False-positive Findings on $^{18}$F-FDG-PET Caused by Non-neoplastic Cellular Elements After Neoadjuvant Chemoradiotherapy for Non-small Cell Lung Cancer

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We report two patients with non-small cell lung cancer who had a pathologically complete response after neoadjuvant chemoradiotherapy, although they had positive $^{18}$F-fluoro-deoxyglucose positron emission tomography ($^{18}$F-FDG-PET) scans. They underwent concurrent chemoradiotherapy, which resulted in a partial response determined by computed tomography (CT). While $^{18}$F-FDG-PET after chemoradiotherapy was positive, pathological examination showed that the tumors were fibrotic lesions with infiltration of lymphocytes and macrophages, with the appearance of metaplastic epithelial cells. The reasons for the false-positive results on $^{18}$F-FDG-PET were considered to be the high uptake of FDG in non-neoplastic inflammatory cellular elements, i.e. macrophages, lymphocytes and metaplastic epithelial cells, and squamous metaplasia induced by chemoradiotherapy. Although several studies demonstrated that $^{18}$F-FDG-PET could predict the response of neoadjuvant treatment of non-small cell lung cancer, one should bear in mind that false-positive results could be observed in pathological complete response of non-small cell lung cancer after neoadjuvant chemoradiotherapy.

Key words: FDG-PET – lung cancer – false positive – chemotherapy – radiation

INTRODUCTION

In recent years, $^{18}$F-fluoro-deoxyglucose positron emission tomography ($^{18}$F-FDG-PET) has been used to evaluate pulmonary nodules and tumor stages (1–3). Several studies have shown that $^{18}$F-FDG-PET is superior to computed tomography (CT) in staging mediastinal lymph node status and is a good predictor of response to neoadjuvant treatment for non-small cell carcinoma (4,5). However, there has been no specific report of false-positive cases in $^{18}$F-FDG-PET of non-small cell lung cancer after neoadjuvant treatment.

From December 2001 to February 2004, we prospectively studied 20 consecutive patients who had biopsy-proven lung cancers. They had CT of the chest and whole body $^{18}$F-FDG-PET, and were administered neoadjuvant treatment. After neoadjuvant treatment, we restaged the patients with CT and $^{18}$F-FDG-PET, and then performed pulmonary resection and lymphadenectomy. The tumors were considered to be positive on the $^{18}$F-FDG-PET if a standardized uptake value (SUV) of $\geq$2.5 was obtained.

Here we report two patients with non-small cell lung cancer whose $^{18}$F-FDG-PET was false positive.

CASE 1

A 64-year-old male was admitted to our hospital because of a tumor of the left upper lung and back pain in February 2003. He had had a diagnosis of poorly differentiated pulmonary adenocarcinoma and had been given six courses of chemotherapy consisting of paclitaxel and carboplatin with radiotherapy (2 Gy given 30 times, total 60 Gy) in March 2002 in another hospital. A chest roentgenogram demonstrated an undefined opacity in the left upper lung. Chest CT showed a tumor located in the left upper lobe without swelling of the mediastinal lymph nodes (Fig. 1A). $^{18}$F-FDG-PET, which was performed 11 months after the chemoradiotherapy, revealed accumulation at the tumor site with an SUV of 4.3 (Fig. 1B). In May 2003, 11 months after the chemoradiotherapy, left upper...
lobectomy was performed because of the remaining tumor shadow on CT and the positive result in the \[18F\]FDG-PET. Histopathological examination showed fibro-inflammatory lesions with macrophages, lymphocytes and proliferative epithelial lesions such as columnar epithelial proliferation and squamous metaplasia possibly caused by neoadjuvant chemoradiotherapy. There were no viable cancer cells in the lesion (Fig. 2).

**CASE 2**

A 64-year-old male was referred to our hospital for an examination of an abnormal shadow on chest X-ray in January 2003. CT showed a tumor located in the right upper lobe and swelling of mediastinal lymph nodes. \[18F\]FDG-PET revealed accumulation at both the tumor site and mediastinal lymph nodes. Mediastinoscopy showed metastasis of poorly differentiated adenocarcinoma in the pre-tracheal lymph nodes. He had been given two courses of chemotherapy consisting of carboplatin and vinorelbine and concurrent radiation therapy (2 Gy given 15 times, total 30 Gy). CT and \[18F\]FDG-PET were taken 1 month after chemoradiotherapy (Fig. 3A and B). The size of the tumor had decreased from 4.5 to 2 cm in CT after chemoradiotherapy. The SUVs of the tumor and mediastinal lymph nodes were decreased from 6.2 to 3.1 and from 5.4 to 2.9, respectively. On April 2004, a right upper lobectomy with systematic lymph node dissection was performed. Histopathological examination of the primary tumor showed active inflammatory changes with the infiltration of macrophages, lymphocytes and the appearance of atypical metaplastic epithelial cells, but without viable cancer cells (Fig. 4).

**DISCUSSION**

Several studies have shown good results of \[18F\]FDG-PET for the staging of lung cancer, even for the patients who had...
received neoadjuvant treatment (4,5). However, we experienced two patients whose [18F]FDG-PETs were positive although there were no cancer cells in the tumor after chemoradiotherapy. Several reasons were considered to explain the false-positive findings of [18F]FDG-PET. First, it is speculated that an inflammatory lesion with invasion of macrophages and lymphocytes resulted in the uptake of FDG and was then shown to be false positive. Kubota et al. showed that FDG accumulates not only in the tumor cells but also in the inflammatory cellular elements, which could appear in association with necrosis of the tumor, and also showed that accumulation of FDG is relatively higher in macrophages and young granulation tissue than in the tumor cells (6,7). Shiraki et al. demonstrated that false-positive results of [18F]FDG-PET in mediastinal and pulmonary lymph nodes were closely related to the proportion of macrophages and lymphocytes (8). The second reason is that metaplastic and proliferative epithelial elements caused by chemoradiotherapy might have caused FDG accumulation. Nishikawa et al. showed that chemotherapy and radiation cause a change of the normal bronchioloalveolar cells in highly proliferative epithelial lesions during the fibrosing process (9). They also showed that proliferative epithelial lesions such as atypical bronchioloalveolar hyperplasia and squamous metaplasia caused by chemoradiation therapy were prominent in autopsy cases. In both of the present cases, atypical epithelial cells were distinguished in the pulmonary tumors. High FDG uptake by these metaplastic epithelial elements could cause false positivity in these cases.

Another interesting finding is the time after chemoradiotherapy. [18F]FDG-PET of case 1 was taken at 11 months after neoadjuvant treatment, and case 2 was taken 1 month after the neoadjuvant treatment. False positivity could occur even 11 months after chemoradiotherapy so long as tissue inflammation continues.

These cases suggest that one should bear in mind that higher FDG uptake in lung tumors may reflect not only tumor cell viability or proliferation, but also the contribution of inflammatory tissue and non-neoplastic epithelial proliferation in the lesion after neoadjuvant treatment.

References