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Intratumoral Heterogeneity of Subcutaneous Nodules in a Never-Smoker Woman of Lung Squamous Cell Carcinoma Detected on ^{18}F-Fluorodeoxyglucose Positron Emission Tomography and Computed Tomography

A Case Report

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Abstract: Subcutaneous tissue is a rare site of metastasis, accounting for only 1–2% of all lung neoplasms. Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) has been reported to increase the diagnostic accuracy of subcutaneous metastasis.

A 58-year-old woman presented with complaints of dry coughing, in which three positive subcutaneous nodules were found on ^{18}F-FDG positron emission tomography and computed tomography (PET/CT). Pathologic examination confirmed that each of the nodules contained 1) necrotic fat, 2) small amounts of blood cells and glandular epithelium, and 3) subcutaneous metastasis of moderately differentiated lung squamous cell carcinoma, respectively.

Although PET/CT is useful for the detection of subcutaneous metastasis of primary lung cancer, we noted heterogeneous accumulation of ^{18}F-FDG in subcutaneous tumors. This case highlights the importance of obtaining histological confirmation of malignant diseases whenever possible.

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Abbreviations: CK = cytokeratin, CT = computed tomography, FDG = fluorodeoxyglucose, ITH = intratumoral heterogeneity, LCINS = lung cancer in never-smokers, NSCLC = nonsmall lung cancer, PET = positron emission tomography, SCC = squamous cell carcinoma, SUV = standard uptake value, TTF-1 = thyroid transcription factor 1.

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INTRODUCTION

The integration of modern imaging techniques, such as positron emission tomography and computed tomography (PET/CT), has improved the ability to accurately assess the initial stages of subcutaneous metastases. Heterogeneities of solid tumors appear as alterations in phenotypic features such as cellular morphological characteristics, gene expression, metabolism, and metastatic potential.[1–3] The maximum standard uptake value (SUV_{max}), tumor size, and density fractal dimension (d-FD) obtained from ^{18}F-fluorodeoxyglucose (FDG) PET/CT images provide different types of information used to measure intratumoral heterogeneity (ITH) and can help differentially diagnose malignant and benign nodules.[4] Here, we report a case of ITH among 3 subcutaneous nodules that showed different morphological features of SUV_{max} and tumor size on ^{18}F-FDG-PET/CT.

CASE REPORT

A 58-year-old woman presented with complaints of dry coughing without phlegm and chest tightness that was aggravated by activity but reduced after rest. She denied tobacco use, second-hand smoking, or occupational exposure to tobacco smoke. A follow-up ^{18}F-FDG -PET/CT scan was consistent with a significant increase in metabolic activity and atelectasis in the upper lobe of the right lung. Three lesions of increased FDG accumulation were observed in the subcutaneous soft tissue, revealing 2 focal lesions with increased FDG uptake in the right upper extremity, referred to as ''mass A'' and ''mass B'' (Figure 1A: arrows, $SUV_{max} = 3.83$; Figure 1B: arrows, $SUV_{max} = 6.18$). Focally intense uptake was also present in a lesion on the thoracic wall, ''mass C'' (Figure 1C: arrows, $SUV_{max} = 4.98$).

On physical examination, mass A in the right upper extremity was 1.5 cm, firm, immobile, and nontender, whereas mass B could not be palpated because of its deep location. According to requirements by her family, the patient underwent wide excision of mass A. Subsequent pathologic examination showed fat necrosis and fibroplasia but no signs of malignancy (Figure 2A). An ultrasound-guided gun biopsy was taken from mass B in the right arm (Figure 2B). Histopathology from mass B revealed metastatic, moderately differentiated lung squamous cell carcinoma (SCC). Immunohistochemistry showed that malignant cells were positive for CK5/6 and P63 (Figure 3), which were markers of squamous differentiation. Overexpression of CK5/6 and P63 has been consistently identified in lung SCC.[5] In addition, the cells showed positive staining for CAM5.2 and CK7; although the intensity was weaker than that

