CT for evaluation and pre-operative staging of patients with non-small cell lung cancer (NSCLC) [1-4]. FDG PET/CT has demonstrated good sensitivity in detecting FDG-avid NSCLC and also hilar and mediastinal nodal metastases [5-7]. Increasing acceptance and availability of FDG PET/CT has led to this modality being included in the recommendations of the Fleischner Society in the workup of patients with pulmonary nodules [8]. Unfortunately, the specificity of FDG PET/CT for lung cancer is decreased by benign processes that result in pulmonary nodules and ipsilateral FDG-avid lymph nodes [9]. Such cases can be incorrectly interpreted as highly worrisome for metastatic lung cancer. False positive cases often lead to further testing, including more invasive methods such as transbronchial or CT-guided biopsy. These additional tests expose patients to increased risk, often in the service of diagnosing benign disease. Among the most common causes for these false positive FDG-avid lung nodules, particularly in endemic regions, is active granulomatous inflammation due to fungal infection [10]. Patients with pulmonary fungal infections also commonly have enlarged draining lymph nodes, which may further increase worry for a malignant process.

Typically, an untreated primary site of lung carcinoma steadily increases in size and FDG activity over time and maintains a greater degree of FDG activity than subsequent smaller metastatic lymph nodes. Granulomatous disease shows

Table 1. Flip-flop fungus sign criteria

Positive Flip Flop Fungus Sign Criteria
At least 1 pulmonary nodule is present
Solid or part solid (not ground glass)
8-30 mm mean diameter
Not necrotic, invasive, or calcified
Any level of FDG activity
At least 1 FDG-avid draining lymph node is present
SUVmax node > mediastinal blood pool
Station 11 (ipsilateral), 4 (ipsilateral) or 7
At least 1 draining lymph node has ≥ SUVmax than the pulmonary nodule(s)
Absence of FDG avid lesions worrisome for cancer
No obvious extrathoracic malignancy
FDG avid lesions in reticuloenthelial system (lymph nodes, spleen, liver) permitted

increased pulmonary and mediastinal lymph node activity in the acute phase. We have observed that granulomatous lung nodules decrease in activity more rapidly than draining lymph nodes, which may remain FDG avid for months during a prolonged sub-acute phase of infection. Therefore the pattern of FDG activity in granulomatous infection can be a "flip-flop" of what is seen in metastatic lung cancer. Specifically, we have observed that equal or lesser FDG activity in a lung nodule compared with the ipsilateral draining hilar and/or mediastinal lymph nodes is a sign of benign disease, and termed this the "flip-flop fungus" (FFF) sign. A prior report noted this pattern of activity might be more prevalent in granulomatous disease [11]. The purpose of our study was to evaluate the utility of this sign in differentiating benign FDG avid disease from metastatic lung cancer, potentially obviating further more invasive testing in these patients.

Methods

Patient selection

Following IRB approval, a retrospective review of PET-CT exams performed at a single tertiary care center between September 2009 and March 2013 was performed. The need for informed consent was waived. PET/CT studies with an indication of "pulmonary nodule" or "pulmonary mass" were included. Images were assessed, and studies with a noncalcified pulmonary nodule ≥ 8 mm (with or without FDG avidity) and at least one FDG-avid (SUVmax > mediastinal blood pool) ipsilateral draining hilar or mediastinal lymph node were included. The first 263 consecutive cases selected based on these inclusion criteria were reviewed further. Following a detailed chart review, patients with current known malignancy or any form of cancer within the last 10 years were excluded. Patients with insufficient follow-up to make a clinical diagnosis of benign or malignant disease were also excluded. Pathologic diagnosis or at least 2 years of imaging follow-up with lack of progression was required. With application of these exclusion criteria, 209 cases remained. Based on preliminary data, we had estimated 207 cases would be needed to reach > 80% power (alpha=0.05).

