Lung Adenocarcinoma with Chronic Lymphocytic Leukemia Mimicking Bone Metastasis: A Case Report

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Abstract:
A 77-year-old man was referred to our hospital for abnormal thoracic radiographs. Computed tomography (CT) revealed a 20-mm subpleural ground-glass opacity in the right S⁶ area. A CT-guided biopsy revealed lung adenocarcinoma. Fluorodeoxyglucose-positron emission tomography revealed multiple abnormal bone accumulations, and a subsequent biopsy of a left iliac bone lesion revealed chronic lymphocytic leukemia. A right lower lung lobectomy was performed for the lung adenocarcinoma (cT1bN0M0, stage IA2). An aggressive biopsy of the bone lesion confirmed a rare case of double primary malignancies, which determined the patient’s treatment and outcomes.

Key words: lung adenocarcinoma, lung cancer, chronic lymphocytic leukemia, double malignancy, bone lesion, bone metastasis

Introduction
Bone metastases occur in 30%−40% of patients with advanced lung cancer (1). However, in these patients, it is difficult to distinguish lesions of bone metastases from complications of other diseases based on imaging findings alone. We herein report an unusual case of lung adenocarcinoma with bone lesions caused by chronic lymphocytic leukemia (CLL), a second separate malignancy. This case highlights the need for a thorough evaluation of bony lesions in patients with lung cancer in order to make fully informed treatment decisions and improve their prognoses.

Case Report
A 77-year-old asymptomatic man was referred to our hospital because of an abnormal shadow in the right middle lung field on a radiograph. He had a 2.5-pack-year smoking history and had undergone surgeries for prostate cancer and an inguinal hernia at 61 and 75 years old, respectively. He was not under treatment for any disease at the time of presentation.

At presentation, his vital signs were as follows: blood pressure, 117/53 mmHg; pulse rate, 59 beats/min; body temperature, 35.8 °C; and percutaneous oxygen saturation, 98%. His neck and supraclavicular lymph nodes were non-palpable, and there were no obvious abnormalities in the respiratory or heart sounds. A blood examination at the first visit revealed no abnormalities in the tumor markers, such as the carcinoembryonic antigen, cytokeratin 19 fragment, progastrin-releasing peptide, or prostate-specific antigen.

Chest radiography revealed an ill-defined patchy shadow, 20 mm in size, in the right middle lung field (Fig. 1). Computed tomography (CT) revealed a subpleural ground-glass opacity, 20 mm in size, and with pleural indentation and spiculation, in the superior segment of the right lower lobe (S⁶). Fluorodeoxyglucose-positron emission tomography (FDG-PET) (Fig. 2A, 2B) revealed an uptake of FDG (maximum standardized uptake value [SUVmax] = 2.0) consistent with the nodular shadow in the right S⁶. Substantial abnormal accumulation (SUVmax=approximately 6.0) was observed in the bilateral ribs, lumbar vertebrae, bilateral femurs, and left ilium; no accumulation was observed in the...
Figure 1. Chest radiography (left) and chest CT (right) findings. Chest radiography shows a ground-glass opacity (arrow) in the right middle lung field. Chest CT shows a subpleural part-solid nodule, 20 mm in size, with spiculation and pleural indentation in the right S6 area. CT: computed tomography.

Figure 2. FDG-PET/CT and histological findings of the lung nodule biopsy specimen. A: Coronal image from whole-body PET shows the accumulation of FDG in the primary lung lesion (black arrow) and multiple bone lesions (red arrowheads). B: FDG-PET/CT shows the uptake of FDG in the right lung nodule. C: Histological findings of the lung nodule biopsy specimen show fibrosis of the alveolar tissue and growth of a moderately differentiated adenocarcinoma with an acinar pattern within the fibrosis (Hematoxylin and Eosin staining: ×20).

The lesion could not be reached via bronchoscopy, and a CT-guided percutaneous biopsy was performed. The obtained tissue was identified as lung adenocarcinoma [positive for an epidermal growth factor receptor mutation (L858R); Fig. 2C].

The pathological diagnosis and FDG-PET findings together suggested lung adenocarcinoma (cT1bN0M1c, cStage IVB) with multiple bone metastases. However, there was no metastasis to the regional lymph nodes, and no lesion was found on CT at the FDG-PET accumulation site, suggesting that the multiple bone lesions were not typical of lung can-
Figure 3. MRI scans of the pelvic cavity. Diffuse high-signal lesions are noted in the lumbar spine, pelvis, and femur on T1-weighted in-phase images and diffusion-weighted images; these lesions have a low signal on T1-weighted out-of-phase images (yellow circle: left iliac lesion).