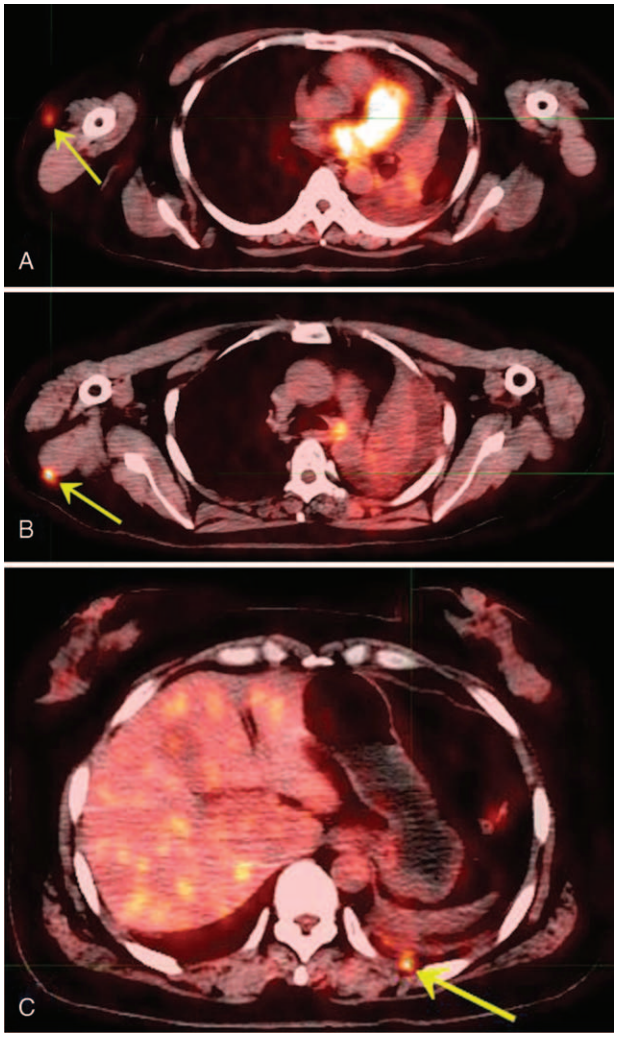

FIGURE 1. Coronal series showed 3 dense consolidation with areas of increased uptake, and these lesions were pointed by yellow arrows. A and B, These were mass A and mass B in the right upper extremity, respectively. C, It was mass C in thoracic wall.

of CK5/6 and P63, their presence was distinct in SCC.[6] Staining for TTF-1 was negative. Based on these pathologic findings, mass B was diagnosed as a subcutaneous metastasis of SCC. Similarly, a CT-guided biopsy of the subcutaneous nodule (mass C) in the chest wall was performed to rule out metastasis; this biopsy revealed muscle and a small amount of adipose tissue (Figure 2C).

The patient has consented for the publication of the present case report.

DISCUSSION

Here, we presented a case of lung SCC in a never-smoker woman with 3 intense, hypermetabolic subcutaneous nodules noted on ^{18}F-FDG-PET/CT. Histopathological findings confirmed subcutaneous metastasis in 1 of the 3 nodules. Subcutaneous metastasis has been described historically as extremely rare in lung SCC, and the prognosis after metastasis from a primary lung cancer is poor.[7]

