False-positive 18-fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET/CT) scans mimicking malignancies

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ABSTRACT

Aim 18-Fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET/CT) is an imaging modality that is often used to help differentiate benign from malignant pulmonary lesions and it has been shown to be more efficacious than conventional chest computed tomography (CT). However, some benign lesions may also show increased metabolic activity which can lead to false-positive PET findings. We aim to illustrate false positive findings of PET scan that simulate lung cancer in a variety of diseases.

Methods Patients referred to Yedikule Chest Diseases and Surgery Teaching and Research Hospital with increased FDG uptake for which histological results were available over a 2-year period (2013-2014) were reviewed. Seven patients with false-positive PET/CT findings were reported in this study.

Results The majority of lesions showing increased metabolic activity were due to malignant diseases. However, increased 18 F-FDG uptake was also seen in benign lesions such as active pulmonary inflammation or infection, granulomatous processes and fibrotic lesions.

Conclusion. The integration of clinical history, morphologic findings of lesions on the CT component, and metabolic activities of PET/CT scan can help reduce false interpretations. Interventional procedures may be needed for tissue confirmation for differential diagnosis.

Key words: false-positive, FDG, PET scan, mimicking malignancies
INTRODUCTION

Fluorine-18 fluoro-2-deoxyglucose (18F-FDG) positron emission tomography combined with computed tomography (PET/CT) is a useful test to evaluate malignancies (1). Mechanism of 18F-FDG uptake in malignant tissues depends on the metabolic activity of the lesion, e.g. the extent of uptake is proportional to the number of malignant cells and their proliferative activity (1,2). Malignant lesions have been shown to have elevated expression of the glucose transporter (GLUT-1) and tend to have increased metabolic activity evidenced by increased FDG uptake (2). Notwithstanding the controversial views, SUVs of 2.5 or greater have been used as a cutoff value indicative of malignancy (1-3). However, inflammatory diseases may also show increased uptake of 18F-FDG and cause false-positive PET scan results, necessitating further investigations to rule out malignant conditions (3,4). The rationale underlying this belief is that activated macrophages and neutrophils in inflammatory tissue use glucose as an energy source for chemotaxis and phagocytosis, whereas fibroblasts use glucose for proliferation (3).

The aim of this study was to describe benign lung lesions with increased 18F –FDG uptake that simulate malignancies at series of seven cases, and their imaging characteristics that may help in differentiating them from malignant metastases.

PATIENTS AND METHODS

This study retrospectively analyzed seven patients in order to describe false-positive 18F-FDG uptake increase according to PET/CT scans and to review the diagnosis and management of the patients with increased uptake on PET/CT scan. This study included 7 patients with suspected lung cancer (patients with pulmonary lesions of ambiguous nature) who were referred to Yedikule Chest Diseases and Surgery Teaching and Research Hospital clinic over 2 years (2013-2014). The presented data were collected from patients’ records: patient’s age and sex, clinical features on presentation, results of investigations including X-ray, CT, PET/CT, treatment and outcome. There were three women and four men, in the age between 27 and 78 years.

The metabolic activity of the lesions determined by the chest CT were evaluated for F-18 FDG PET/CTF-18 FDG uptake. The patients underwent 18F-FDG PET/CT examination using a multidetector CT integrated high-resolution PET/CT scanner (Biograph, Siemens Medical Solutions, USA Inc.). They fasted for 6 h before receiving an intravenous injection of 296-555 MBq of 18F-FDG. The PET/CT acquisitions started 60 min after tracer injection. The PET scan (6–7 fields of view, 3 min/field) and low-dose non-enhanced CT scan were acquired from the skull to the mid-thigh (5). As a limit value for lesions suspected of neoplastic nature, SUVmax higher than 2.5 was accepted.

In case of hypermetabolic lesions, histological or cytological examinations of the material obtained from biopsies (CT-guided fine needle aspiration cytology, FNAC), endobronchial ultrasound-guided transbronchial aspiration (EBUS-TBNA),video-assisted thoracic surgery (VATS) biopsy and lobectomy, were diagnosed.

