Dilemma Concerning the Differential diagnosis of Hematological Malignancy and Bone Metastasis Arising from Lung Cancer

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Bone a major site of metastases arising from lung cancer. If patients with lung cancer are complicated with multiple bone lesions showing the intense accumulation of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) on positron emission tomography (PET), it may be difficult to distinguish bone metastasis due to lung cancer from complications of other diseases. In this issue of the journal, Matsuoka et al. reported a case of lung adenocarcinoma harboring chronic lymphocytic leukemia (CLL) mimicking bone metastasis (1). This case was definitively diagnosed as double primary malignancies with early-stage lung adenocarcinoma (cT1bN0M0) and CLL with multiple bone lesions. However, while this case is indeed a rare entity with misleading bone lesions, careful attention should be paid to the differential diagnosis in order to ensure the optimal treatment is delivered to the patient.

$^{18}$F-FDG PET is useful for making the differential diagnosis between benign and malignant lesions and is the best modality for detecting bone metastases due to lung cancer (2). Indeed, $^{18}$F-FDG PET and bone scanning reportedly have accuracies of 96% and 66%, respectively, for the detection of bone metastasis due to non-small-cell lung cancer (NSCLC) (2). However, when the presence of double primary neoplasms is synchronously observed, it is difficult to perform a differential diagnosis based on the uptake of $^{18}$F-FDG within tumor tissues. A thorough understanding of the clinical feature and course may aid in detecting the presence of synchronous double primary cancers.

We sometimes encounter different primary neoplasms in patients with lung cancer. A previous study found that the risk of developing second cancers (n=840) increased significantly in CLL patients (n=9456) with a complication rate of 8.9%, and significant excesses were observed for cancers of lung, brain, and melanoma (3). Although the precise reason for this increased risk of developing a second malignancy remains unclear, potential risk factors, such as viral agents, smoking, and the HER-2/neu oncogene, have been reported (4, 5). Several interesting hypotheses regarding immunologic or genetic factors have been proposed, but we are unable to explain the pathogenesis regarding the concomitant occurrence of second cancers in CLL patients.

In the case of Matsuoka et al., no lesions were noticed on computed tomography (CT) at $^{18}$F-FDG uptake sites of multiple bone abnormalities, so the authors considered the multiple bone lesions not to be typical of lung cancer (1). Additional magnetic resonance imaging (MRI) of the multiple bone lesions was then performed, and the possibility of mixed tumors was considered. A pathological examination of the bone lesions ultimately resulted in a definitive diagnosis of CLL (1).

$^{18}$F-FDG PET is generally considered the best modality for detecting bone metastases resulting from lung cancer, outperforming bone scintigraphy and CT. Thus, most clinicians refer the findings of significant $^{18}$F-FDG accumulation to metastatic bone lesions. Bone metastases without morphological mass on CT are sometimes observed despite a positive $^{18}$F-FDG uptake. If multiple bone lesions with the accumulation of $^{18}$F-FDG are radiographically recognized, a further pathological examination, such as a biopsy, may be omitted. However, the potential of synchronous double primary neoplasms should always be considered in order to ensure that appropriate treatment is administered, and a careful initial evaluation, such as via a pathological approach, is needed in order to avoid a misleading diagnosis when multiple bone lesions are recognized.

The clinical manifestation of CLL is clarified as lymphadenopathy, splenomegaly and hepatomegaly with some symptoms. Multiple bone lesions resulting from CLL as the initial manifestation are extremely rare (6) and make it diffi-
cult to perform a differential diagnosis. CLL accounts for approximately 30% of all leukemias (7), but the incidence of other hematological malignancies with multiple bone lesions and lung cancer is also rare, so a tissue biopsy is indicated when multiple bone lesions are potentially not metastases due to lung cancer or when the clinical features are inconsistent with a diagnosis of bone metastasis. In general, we clinically diagnose an entity as bone metastasis when multiple bone lesions with an intense $^{18}$F-FDG uptake are found in a patient with lung cancer. Since the therapeutic strategy of lung cancer based on disease staging is apparently different, an initial systemic evaluation is warranted in order to provide appropriate treatment. If the possibility of bone lesions secondary to other disease is doubtful, a tissue biopsy should be considered without hesitation.

There are several studies regarding the detection of bone metastasis resulting from NSCLC using different radiological modalities (8-10). Takenaka et al. reported that whole-body MRI with diffusion-weighted imaging (DWI) can evaluate bone metastasis of NSCLC as accurately as $^{18}$F-FDG PET and bone scintigraphy (8). Aside from DWI MRI, the utility of PET with $^{18}$F-3-fluoro-alpha-methyl tyrosine ($^{18}$F-FAMT), $^{18}$F-choline (FCH), F-dihydroxyphenylalanine (DOPA), and $^{18}$F-fluoride has been previously investigated for the assessment of bone metastasis (9,10). However, a recent meta-analysis demonstrated that $^{18}$F-FDG PET was a better imaging modality for diagnosing bone metastasis from lung cancer than MRI, bone scintigraphy, and other approaches (11). As a limitation of $^{18}$F-FDG PET, it is impossible to distinguish lung cancer-related bone metastasis from hematological diseases based solely on the degree of the $^{18}$F-FDG uptake. Clinicians should be alert for synchronous complication with hematological disorder when assessing bone lesions with an intense $^{18}$F-FDG accumulation.

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References

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