Hypertrophic Pulmonary Osteoarthropathy in Anaplastic Lymphoma Kinase (ALK)-positive Lung Cancer

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Abstract

A 49-year-old man was admitted to a hospital with chest pain and polyarthralgia. Chest radiography showed abnormal findings, and chest computed tomography showed a mass in the right lung. A transbronchial lung biopsy led to a diagnosis of anaplastic lymphoma kinase (ALK)-positive adenocarcinoma. Bone scintigraphy revealed bilateral symmetrical accumulations of $^{99m}$Technetium complexes in the long bones, suggesting co-existing hypertrophic pulmonary osteoarthropathy (HPO). The patient underwent four courses of chemotherapy with cisplatin plus pemetrexed, which led to decreased $^{99m}$Technetium accumulations in the long bones. To the best of our knowledge, this is the first reported case of HPO associated with ALK-positive lung cancer.

Key words: non-small-cell lung cancer, hypertrophic pulmonary osteoarthropathy, anaplastic lymphoma kinase, vascular endothelial growth factor


Introduction

Hypertrophic osteoarthropathy (HOA) is a condition characterized by digital clubbing, arthralgia/arthritis, and periostosis of the tubular bones (1). It can be classified as primary HOA or secondary HOA, which occurs in association with pulmonary, cardiac, or hepatic disease and accounts for 95% of all HOA cases (2, 3). When associated with pulmonary diseases, HOA is sometimes referred to as hypertrophic pulmonary osteoarthropathy (HPO). HPO occurs as a rare paraneoplastic manifestation, with an estimated 1.87% of patients with lung cancer also presenting with HPO (4). We herein describe the case of a patient who was diagnosed with HPO in concomitance with anaplastic lymphoma kinase (ALK)-positive lung cancer.

Case Report

A 49-year-old man visited his local hospital due to cough with chest pain. A chest computed tomography (CT) scan showed a mass in the right middle lobe of the lung (Fig. 1A) and small nodular opacities in the bilateral lung, thus suggesting a metastatic pulmonary tumor. The patient also exhibited enlarged paratracheal lymph nodes, suggesting lymph node metastases (Fig. 1B).

Two weeks later, this patient was referred to our department at the Shinshu University Hospital. For 6 months prior to the onset of cough with chest pain, the patient had experienced arthralgia of the bilateral elbows and knees. A physical examination revealed palpable right supraclavicular lymph nodes and visible digital clubbing on the fingers and toes (Fig. 2). The patient had normal vital signs, oxygen saturation, and breath sounds. No other abnormal signs were evident during the physical examination. The patient was a...
current smoker with a 12 pack/year history.

The laboratory data showed a markedly elevated alkaline phosphatase (ALP) level of 1,204 IU/L, with normal subset distribution (31.9% ALP2 and 68.1% ALP3). The patient also had an elevated carcinoembryonic antigen (CEA) level of 13.6 ng/mL (reference range: <5.0 ng/mL) and an elevated cross-linked carboxy-terminal telopeptide of type I collagen (I-CTP) level of 24.3 ng/mL (reference range: <4.5 ng/mL). The serum level of growth hormone was normal, but the plasma level of vascular endothelial growth factor (VEGF) was elevated (312 pg/mL; reference range: <38.3 pg/mL).

Bone scintigraphy with $^{99m}$Technetium ($^{99m}$Tc) complexes revealed a bilaterally symmetrical linear uptake in the femoral and tibial bones (Fig. 3A). A transbronchial lung biopsy of the right middle lobe led to the histopathological diagnosis of acinar adenocarcinoma (Fig. 4A). Additionally, immunohistochemistry (IHC) and fluorescence in situ hybridiza-
tion revealed the rearrangement of ALK with echinoderm microtubule-associated protein-like 4 (EML4) on tumor tissues (Fig. 4B). A genetic mutation analysis of the tumor revealed no mutation of the epidermal growth factor receptor (EGFR) gene. Therefore, the final diagnosis was ALK-positive lung adenocarcinoma at stage IV (cT4N3M1a; TNM classification 7th edition) with the complication of HPO.

The patient received first-line chemotherapy with cisplatin (80 mg/m²) and pemetrexed (500 mg/m²) administered every four weeks for up to four cycles. He showed a partial response evaluation criteria in solid tumors (RECIST) to the therapy. Subsequent maintenance chemotherapy with pemetrexed (500 mg/m²) was administered every four weeks, which maintained the partial response (Fig. 1C, D). The HPO-related symptoms of arthralgia of the bilateral elbows and knees improved promptly after the first course of chemotherapy. After four courses of cisplatin plus pemetrexed, the abnormal uptake of ⁹⁹mTc in bone scintigraphy was obviously decreased (Fig. 3B), as were the biochemical markers of bone metabolism (ALP and I-CTP) and the plasma level of VEGF (Fig. 5). Because the chemotherapy was effective,
the treatment did not include an ALK inhibitor.

**Discussion**

We herein described the diagnosis and treatment of a case in which HPO was diagnosed in conjunction with ALK-positive lung adenocarcinoma. Courses of chemotherapy led to improvements in the abnormal clinicopathological, radiographical and serological findings. To the best of our knowledge, this is the first case report describing HPO as a complication in a patient with ALK-positive lung cancer.

HPO is characterized by digital clubbing, periostosis and arthritis (1). Although HPO is a rare paraneoplastic syndrome, most cases of HPO are associated with lung cancer (3). Qian et al. investigated the clinicopathological characteristics of lung cancer with HPO and reported that among 6,151 patients with lung cancer, 115 patients (1.87%) also exhibited HPO (4). The lung cancer patients with HPO had a median age of 62 years (range, 31-78 years) and were predominantly men, heavy smokers, and had more severe disease. Adenocarcinoma was the predominant histopathological type, accounting for 47.8% of cases in the study by Qian et al. (4) and 11-50% of other reported cases of lung cancer associated with HPO (5). The present case showed clinical characteristics that were associated with HPO in the previously reported studies, including male sex, smoking history, advanced stage of lung cancer, and pathological classification of adenocarcinoma.

In 2007, the fusion of ALK with EML4 was identified in non-small-cell lung cancer (NSCLC) (6). An EML4-ALK fusion is now a therapeutic target in cases of NSCLC. ALK-positive lung cancer constitutes approximately 3-5% of all NSCLC cases (7, 8) and tends to be more common in non-smokers and slightly more common in women. The mean age of ALK-positive lung cancer occurrence is reportedly within “middle age,” implying that it is more common in younger patients (7). The present case was relatively young.

The pathogenesis of HPO remains unclear. It was recently suggested that VEGF or platelet-derived growth factor (PDGF) may be involved (9, 10), but the mechanisms have not yet been elucidated. It is interesting that the HPO symptoms of the present case improved along with the recovery of the plasma VEGF level after chemotherapy. Dejean et al. (11) also reported increased VEGF levels in tropomyosin 3 (TPM3)-ALK-positive anaplastic large cell lymphoma (ALCL) in mice. It is possible that increased VEGF levels are related to the molecular pathway involved in ALK-positive diseases. Although other driver mutations, such as EGFR or K-RAS, are also associated with VEGF levels (12, 13), there are few reports about HPO in EGFR-mutation-positive NSCLC (14). HPO may be caused by several factors including VEGF. Further studies are necessary to clarify the pathogenesis of HPO.

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

**Fig. 5. Clinical course.**

**References**