Abnormal FDG Uptake on 18F-Fluorodeoxyglucose Positron Emission Tomography in Patients with Cancer Diagnosis: Case Reports of Tuberculous Lymphadenitis

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Abstract

Although 18F-FDG-PET is very sensitive for a variety of malignancies, it can lack specificity. In addition to malignant tissue, any active infectious or inflammatory process can demonstrate FDG avidity. We report 3 patients with different types of cancer who had abnormal 18F-FDG uptake on PET scan caused by tuberculous lymphadenitis. All were found to have incidental multiple lymph adenopathies with increased FDG uptake on PET scan. All three patients were proved to have tuberculosis lymphadenitis by pathologic examination and were successfully treated with anti-tuberculous therapy.

Key words: positron emission tomography, tuberculosis, cancer

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Introduction

The incidence of tuberculous is high among patients with cancer diagnosis (1), and the incidence is relatively high in our country compared to other countries. Fluorine-18-fluorodeoxyglucose (FDG) whole-body positron emission tomography (PET) scanning has been useful in staging and monitoring the treatment of different types of malignant diseases (2, 3) and has been applied in cancer screening in healthy people (4). However, 18F-FDG is not a cancerspecific agent, and benign diseases related mainly to infection or inflammation have sometimes been reported to cause intense FDG uptake that is difficult to differentiate from malignant disease (5-8). We report three cases of intense F-18 FDG uptake related to tuberculous lymphadenitis mimicking recurrent malignancy.

Case Report

Case 1

A 47-year-old woman diagnosed with T1N0M0 breast cancer achieved complete remission (CR) after the administration of 6 cycles of CAF (cyclophosphamide, doxorubicin, and 5-FU) chemotherapy combined with radiotherapy and followed by oral tamoxifen for five years. Unfortunately, 6 years after CR she was admitted to the hospital with the complaint of weight loss of 7 kg in the previous three months and weakness. Physical examination revealed multiple lymph adenopathies in bilateral neck, axillary and supraclavicular regions. Sputum and urinary cultures for mycobacterium tuberculosis were negative. F-18 FDG PET study showed increased focal FDG uptake in the related lymph node regions with high standardized uptake values (SUV max: 16) suggesting lymphoma (Fig. 1). Excisional lymph node biopsy showed granulomatous lymphadenitis with caseous necrosis consistent with tuberculosis.

Case 2

A 56-year-old woman was diagnosed Dukes A colon cancer 12 years previously and underwent transverse colectomy. Seven years later, she underwent a second colectomy due to local recurrence and 3 cycles of FUFA (5-FU, calcium folinate) were administered afterwards. After the 3rd cycle, a solitary metastatic liver mass was detected in the right lobe.

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Figure 1. Coronal FDG-PET images showed multiple foci of increased FDG activity (SUV max: 16) in right supraclavicular region (short arrows) and inferior cervical area (long arrow) in a 47-year-old woman, who underwent FDG-PET scan for evaluation of supraclavicular lymph nodes for recurrent breast cancer. On subsequent biopsy, histopathologic examination showed granulomatous lymphadenitis with caseous necrosis consistent with tuberculosis. Whole body FDG PET scan also showed diffuse mildly increased FDG activity (doted lines) in thyroid gland consistent with Hashimoto’s thyroiditis.

of the liver and successfully resected by lobectomy. Unfortunately, she developed ileus and underwent an explorative surgery two years after the liver surgery. The histopathologic examination of the mass which was resected from the abdominal wall revealed adenocarcinoma metastasis.