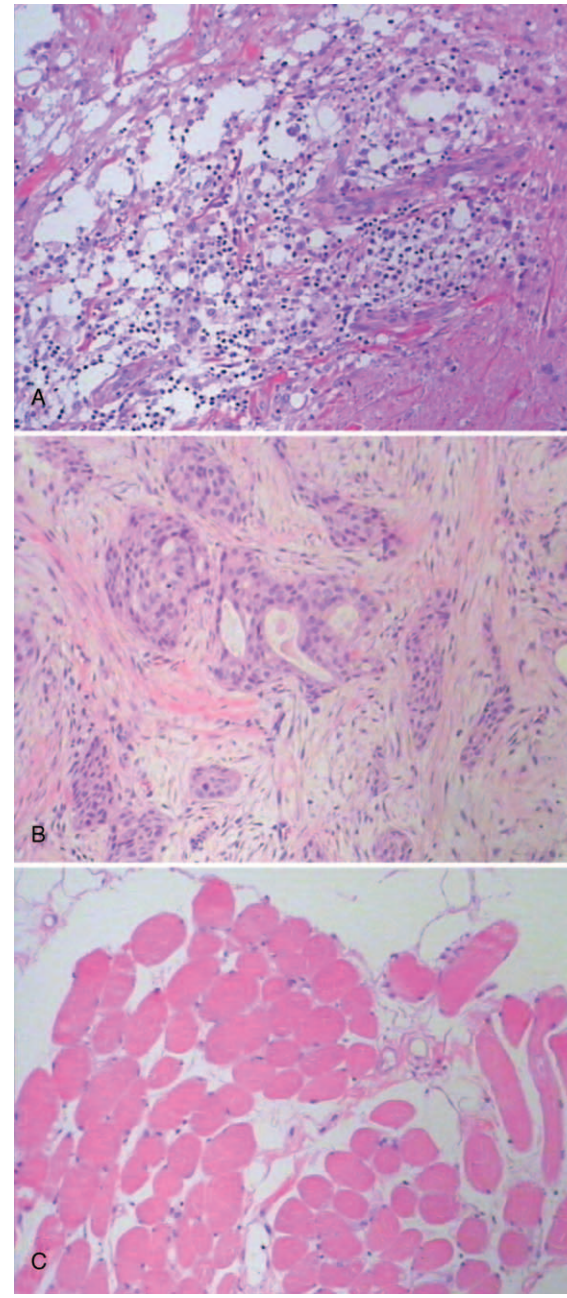

FIGURE 2. Pathological results of subcutaneous nodules were observed under a light microscope (Olympus BX51, Tokyo, Japan; hematoxylin-eosin staining, original magnification 100×) and representative photos were taken. A, Histopathological findings of mass A in the right upper extremity revealed fat necrosis and fibroplasia. B, Ultrasound-guided gun biopsies taken from mass B in the right upper extremity revealed metastatic, moderately differentiated squamous cell lung cancer. C, CT-guided biopsy of mass C in the chest wall showed muscle and a small amount of adipose tissue. CT = computed tomography.

According to the World Health Organization, the incidence of lung cancer in never-smokers (LCINS) is approximately 25% of all cases, comprising nearly 40% of all lung cancer cases in women in Asia.[8] According to Toh et al., adenocarcinomas characterize 60.8% of cases in LCINS, followed by nonsmall

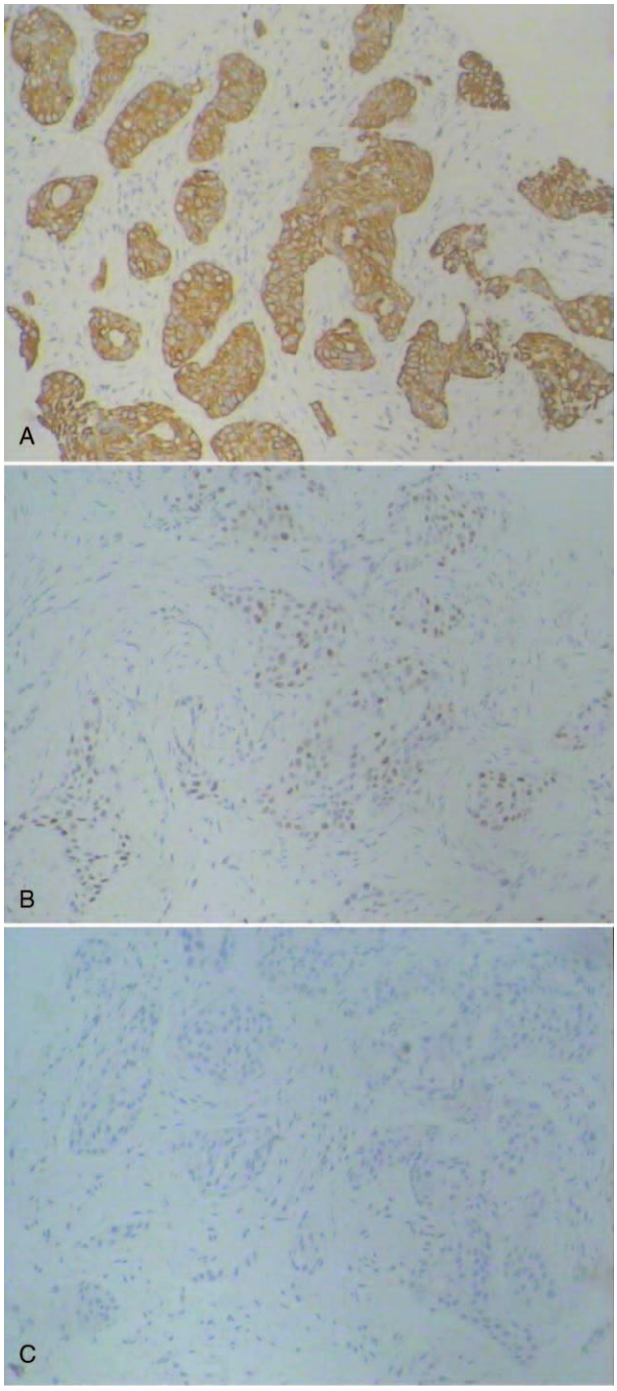

FIGURE 3. In the immunohistochemical detection of mass B, CK5/6 and P63 were positive in (A, B) with magnification of 100×. TTF-1 was negative in (C) with magnification of 100×. CK = cytokeratin, TTF-1 = thyroid transcription factor 1.