RESULTS AND DISCUSSION

Case 1: Pulmonary tuberculosis and tuberculous lymphadenopathy

A 57-year-old female presented with dyspnea, cough and weight lost on exertion. She has a 20-pack-year smoking history and continues to smoke. Family history is positive for her father with lung cancer who was heavy smoker. There is history of loss of appetite. Physical examination is normal. Laboratory data revealed normal blood count, erythrocyte sedimentation rate (ESR) rate 33/1h. The sputum smear was negative for acid fast bacillus (AFB) testing. A chest X-ray done for evaluation of dyspnea and cough on exertion revealed mediastinal enlargement, and there was heterogeneous density at the right upper lobe (RUL). The CT chest revealed a patchy consolidation in the right upper lobe and also hilar, mediastinal lymph node enlargement. The 18F-FDG PET/CT scan showed increased uptake in parenchymal right upper lobar lesion (peak standardized uptake value [SUV] = 3.9) and in mediastinal, hilar lymph node (peak SUV = 6.5) (Figure1). Given the patient’s high risk based on tobacco use and family history of lung cancer, fiberoptic bronchoscopy was performed and no endobronchial lesion was found. EBUS-TBNA biopsy of mediastinal and hilar lymph nodes was performed. Pathology of both lymph...
nodes revealed chronic inflammation with granulomatous formation, no evidence of malignancy. *Mycobacterium tuberculosis* was demonstrated in bronchoalveolar lavage and was susceptible to all the tested anti-tuberculous agents.

Tuberculoma is one of the most well-known diseases that show intense FDG uptake. Active granulomatous processes such as tuberculosis have been reported to accumulate FDG (1-4, 6). In tuberculosis, granulomatous lesions are mainly composed of lymphocytes and macrophages, which use 18F-FDG as an energy source (7). Activated inflammatory cells have markedly increased glycolysis. The hexose monophosphate shunt is stimulated by phagocytosis, with increases of 20-30 times that of baseline values, which is the cause of high FDG uptake (6). Tuberculous lymphadenopathy can be understood in the same manner as tuberculoma in the lung parenchyma.

**Case 2: Sarcoidosis**

A 27-year-old nonsmoking male presented with a 1-month history of cough, weight loss and increasing shortness of breath. He had no history of fever, night sweats, chest pain, palpitation, arthralgia or skin rash. There was no history of allergy or systemic disease. On admission, he was afebrile with a respiratory rate of 22. The physical examination was unremarkable. Chest radiograph on admission showed mediastinal enlargement and bilateral millimetric nodules in the upper and middle lung zone. The laboratory tests including the complete blood count, biochemical and tumor markers were within normal limits. The CT chest revealed hilar, mediastinal lymph node enlargement and numerous millimetric-dimensional parenchymal nodules predominantly viewed in the upper and middle zone. Heterogeneous and numerous millimetric hypodense areas with unclear borders seen in liver parenchyma and spleen. Quanti FERON Gold blo-

**Case 3: Pulmonary actinomycosis**

A 56-year-old woman was admitted with the complaints of intermittent cough with blood-tinged sputum for 2 years, fatigue and weight loss. She smoked cigarettes 1 pack a day for over 20 years.
Respiratory examinations found no cervical lymphadenopathy, musculoskeletal disorder or other abnormalities. The remainder of her physical exam was unremarkable. Laboratory data revealed normal blood count, ESR, C-reactive protein (CRP), and renal and liver functions. Sputum examinations (three consecutive samples) were negative for acid-fast bacilli, malignant cells, or fungal elements. The contrast-enhanced computerized tomography (CT) showed a speculated mass, 14.17mm in diameter, in the right lower lobe, which was highly suspected as a malignancy. The FDG PET/ BT revealed a hypermetabolic lesion over the right lower lobe of the lung, with a maximum SUV of 5.2 which favors a malignancy (Figure 3). Bronchoscopy revealed normal airways and mucosa and bronchoalveolar lavage was negative for malignant cells or fungal elements. CT-guided FNAC was done from the right lung mass lesion. The smears were prepared and stained with haematoxylin and eosin, periodic acid Schiff (PAS), and Giemsa stains. The smears revealed radiating filamentous colonies of *Actinomyces* in a background of neutrophilic exudates; PAS stain also showed *Actinomyces* colonies, resulting in the confirmation of the diagnosis of pulmonary actinomycosis. The patient was treated with intravenous penicillin for a month and then given oral penicillin for six months. The patient responded well to the treatment.

Pulmonary actinomycosis is a rare bacterial lung disease and causes lung cavities, lung nodules, and pleural effusion (10). Radiographic and clinical features of pulmonary actinomycosis varied and could mimic a wide spectrum of benign and malignant diseases (11). Mabeza et al. reported that up to 25% of cases with thoracic actinomycosis were initially misdiagnosed as malignancy (12). In general, high uptake on FDG PET suggests that the nodule contains active and proliferative lesions such as lung cancer, infiltration tumor, tuberculosis, and pulmonary mycosis (13).