Following the last surgery, second line capecitabine (days 1-14, every 3 weeks) chemotherapy was applied for 6 cycles. Four weeks after the completion of the treatment, whole body FDG PET study was performed for the response evaluation. Markedly increased focal FDG uptake in the right axillary and mediastinal lymph nodes (SUV max: 24), as well as mildly increased heterogeneous FDG uptake consistent with a granulation tissue due to the surgical intervention on the abdominal wall, were detected on FDG PET scan (Fig. 2A). Axillary and mediastinal lymph node biopsies revealed caseous granulomatous lymphadenitis, specifically tuberculous, whereas the bronchial lavage revealed the presence of acid-fast bacilli, which was confirmed with a positive culture for mycobacterium tuberculosis. The patient was treated simultaneously with chemotherapy and antituberculous medication. All of the FDG positive sites were normal after the administration of antituberculous treatment for 6 months indicating response to specific treatment (Fig. 2B).

Case 3

A 58-year-old woman with gastric lymphoma achieved CR after the administration of 6 cycles of CHOP (cyclophosphamide, cytarabine, vincristin, and prednisone) chemotherapy and radiotherapy. Four years later, she presented with weight loss of 5 kg and recurrent night sweats over the four preceding weeks. Pathologic lymph nodes measuring 3x2 cm in the largest dimension were detected in right cervical, supraclavicular and axillary region on physical examination, which were consistent with the necrotic lymph nodes detected on computed tomography (CT). The acid-fast bacilli search and tuberculosis polymerase chain reaction on the sputum and urine cultures were negative. Markedly increased FDG-uptake (SUV max: 20) was detected in enlarged lymph nodes which was highly suspicious for recurrent malignant disease (Figs. 3A, 3B). However, the histopathologic examination revealed epitheloid cell granuloma with necrosis which was consistent with tuberculous lymphadenitis and no evidence of malignancy. This patient has also completely recovered after the administration of antituberculous treatment for 6 months.
**Figure 2.** Pre-treatment (A) coronal FDG-PET images showed multiple markedly increased FDG foci in the right axillary (SUV max: 24) (short thin arrows), supraclavicular (long thin arrow), mediastinal (short dotted lines) and left hilar (thick arrow) lymph nodes in a 56-year-old woman, who underwent FDG-PET scan for response evaluation of anti cancer therapy for colon cancer. Histopathological examination of the axillary lymph nodes showed caseous granulomatous lymphadenitis, specifically tuberculous, whereas the bronchial lavage revealed the presence of acid-fast bacilli, which was confirmed with a positive culture for mycobacterium tuberculosis. She was treated with antituberculous treatment (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) for 6 months. Post-treatment (B) coronal FDG-PET images showed no pathologic FDG uptake corresponding to the pre-treatment FDG uptake sites, indicating response to specific treatment, besides minimal FDG activity in mediastinal lymph nodes (arrow heads) related with inflammatory reaction.

**Discussion**

Here, we report three cases of tuberculous lymphadenitis detected on FDG PET scan, in patients with concomitant cancer diagnosis. Although the culture results for the first and the third patients were negative for mycobacterium tuberculosis, due to high incidence of tuberculosis in our country, we treated all three patients with antituberculous treatment consisting of isoniazid 5 mg/kg, rifampicin 10 mg/kg, pyrazinamide 25 mg/kg and ethambutol 15 mg/kg. The treatment was given first as intensive therapy daily during the first two months. Then, the continuation phase of the treatment was done three times a week for 4 months using isoniazid and rifampicin. All three patients recovered successfully with this treatment.

The first patient with a previous history of breast cancer showed multifocal intense 18F-FDG uptake corresponding to the widespread lymphadenopathy in cervical, axillary and supraclavicular regions. The second patient showed 18F-FDG uptake in the abdomen, as well as in axillary and mediastinal lymph nodes. The third patient also showed multiple nodular FDG uptakes in cervical and supraclavicular regions. Although, visual assessment of the intensity of FDG uptake suggested malignancy, histopathologic examination revealed tuberculosis in all three cases. Our cases are interesting, because all three patients had a previous history of cancer diagnosis, and lived in a good sanitized environment with a high socioeconomic status. In the first case, intense multifocal FDG uptake related to widespread tuberculous lymphadenitis was interpreted as lymphoma. On the other hand, high 18F-FDG uptake in the second and third cases was false positively interpreted as the recurrence of the primary malignancy.