Imaging protocol

PET/CTs were performed on 3D scanners (Discovery LS, RX, 690, or 710; GE Healthcare, Waukesha, WI, USA) according to the standard clinical protocols. Weight, height, and blood glucose levels were recorded for all patients at the time of FDG injection. All patients had a blood glucose level of less than 200 mg/dl and were injected with 10-15 mCi of FDG, with an incubation period of 60-70 min. The amount of injected radioactivity was measured by means of quantifying the radioactivity within the syringe before and after injection or with an automated injection system (Medrad Intego PET infusion system, Bayer Healthcare, Whippany, NJ, USA). Patients were imaged with arms up if possible, covering at least from orbits to midthighs (3D ordered subset expectation maximization (OSEM), 128 × 128 matrix, 3-5 min per bed position depending on body mass index). Low-dose helical CT images with free breathing were obtained for attenuation correction and anatomic localization per standard clinical protocol.

Image review

A thoracic radiologist board-certified in radiology and nuclear medicine with 7 years of clinical experience and who was not involved in patient selection reviewed all PET/CT scans. The imag-

Table 2. Strict exclusion criteria that improve specificity for benign disease

Strict Exclusion Criteria
Presence of calcified pulmonary nodule(s)
Indicating prior exposure and possible immunity
Nodule(s) is/are part-solid and stable, slowly growing, or slowly becoming more dense (even if shrinking) over more than 1 month
More likely to be neoplastic
Nodule(s) is/are solid and growing for more than 1 month
More likely to be neoplastic
Nodule(s) is/are solid and stable for more than 1 year
More likely to be an old granuloma unrelated to FDG avid lymph node
Presence of pathologic FDG avid lesions outside of the thorax (including nodes, spleen, liver)

es were reviewed blinded to other imaging and to the electronic medical record. SUVmax measurements were obtained with a spherical VOI, and SUVmax per body weight was recorded for lung nodules and FDG-avid lymph nodes. Images were reviewed on an OsiriX 64-bit (Pixmeo, Geneva Swizterland) MacPro workstation. Images were reviewed for the presence or absence of the FFF sign, defined as FDG activity (SUVmax) in draining lymph nodes equal to or greater than the FDG activity present in a primary noncalcified lung nodule(s) ≥ 8 mm without the following findings that are worrisome for cancer: obvious nodule invasiveness beyond lung parenchyma, necrosis of the nodule, nodules larger than a mean diameter of 3 cm, or lesions concerning for metastases outside of the reticuloendothelial system (lymph nodes, spleen, liver) (**Table 1**). Those that met these criteria were designated "positive" for the FFF sign. Thus, the FFF sign is only based on the evaluation of a single FDG PET/CT performed for the indication of indeterminate pulmonary nodule/mass, in a patient with no known history of cancer during the prior 10 years.

In an effort to further maximize specificity for benignity, we reviewed the impact of additional "strict" exclusion criteria that would be readily available in the typical clinical setting, including imaging features on PET/CT pointing towards a diagnosis of cancer or benign disease and findings on prior comparison imaging. Pilot data had suggested these criteria might improve specificity when present, but were likely to reduce sensitivity for benign disease. These criteria included absence of any malignant FDG avid extrathoracic lesions (including lymph nodes, spleen, and liver), absence of calcified granulomas that might suggest prior fungal exposure and immunity, and absence of nodule growth pattern that would clearly point to a neoplastic etiology or old granuloma (**Table 2**). Comparison to prior imaging was performed by consensus of two thoracic radiologists blinded to all imaging after the date of the FDG PET/CT in question and blinded to the electronic medical record. All cases underwent additional chart review assessing for the presence of fungal serologies, as well as any available histopathologic correlation and/or follow-up imaging confirming stable or decreasing size of findings over a period of at least 2 years.

Statistics

Statistical analysis was performed using JMP software on a Mac (JMP Pro, version 11.2.1, SAS Institute Inc.). Continuous variables are expressed as mean ± SD. Categorical variables are presented with absolute and relative frequencies. *P* values for between-group comparisons of continuous data were calculated from Kruskall-Wallis one-way analysis of variances (ANOVA). Multivariate analysis was performed and correlation expressed by Pearson correlation coefficient. Statistical significance was established for *P* values of less than 0.05.