Figure 4. FDG-PET/CT and histological findings of the iliac lesion biopsy specimen. A: A bone biopsy of the ilium was performed (black arrow). B: FDG-PET/CT shows the uptake of FDG in the left ilium. C: CT shows a CT-guided percutaneous needle biopsy of the left iliac bone. D: Hematoxylin and Eosin staining of the iliac biopsy specimen shows infiltration of small, atypical lymphocyte-like cells along the trabecula. E, F, G: Immunohistochemically, the tumor cells are positive for CD20 (E) and CD5 (F) and negative for CD3 (G). CT: computed tomography, FDG-PET: 18F-fluorodeoxyglucose-positron emission tomography.

cancer metastasis. MRI (Fig. 3) of the pelvic cavity, including the left iliac bone (which showed strong accumulation on FDG-PET), was performed. The lesions were diffusely spread over the lumbar spine, pelvis, and femur; they had a high signal intensity on T2-weighted, short TI inversion recovery, and diffusion-weighted imaging and a low signal intensity on T1-weighted phase contrast imaging. This suggested the possibility of re-conversion to the red marrow. However, because some areas in the red bone marrow had a high SUVmax, the possibility of mixed tumors was considered, and a CT-guided biopsy of the left iliac bone was performed (Fig. 4). A pathological examination of the resultant specimen revealed that the iliac lesion was infiltrated with small atypical lymphocyte-like cells (CD5-positive, CD20-positive, CD43-positive, CD3-negative, CD10-negative, CD33-negative, and cyclin D1-negative) along the bone trabeculae without lung cancer metastases, leading to a diagnosis of a low-grade B-cell lymphoma. A bone marrow examination revealed B-cell clusters in some areas, CD20 positivity, and CD5 positivity, consistent with low-grade B-cell lymphoma, chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL). Based on the above findings, we concluded that the multiple bone lesions were not metastases of lung cancer; the clinical stage of the lung cancer was cT1bN0M0, stage IA2.

Radical surgery for lung cancer was indicated in this patient, and right lower lobectomy with video-assisted thoracic surgery was performed. The postoperative diagnosis was right lower lobe lung adenocarcinoma (pT1bN0M0, pStage IA2; postoperative total tumor diameter: 20×12×28 mm and
invasive diameter: 12×7 mm). Treatment for CLL was not indicated at the time of the diagnosis, and the patient was followed up every three months in the hematology department.

Follow-up FDG-PET performed 7 months after the initial visit revealed no local recurrence of lung cancer; however, the enhancement (SUVmax=approximately 10) of and an increase in the bone lesions (new accumulations in the left submandibular and peri-mesenteric lymph nodes) were noted (Fig. 5A). A biopsy of the left submandibular lymph node, which was found to be a new lesion on PET, was performed, and the patient was diagnosed with diffuse large B-cell lymphomas (DLBCL). The patient then received six cycles of chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone [R-CHOP]), after which FDG accumulations were obscured, indicating a complete metabolic response (CMR) (Fig. 5B). Based on these findings, the bone lesion was finally diagnosed as having originated from the CLL.

Discussion

The present case involved double primary malignancies (lung cancer and CLL). Multiple primary malignancies are often defined based on the following three conditions proposed by Warren and Gate: i) each tumor must be histopathologically malignant, ii) the tumors must occur in different parts or organs, and iii) metastasis must be excluded (2).

When multiple bone lesions are observed in patients with lung cancer, it is difficult to determine based on imaging findings alone whether they are bone metastases of lung cancer or complications of other diseases (1). In the present case, multiple bone lesions that could not be detected by CT were observed on FDG-PET. The patient had a history of prostate cancer, but the PSA value was within the normal range. Furthermore, no osteosclerotic changes were noted in the bone lesions. Thus, recurrent bone metastases from prostate cancer seemed unlikely. SUV is often used to express the degree of the accumulation of FDG in lesions on FDG-PET. Because FDG is heterogeneously distributed among the lesions, the highest concentration value (SUVmax) is often used to determine the degree of accumulation. Although an SUVmax >2.5 is often used as a criterion to define malignancy (3), false-negative findings are known to occur in cases of small lesions, well-differentiated lung adenocarcinomas, bronchioalveolar carcinomas, and carcinoids due to a low FDG uptake. The average SUV of lung adenocarcinomas, including ground-glass shadows, is approximately 0.9 (4). In the present case, the nodular shadow in the right S6 area was caused by a moderately differentiated lung adenocarcinoma, and the SUVmax was 2.0. Among multiple bone lesions, lesions in the left ilium had the highest SUVmax, around 6.0.

Hematogenous metastasis is reported in 18% of patients with negative lymph-node metastasis of lung adenocarcinomas <2.0 cm in diameter (5). In the present case, there were no regional lymph node metastases, and the primary tumor was small (20 mm in length); therefore, a CT-guided bone biopsy was performed by an experienced radiologist because

![Figure 5. FDG-PET monitoring. A: FDG-PET scan taken seven months after the initial visit reveals an increase in the bone lesions (Fig. 1A). A biopsy of the left submandibular lymph node (red arrowhead) was performed. B: FDG-PET taken after six cycles of R-CHOP therapy. All accumulation of FDG is obscured. FDG-PET: 18F-fluorodeoxyglucose-positron emission tomography, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone](image)
Bone metastasis of a lung adenocarcinoma was considered atypical. In a previous study, complications of a CT-guided bone biopsy were reported in 3 out of 183 patients (1.6%) and mainly included different kinds of pain and numbness (6).