FDG may accumulate in various normal organs which use glucose for metabolism. Additionally, inflammatory cells such as neutrophils, lymphocytes and activated macrophages at the site of inflammation or infection show increased FDG accumulation. Due to the high glucose utilization in granulomatous diseases, false positive FDG uptake in patients with tuberculosis is not unexpected (5, 9). In an experimental study of FDG accumulation in inflammatory tissue, a maximum FDG uptake was observed in the chronic inflammation phase (10). On the other hand, the newly formed
granulation tissue around the tumor and the macrophages infiltrating heavily at the marginal areas surrounding the necrotic area of the tumor showed a high uptake of FDG, and about 24% of the FDG concentration in a tumor mass was derived from non-tumor tissue (10).

Elevated blood glucose levels can accelerate false positive results in inflammatory conditions. Therefore, lesions containing such cells are more likely to be interpreted as malignant lesions under such conditions (9). Active granulomatous processes such as tuberculosis have been reported to accumulate FDG due to increased glycolysis of cellular infiltrate composed of lymphocytes and macrophages (11-13). In addition, some reports have pointed out that pulmonary tuberculosis causes false-positive results that mimics malignant disease (14, 15). Positivity of FDG-PET in tuberculosis is due to increased glycolysis in the hexose monophosphate shunt which is stimulated by phagocytosis. The same imaging features are also observed in malignant lesions which may be confounded with tuberculomas (11). The foci of FDG uptake in lymph node region in our patients were consistent with recurrence of the primary cancer or lymphoma. In retrospective analysis, they were also consistent with tuberculosis dissemination to lymph nodes (16).

Notwithstanding the controversial views, SUV of 2.5 or greater has been used as a cutoff value indicative of malignancy (17). Hara et al noticed that in lung cancer patients, SUV of FDG was very high in large tumors but could be very low in small tumors. In contrast, in pulmonary tuberculosis patients, the SUV of FDG was very high for every mass size (18). Unfortunately, infections, including tuberculosis, atypical mycobacterial infections, and fungal infection, can also present with an identical appearance on FDG PET with showing very intense FDG uptake and can not be distinguished from each other. Therefore, despite its high sensitivity for the detection of malignancy, FDG PET has a low specificity. Moreover, patients who have cancer diagnosis and also with significant infection or inflammation, may show increased activity within regional lymph nodes, representing either reactive or neoplastic lymphadenopathy (19). On the other hand, the role of 18F-FDG PET in the diagnosis of vasculitis is less clear. Vasculitis of medium and small vessels (especially in Churg-Strauss syndrome, Wegener’s disease, and panarteritis nodosa) is usually detected on FDG PET only if large vessels are also involved (20) or if inflammatory damage is present in the adjacent tissue (21).

In all three of the present patients, imaging and laboratory findings as well as the symptoms were suggestive of a recurrent disease or lymphoma. Tuberculin skin test was not done, because it is often non-reactive in such cases. Interferon-gamma release assay was not available yet at the time of diagnosis. CT scan was also of moderate interest, with a reported limited sensitivity of 69% in the prediction of tuberculosis (22). The pathologic examination revealed chronic granulomatous reaction and inflammation, specifically tuberculoma. Tuberculoma typically appears as a discrete nodular mass in which repeated extensions of infection have produced a core of caseous necrosis bounded by a mantle of epitheloid cells and collagen, with peripheral round cell infiltration. In our cases, this feature was consistent with tuberculosis, and was reinforced by the absence of malignant cells.

In conclusion, it should be considered that patients treated or followed with cancer diagnosis could be more prone to tuberculosis than the normal population. It should also be remembered that tuberculomas could have increased FDG uptake on FDG PET studies. Therefore, positive results on FDG PET should be interpreted with caution in differentiating benign from malignant lesions, especially in geographic regions with a high prevalence of tuberculosis and should be confirmed by pathologic examination before the initiation of a definitive treatment.

References