Results

Of ~33,000 PET/CTs performed in the time frame, the first 1040 consecutive FDG PET-CT scans with the indication "pulmonary nodule" or "pulmonary mass" were reviewed. 263 exams met inclusion criteria, and after applying exclusion criteria, 209 cases remained for analysis, thus crossing the 80% power threshold for this study. 49% of patients were male. Average age of the patients was 69.1 years (± 10.3 years). Diagnosis was made by pathology in 191 (91%) of cases and by follow-up imaging and/or positive fungal serologies in 18 (9%).

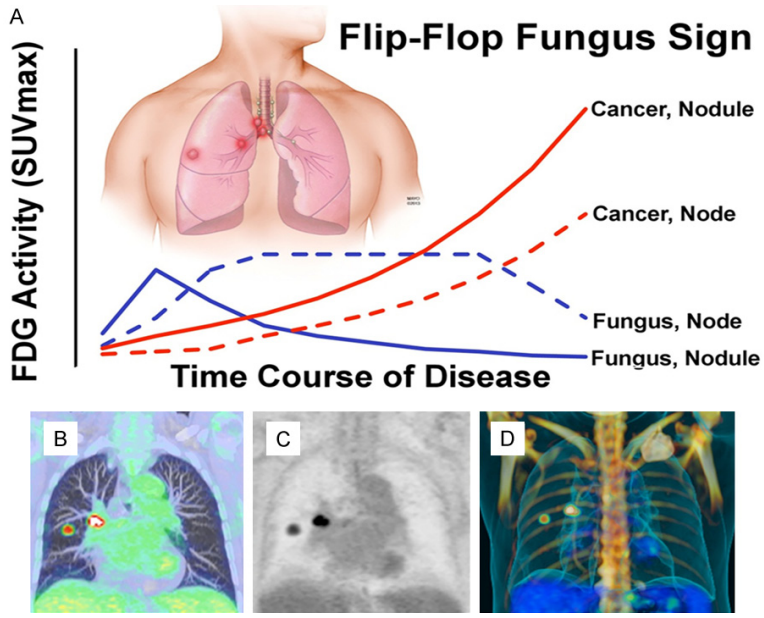

Figure 1. Hypothesized time course of FDG findings in patients with fungal granulomatous disease, which leads to the FFF sign. A. Artist's rendering of the FFF sign, hypothesized to occur in the subacute time period of fungal infection. B-D. 3D reconstructions of a PET/CT in a patient with a positive FFF sign.

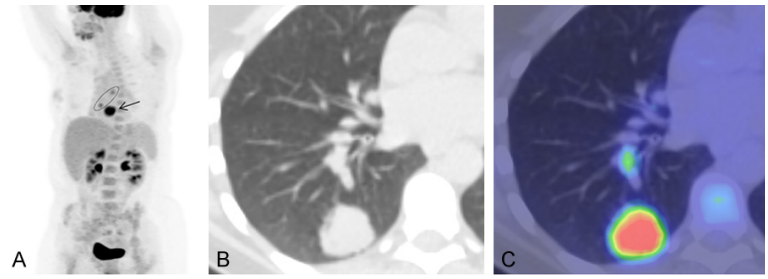

Figure 2. Expected PET/CT findings in lung cancer with nodal metastatic disease. PET MIP (A), axial low-dose CT (B) and fused PET/CT (C) images demonstrate an intensely FDG-avid pulmonary nodule in the right lower lobe (arrow) with more mildly FDG-avid draining lymph nodes (circle). Pathology demonstrated pulmonary adenocarcinoma with lymph node metastases.