Bone metastases are pathologically classified as osteogenic, osteolytic, mixed, and intertrabecular (7). The bone lesions in the present case were not observed on CT but were detected on MRI and PET; this is consistent with the imaging features of intertrabecular bone metastases. A bone biopsy also revealed infiltration of small, atypical lymphocyte-like cells along the bone trabeculae, consistent with the pathological findings of intertrabecular bone metastases, which tend to be seen in medullary carcinomas that have a poor tumor stroma, such as small-cell lung cancers, hepatocellular carcinomas, and hematologic malignancies (8). However, the intertrabecular bone metastasis type is considered a pathologic classification, and if it is not detected by simple radiography, CT, or bone scintigraphy, an imaging diagnosis is difficult because of the possibility of false-negative findings. Therefore, it is not generally included in the clinical classification of bone metastasis and has not been extensively reported (8, 9). Understanding the characteristics of intertrabecular bone metastases and actively performing MRI and FDG-PET examinations when searching for metastases are expected to improve the diagnostic rates for bone metastases.

Although CLL accounts for approximately 30% of all leukemias in Europe and the United States, it has a relatively low incidence (approximately 5%) in Japan (10). Furthermore, there are reports of CLL/SLL being complicated with other malignant tumors in Europe and the United States; however, there are very few such reports in Japan because of the relatively low incidence of CLL/SLL (11). CLL with features resembling bone metastases is very rare; this form is generally osteolytic and affects <5% of all patients with CLL (12). Osteolytic changes often indicate hypercalcemia (13); however, in the present case, the calcium levels were within the normal range throughout the course of the disease. One study reported that 87% of all CLL bone lesions occurred in the axial and proximal long bones, with the most common metastatic sites being the femur and vertebrae (12). In the present case, the bone lesions were found in the ribs, lumbar vertebrae, femur, and ilium. The iliac bone, which had the highest FDG accumulation, is a flat bone and part of the appendicular skeleton. The ribs and lumbar vertebrae are axial bones, and the femur is a long bone. The locations of the bone lesions are consistent with those reported previously.

CLL mostly arises from a malignant clone of B cells. SLL is defined as a tumor identical to CLL, without infiltration of the peripheral blood or bone marrow. CLL and SLL result in lymph node enlargement and an increase in the tumor cells in the peripheral blood, which are mutually transitional. Therefore, CLL and SLL are grouped together as CLL/SLL. The clinical course of CLL is extremely varied; some patients live for decades without the need for treatment, while others have a rapidly aggressive clinical course (14). Most tumors are low-grade B-cell lymphomas; however, in a phenomenon called Richter’s syndrome (RS), indolent B-cell tumors may transform and develop as aggressive lymphomas (mostly DLBCL and rarely Hodgkin lymphomas). RS has an annual incidence of approximately 0.5%–1% in patients with CLL, and its overall incidence in these patients is approximately 5%–16%. It is generally characterized by an aggressive clinical course and a poor prognosis (15-17).

In the present case, CLL showed a Rai stage of 0 at the diagnosis and a Binet stage of A. There were no indications for treatment; thus, the patient was followed up every three months in the hematology department. Follow-up FDG-PET performed 7 months later revealed no local recurrence of lung cancer; however, the enhancement (SUVmax=approximately 10) of and an increase in the bone lesions were noted (Fig. 5A). In a previous study, approximately 40% of the patients with an SUVmax of 5 to <10 and two-thirds of patients with an SUVmax ≥10 were diagnosed with RS; this emphasized the need for a tissue biopsy in patients with an SUVmax ≥5 (18). The present patient underwent a left submandibular lymph node biopsy, was diagnosed with DLBCL, and received six cycles of R-CHOP. The median time from the diagnosis to CLL transformation has been reported to be two to five years (19). In the present case, this duration was seven months. During the clinical course, the patient had no subjective symptoms and the lymphocyte count, lactate dehydrogenase (LDH) level, and calcium level were within their normal ranges. The soluble form of the interleukin 2 receptor level was within the normal range at the initial visit (normal: 121–613 U/mL); however, 7 months later, it had slightly increased to 812 U/mL. After six cycles of R-CHOP, FDG-PET was performed again; all prior points of the accumulation of FDG were obscured, indicating CMR (Fig. 5B). Based on these findings, the bone lesion was finally diagnosed as having originated from the CLL.

**Conclusion**

In the present case, radical surgery was performed for lung cancer; CLL was diagnosed as a second malignancy, even though there were no findings other than bone lesions. This enabled a follow-up examination for CLL, which in turn allowed for an early diagnosis of DLBCL and prompt initiation of treatment. Keeping in mind that lung malignancies can metastasize to various organs and overlap with malignancies in other organs, it is important to aggressively consider a biopsy even when metastasis is suspected so as to not miss radically resectable lung cancer and coexisting malignancies.

The authors state that they have no Conflict of Interest (COI).

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References


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