Case 4: Reumatoid nodules

A 65-year-old woman with a history of rheumatoid arthritis (RA) presented with dyspnea on exertion. The RA was diagnosed 16 years earlier and has been treated with salisilazosulfapiridin and prednisolon since the time of diagnosis. She has a 15-pack-year smoking history. Family history is positive for lung cancer. There is history of loss of appetite and weight over a period of 6 months. Physical examination including joint examination is normal except for decreased breath sounds. Laboratory data revealed normal blood count, ESR,CRP, and renal and liver functions. The CT chest revealed a 23.15 mm noncalcifiednodule in the right lower lobe and bilateral millimetric nodules. The 18F-FDG PET/CT scan showed moderately increased uptake with a maximum SUV of 4.3 in the right lower lobe (RLL) nodule (Figure 4). Subsequent VATS biopsy of the right lower and middle lobe nodules was performed. Pathology of both nodules revealed chronic inflammation with necrotizing granulomatous formation consistent with rheumatoid nodules and no evidence of malignancy. Fungal and acid-fast bacilli stains and cultures were negative.

Reports of the use of PET and PET/CT in extra-articular RA are limited to subcutaneous nodules, lymph nodes, and the lung (14,15). Gupta et al. described a patient with RA found to have mild increased uptake in pulmonary nodules on PET scan (16). Histological examination of these nodules revealed the presence of rheumatoid nodules. On the other hand, Rodríguez et al. described two patients with RA in whom pulmonary nodules showed increased SUV on 18F-FDG PET scan (17). Biopsy of the nodules demonstrated bronchogenic carcinoma developing wi-
thin preexisting rheumatoid nodules. Clinicians need to keep in mind that rheumatoid nodules can have increased activity on PET scan in the management of lung nodules in rheumatoid arthritis.

**Case 4: Anthracosilicosis**

A 78-year-old asymptomatic man was admitted to our hospital for evaluation of an abnormal shadow on chest roentgenogram. He has 45-pack-year smoking history and did not have history of industrial exposure. On admission, physiological and laboratory examinations, including tumor markers, were within normal limits. Chest X-ray showed an abnormal mass in right middle field of the lung and mediastinal enlargement. Chest CT revealed an approximate 1.8cm sized mass in the right middle lob, and enlarged mediastinal lymph nodes. The FDG-PET showed high uptake with a maximum SUVmax 9.1 in hilar and mediastinal nodes and 1.5 in the RML mass lesion which favors a malignancy. Since malignancy could not be excluded by PET-CT scan, EBUS-TBNA biopsy of mediastinal and hilar lymph nodes was performed. Pathological findings showed that contained polarizable material suggestive of silica with focally contained fine anthracotic pigments, and negative for malignancy.

The silicosis with anthracotic pigments in mediastinal lymph nodes might be caused by inhalation of irritant dusts and attendant distortion of local lymphatic vessels (18). One clinicopathologic form of this reaction is fibrosis, while the other form consists of aggregates of particle-laden macrophages with minimal or no accompanying fibrosis, a reaction that is typically seen with inert dusts such as iron, tin, and barium (18). The FDG-PET studies have revealed increased uptake in pneumoconiosis and progressive massive fibrosis. Some of this uptake is perhaps related to the presence of inflammatory cells such as macrophages, as well as fibroblasts (19).

**Case 5: Vanishing tumor**

A 75-year-old man with operated sigmoid colon tumor presented with cough of several days’ duration but reported no chest pain, dyspnea, fever, or hemoptysis. He also had hypertension. There was a 60 pack-year smoking history, but no alcohol use. A chest radiograph obtained during evaluation demonstrated homogeno-

us densities in the right hemithorax. Laboratory studies were remarkable for a normal leukocyte count, a hemoglobin level of 10 g/dL. The CT scan (mediastinal windows) reveals homogenous, spherical density within the right lower lobe. The opacity is surrounded by a pleural rim and lie along the expected location of the oblique fissure. Malignancies were suspected and PET-CT scan was done for diagnosis. The FDG PET/CT revealed a hypermetabolic lesion over the right lower lobe of the lung of the patient, with a maximum SUV of 8-10 which favors a malignancy. Since malignancy could not be excluded by PET-CT scan, CT-guided biopsy was planned for diagnosis. While carrying out this procedure, we recognized that the lesion had regressed. An echocardiogram obtained and demonstrated left ventricular hypertrophy and mild systolic dysfunction; there was no pericardial effusion. The patient responded well to diuretic treatment. Vanishing tumor refers to the transient localized collection of pleural fluid in the interlobar fissures, usually in association with congestive heart failure from various causes (20). Vanishing tumor is a phenomenon predominantly occurring in the right hemithorax (21). The pathogenesis of vanishing tumors involves the adhesion and obliteration of the pleural space due to pleuritis, thus preventing the free accumulation of fluid (21). In this setting, whenever hydrostatic and/or oncotic forces produce fluid at the pleural surface beyond the resorptive ability of the pleural lymphatics, a localized pleural effusion that is recognized as a vanishing tumor may result. This hypothesis is supported by the finding of adhesive pleuritis at autopsy in cases of known vanishing tumors (22,23).