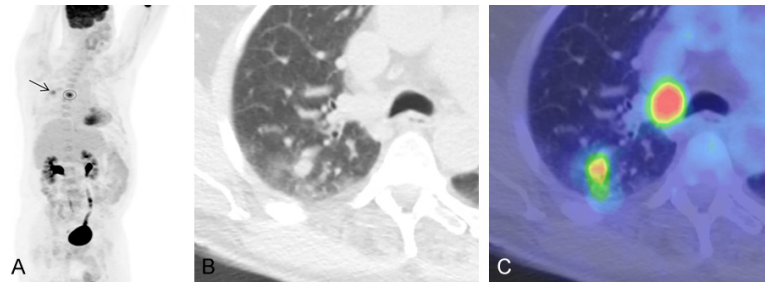

Figure 3. Example of the FFF sign in a 68-year-old nonsmoker with concern for lung malignancy with nodal metastasis on prior CT. PET MIP (A), axial low-dose CT (B) and fused PET/CT (C) images demonstrate an FDG avid pulmonary nodule in the right lower lobe (arrow) and a draining right low paratracheal lymph node with greater FDG avidity than the pulmonary nodule (circle). Pathology after endobronchial biopsy demonstrated necrotizing granulomas. ELISA was positive for histoplasma.

Benign disease was present in 70 cases (34%).

The presence of the FFF sign led to sensitivity of 60.0% (95% CI: 47.6-71.5%), specificity of 84.9% (95% CI: 77.8-90.4%), positive predictive value (PPV) of 67.7% (95% CI: 54.7-79.0%), and negative predictive value (NPV) of 81.0% (95% CI: 73.7-87.0%) (P<0.0001) for benign disease. With application of additional exclusion criteria, the "strict" FFF sign had a specificity of 98.6% (95% CI: 94.9-99.8%) (P<0.0001) and a PPV for benignity of 90.0% (95% CI: 68.3-98.5%). A positive FFF was predominately due to granulomatous disease (91%), most often histoplasmosis (73%). Serology was not always checked, but when a positive FFF sign was combined with positive serology (n=16), the specificity was 100% for benign disease.

Discussion

Benign pulmonary processes resulting in FDG-avid pulmonary nodule(s) and ipsilateral hilar or mediastinal adenopathy are historically difficult to differentiate from malignancy on PET/CT [3, 9]. Both infection and inflammatory granulomatous processes potentially having similar appearances [12, 13]. Our study suggests that there are distinctive patterns of FDG activity that may allow differentiation between benign and malignant pulmonary processes, particularly when combined with additional patient history and imaging

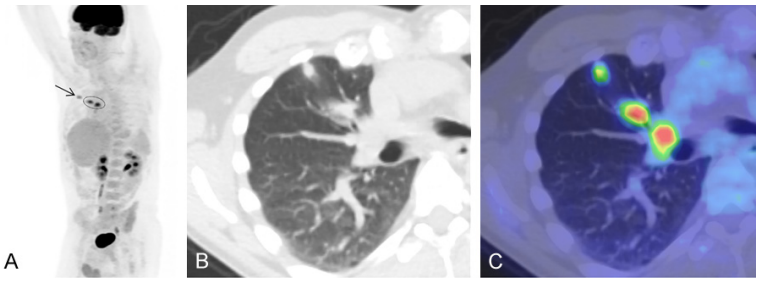

Figure 4. 59-year-old with a new pulmonary nodule and enlarged hilar lymph nodes. PET MIP (A), axial low-dose CT (B), and fused PET/CT (C) images demonstrate an FDG avid pulmonary nodule in the right upper lobe (arrow) and draining hilar lymph nodes with greater FDG avidity than the pulmonary nodule (circle). Pathology after endobronchial biopsy demonstrated non-necrotizing granulomatous inflammation compatible with sarcoidosis.

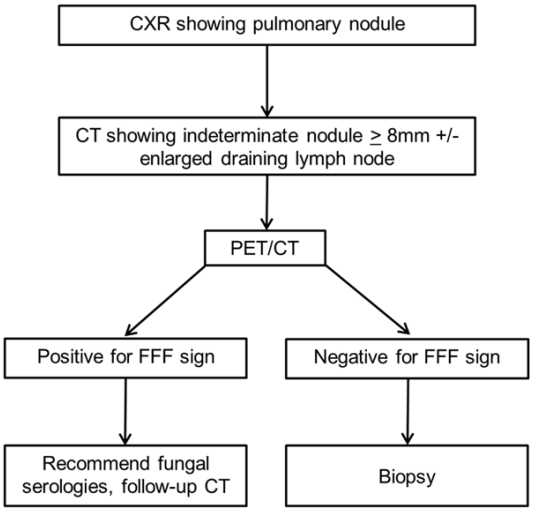

Figure 5. Flow-chart depicting the proposed management for patients with pulmonary nodules and FDG avid draining lymph nodes.

characteristics easily accessible to the radiologist in clinical practice.