cell lung cancer (NSCLC), not otherwise specified (14.4%), bronchoalveolar carcinoma (13.6%), and SCC (8.8%).[9] No significant difference in 5-year survival was seen between LCINS (27.2%) and NSCLC in smokers (31.3%; $P = 0.73$).[10]

Subcutaneous metastases from any cancer are rare, with an overall prevalence of 0.75–9%, but when they do occur, they usually originate from primary tumors in the breast, lung, or colorectum. Lung cancer metastases commonly involve the adrenal glands, bone, and brain. Thus, the subcutaneous skin is not a common site of metastasis, accounting for only 1–2% of all lung neoplasms. Adenocarcinoma is the histological variant of lung carcinoma most commonly associated with soft tissue metastasis.[11,12] Subcutaneous and cutaneous metastases from lung SCC are extremely rare and, therefore, limited to case reports in the scientific literature.[7] Negative prognostic factors of skin metastasis include primary nonresectability, small cell lung cancer, and simultaneous discovery of other cutaneous or extracutaneous metastases. Skin metastasis represented the unique distant localization represents the best-survivor category.[13]

Despite the exact incidence of soft tissue metastatic spread barely known, several pathophysiological mechanisms have been proposed in the literature. The most important hypotheses suggest mechanical (muscle contraction and extremely variable blood flow) or immunologic (cellular and humoral immunity and hypersensitivity) etiologies.[7,14] Furthermore, characteristics intrinsic to soft tissue, such as pH instability and variable oxygen tension, may create a microenvironment unfavorable to the development of macroscopic tumor foci.[14,15] According to these hypotheses, long-term lack of exercise and hypoimmunity are main causes of metastatic spread in our patient.

The increasing use of PET/CT as a whole-body staging tool for various cancers has led to several recent reports describing detection of unsuspected, distant metastases at unusual locations due to their elevated glucose metabolism.[16] An elevated uptake of ^{18}F-FDG is positively correlated with many biological processes, including glucose metabolism, hypoxia, cellular proliferation, and blood ow.[17] SUV_{max}, tumor size, and d-FD obtained from FDG-PET images are capable of demonstrating ITH, which can help characterize and differentiate subcutaneous metastases from benign tumors.[4] The 3 subcutaneous nodules detected by PET scan in our patient, with differing sizes and SUV_{max}, proved to be heterogeneous on histopathological examination.

At the time of clinical diagnosis, most human tumors with similar imaging features display startling heterogeneity. Nowell's theory of clonal evolution states that cancers arise from a single cell of origin, develop genomic instability during replication, and then undergo enrichment for the most aggressive clones through the process of metastasis, followed by the eradication of sensitive clones with cancer treatment.[18] Accordingly, differential gene expression, somatic mutational status, tumor-specific genetic signatures, and microenvironmental selection pressures within individual tumors have implications for ITH.[19,20] Heterogeneities of solid tumors appear as alterations in phenotypic features such as cellular morphological characteristics, gene expression, metabolism, and as variations in behavioral characteristics of angiogenesis and immunogenic, and metastatic potential.[1–3] In MR or CT imaging, texture analysis within a structure can quantify ITH. PET has the additional benefit of indicating ^{18}F-FDG uptake, providing information that characterizes tumor heterogeneity, which is associated with the diagnosis, differential diagnosis, and prognosis of solid tumors.[21–23] In addition, Tixier et al. showed that the ITH of FDG uptake could predict responses of esophageal cancer to radiochemotherapy.[24] The application of PET/CT imaging for detection of ITH should, therefore, be investigated as an important step for personalized treatment.

In our patient, the 3 subcutaneous nodules with increased FDG uptake differed in size and SUV_{max}, and 1 of these nodules

was identified by histopathological examination as an extremely rare subcutaneous metastasis. Based on these findings, clinicians must be aware of the intratumoral metabolic heterogeneities of subcutaneous nodules showing increased ^{18}F-FDG uptake on PET/CT,[12] for which biopsy is crucial to diagnosis. The appropriate strategy must be decided on a case-by-case basis, with consideration of the imaging manifestations of subcutaneous masses, especially in patients with primary carcinoma. Radiotherapy, chemotherapy, or any other treatment for unconfirmed metastatic disease could lead to unnecessary, risky, and costly consequences that do not benefit patients.

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