**Case 6: Aspergillosis**

A 68-year-old man operated for ampullary carcinoma 2 years before presented with cough of several days’ duration. He also had hypertension. There was a 40 pack-year smoking history, but no alcohol use. Chest CT revealed an irregularly shaped lung nodule approximately 11.17mm in diameter in the right upper lobe. The FDG uptake at PET showed that the SUVmax was 5.4. Radiologists did not diagnose the nodule as an aspergilloma. The pathological examination of the FNAC was negative for malignant cells, and the cultures were negative by bronchoscopic
examinations. Because lung cancer was strongly suspected, video-assisted thoracic surgery was performed. An upper lobe wedge resection was performed, including the tumor in the right upper lobe. In the specimen, the tumor was necrotic and a pathological examination during operation had shown no evidence of malignancy. The final pathological examination showed the presence of an aspergilloma. The postoperative evolution was therefore favorable.

Recently, FDG-PET accumulation in cases of pulmonary aspergillosis mimicking lung cancer was reported (24), and in the three cases reported in that study, the FDG uptake during PET scans showed an SUVmax ranging from 4.0 to 8.3 suggesting a tendency for high FDG accumulation in 10 cases.

Case 7: Pulmonary nocardiosis
A 35-year-old male presented with cough and expectoration with episodes of haemoptysis for 2 years. He took an antitubercular treatment for six months. With antitubercular treatment fever had subsided but the amount of sputum and haemoptysis had continued. Two months ago he referred to a general physician with low grade fever associated with productive cough and received some medication without any improvement. His condition became worse. Chest x-ray showed infiltrations in right upper lobe with cavity formation and CT revealed the presence of areas of consolidation with air bronchograms and cavitary lesions containing air and infiltration beginning from the apical segment lying to anterior segment of right lower lobe. The FDG PET/BT revealed a hypermetabolic lesion over the right upper lobe of the lung of the patient, with a maximum SUV of 5.9-7.1 which favors a malignancy (Figure 5). So due to findings he received ceftazidim and ciprofloxacin. But he had no improvement in respiratory symptoms. Several sputum samples were collected and tested for the presence of acid-fast bacilli, but all smears were negative. The patient then underwent bronchoscopy and aspirated material was negative for tuberculosis, fungi (including Pneumocystis jirovecii), and malignancy. The FNAC was done from the right lung lesion. Aspirated material was negative for tuberculosis and malignancy. Because of progressive worsening of clinical status, right upper lobectomy was performed. On gram staining, the organism appeared as gram-positive, beaded, coccoid, thin branching filaments. Modified Ziehl-Neelsen staining showed many branching acid-fast bacilli, consistent with the morphology of Nocardia species. The patient was started on trimethoprim-sulfamethoxazole and improved remarkably both clinically and radiographically.

Pulmonary nocardiosis is an infection caused by gram-positive aerobic bacilli belonging to genus Nocardia. Pulmonary nocardiosis occurs through inhalation and most often affects patients presenting with immunosuppression due to AIDS, neoplasia, as well as kidney or bone marrow transplantation (25). The diverse radiological manifestations of pulmonary nocardiosis reflect its ability to cause both suppurative and granulomatous infection (8). Actively granuloma-forming parenchymal lesions or nodes show increased 18F-FDG uptake because activated lymphocytes and macrophages contribute to increased glucose use in the corresponding lesions (9).

In conclusion, metabolic imaging with FDG-PET is beginning to play an important role in the management of malignancies. However, benign and malignant lesions may have overlaps. Benign focal lung lesions can simulate lung cancer with increased 18F-FDG uptake. The integration of clinical history, morphologic findings of lung parenchymal lesions on the CT component, and metabolic activities on the PET component of integrated PET/CT can help reduce false interpretations. Interventional procedures may be needed for lesions showing increased 18F FDG uptake on PET for tissue confirmation irrespective of their morphology on CT.

Figure 5. Pulmonary nocardiosis in 35- year-old man: axial transverse (mediastinal windows) CT scans reveals cavitary lesions in anterior segment of right lower lobe (left). Increased 18F-FDG uptake is observed on PET image (peak standardized uptake value =5.9-7.1) (right) (Yedikule EAH, 2013)
We must keep in mind that not all increased 18F-FDG uptakes should be considered malignant. These cases exemplify the need of clinicians to exercise clinical and critical thinking skills to consider the broad diagnostic possibilities of lung lesions presenting as a malignancy.

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REFERENCES