The observation that hilar or mediastinal adenopathy of equal or greater FDG avidity than the pulmonary nodule occurs in granulomatous processes (**Figures 1**, **3**, **4**) suggests that the pulmonary nodule, which may be FDG-avid acutely due to the acute immune response, decreases in FDG activity more quickly than the associated adenopathy. The site of greatest FDG avidity then "flips" in the subacute phase of infection to the draining lymph node(s), where additional immunologic processes may be occurring. It is important to note that if the difference in SUVmax between the nodule and node is minimal, or even if they are equal in FDG activity, it is still considered positive for the FFF sign. This is contrast to lung carcinoma, which usually increases in size and FDG activity over time and maintains a greater degree of FDG activity than subsequent smaller metastatic lymph nodes (**Figure 2**).

To our knowledge the integration of fungal serologies into the decision making process based on the PET findings, has not previously been explored [11, 14]. We believe that this can be a key appropriate next step in the workup of the patient. When the FFF sign is seen on a PET/CT, especially if the patient is from a region with endemic fungal disease, the interpreting physician may suggest the findings are more likely benign than malignant. Furthermore, the interpreting physician may suggest testing fungal serologies, and if positive, strongly suggest a benign process is likely and that confirming lack of malignancy with follow-up CT imaging rather than biopsy is an appropriate option (**Figure 5**).

We found that pulmonary nodules were more likely malignant when the nodule had greater FDG activity than the draining lymph nodes, which is concordant with the widely-accepted notion that in many cancers a primary neoplasm typically demonstrates greater FDG avidity than their sites of metastasis on FDG PET/CT (**Figures 1**, **2**). When this imaging pattern is seen related to lung nodules and draining lymph nodes, it appears to be highly specific for malignancy, and immediate biopsy is appropriate.

There are limitations to our study. While our institution is a tertiary care referral center, the majority of our patient population is from an area where histoplasmosis is endemic. This may have led to an overrepresentation of pulmonary granulomatous disease in our patients compared with the general population in the USA, possibly limiting the generalizability of the results. Since this was a retrospective study, it is open to a degree of selection bias as well, since patients needed to have had adequate follow-up at our institution to reach a diagnosis in order to be included in the study. It is important to note that even if patients failed to meet

our inclusion criteria, they could still have fungal disease. Fungal disease should be considered possible in any patient with a pulmonary nodule and FDG-avid ipsilateral hilar or mediastinal adenopathy, especially if the node(s) is more PET avid than the nodule(s), and even more so if the risk of metastasis is felt to be low and the nodule(s) and node(s) are not long term findings and/or growing. We did not evaluate the pulmonary nodule CT morphology as part of the FFF sign (e.g. solid, part-solid, spiculated, etc.), which is typically based on a prior dedicated CT and can often influence differential diagnosis and evaluation recommendations [1]. However, if a nodule had a clear benign morphology on CT, the patient would presumably be less likely to be referred for FDG PET/CT. Combining pulmonary nodule CT characteristics with the FFF criteria presumably further improves accuracy for benign disease and is an area of potential further investigation.

The FFF sign is a novel sign that can help to differentiate a benign from malignant process in cases of a pulmonary nodule with FDG-avid ipsilateral hilar or mediastinal adenopathy. When present, this sign can help to guide the next best steps in workup of the patient's disease. This may include obtaining fungal serologies and non-invasive follow-up with CT imaging in a few months, potentially reducing unnecessary and invasive testing for these patients. When used in conjunction with a simple set of additional clinical history and imaging criteria routinely evaluated in regular clinical practice, this sign can be a highly specific indicator of benign disease. Granulomatous disease, specifically histoplasmosis, was the most common etiology of this sign at our institution. When the basic FFF sign was positive and fungal serology was positive, none of the patients in this study had malignancy.

Disclosure of conflict of interest

None.

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