Abstract. Hypertrophic osteoarthropathy is an important manifestation of lung carcinoma, particularly in a non-small cell tumor, and hampers quality of life. Although removal of the primary tumor usually resolves this syndrome, effective treatment in patients with advanced lung carcinoma has not been established. Recently, an orally active, selective epidermal growth factor receptor tyrosine kinase (EGFR) inhibitor ("Gefitinib") provided clinical anti-tumor activity. We describe a 71-year-old male smoker with cough, who presented with clubbed fingers. A transbronchial lung biopsy (stage T2N3M1-IV) on a cavity lesion in the left lower lobe showed the features of adenocarcinoma, while bone scintigram revealed bilaterally symmetrical abnormal uptakes in the lower extremities, suggesting secondary hypertrophic osteoarthropathy. The serum level of growth hormone was increased to 1.42 ng/ml. Chemotherapy (cisplatin, vinorelbine) was not effective. Gefitinib, as a second-line therapy, induced disappearance of the abnormal accumulation on bone scintigraphy and decrease of the cavity in the lung and of serum growth hormone. The presented case suggests that the EGFR inhibitor might be a promising option for the treatment of hypertrophic osteoarthropathy with advanced lung adenocarcinoma.

Hypertrophic osteoarthropathy is a syndrome characterized by the triad of periostitis, digital clubbing and painful, swollen joints. The syndrome is a relatively common condition in patients with primary malignant tumor in the lung and pleura (1, 2) Clubbing and hypertrophic osteoarthropathy are presenting symptoms in 1% of cases with primary non-small cell lung cancer. Sometimes, hypertrophic osteoarthropathy shows an early curative stage of an occult disease (3). Radiographs of hypertrophic osteoarthropathy usually show subperiosteal new bone formation in the long bone of the lower extremities, and this finding may be considered essential to the diagnosis. Hypertrophic osteoarthropathy is treated by surgical resection of the primary tumor, with rapid remission of the symptoms after surgery. However, other treatments, such as non-steroidal anti-inflammatory drugs, steroid and anti-cancer drugs have been proposed when the primary tumor cannot be surgically removed. Here, we describe a case where the administration of gefitinib dramatically improved secondary hypertrophic osteoarthropathy.

Case Report

A 71-year-old man, who had smoked about 15 cigarettes daily for 49 years, was referred to our hospital because of sputum and cough. He had a history of subtotal gastrectomy caused by gastrointestinal ulcer at 38 years old and of cerebral thrombosis at 57 years old. He had had cough, sputum and enlarged fingers with slight pain during the preceding two months. Physical examination at admission revealed finger clubbing with no clinical signs of inflammation and fine crackles on the left lower lung field. Laboratory tests showed a low level of hemoglobin (10.7 g/dl) and an elevation of C reactive protein (6.68 mg/dl). The serum levels of certain tumor markers were elevated, such as CEA (3.3 ng/ml, normal range; <2.5 ng/ml), NSE (13 ng/ml, normal range; <10 ng/ml) and sialyl Lewis X-i antigen (SLX) (50.0 U/ml, normal range; <38 U/ml). Liver and renal functions were normal. Neither rheumatoid factor nor antinuclear antibodies were detectable. The level of serum growth hormone was increased to 1.42 ng/ml (normal range; GH <0.42 ng/ml).

Chest X-ray revealed reticular opacities on the left lower field (Figure IA). Chest computerized tomography (CT)-scan examination disclosed a cavity surrounded with multiple small nodular opacities in the left S9, a thickening of the bronchovascular bundle and interlobular sepal in the left lung and...
mediastinal lymphadenopathy (paratracheal and subcarinal lymph node), suggesting a complication of lymphangitic carcinomatosis (Figure 1B). A bronchofiberoscopy revealed a mucosal irregularity with edema and the redness in the left main bronchus and papillary adenocarcinoma was histologically diagnosed, based on an analysis of lavage and biopsy specimens obtained from the cavity lesion. A skeletal survey revealed a laminal periosteal reaction in the distal part of the bilateral tibias. Bone scintigraphy showed bilaterally symmetrical and patchy accumulation of radioisotope in the distal end of the bone of the lower extremities (Figure 2A). These radiological findings were compatible with hypertrophic osteoarthropathy. Neither CT-scan nor magnetic resonance tomography (MRI)-scan examination revealed any sign of metastasis in any organs, in particular the hypothalamus-pituitary system.

We made a diagnosis of lung adenocarcinoma complicated with secondary hypertrophic osteoarthropathy, which was cT2N3M1, stage IV disease with intrapulmonary metastasis. On August 25, 2003, he was treated with intravenous chemotherapy of combined cisplatin (80 mg/m², day 1) and vinorelbine (20 mg/m², days 1, 8). As the chemotherapy was not effective, he was started on oral gefitinib 250 mg/day on September 28, 2003. His symptoms dramatically improved along with the disappearance of the abnormal diffuse opacities on chest radiograph about two weeks later (Figure 3). On October 8, 2003, the abnormal accumulation of radioisotope in the bone scintigraphy findings had completely disappeared, along with a decrease of the growth hormone to 0.44 ng/ml (Figure 2B).

**Discussion**

Hypertrophic osteoarthropathy is a syndrome characterized by the triad of periostitis, digital clubbing and painful, swollen joints (2, 4). Bone involvement consists of periosteal new bone formation, mostly bilateral and symmetric, along the metadiaphyseal portions of the tubular bones of both the upper and lower extremities (2, 5). Bone scintigraphy is a highly sensitive method for the diagnosis of hypertrophic osteoarthropathy. The typical scintigraphic presentation is a diffuse, symmetrically increased uptake in the diaphysis and metaphysis of tubular bones, with a distinctive double stripe or parallel track sign (6). In this case, we confirmed the importance of bone scintigraphy to diagnose and monitor the reversibility of hypertrophic osteoarthropathy.

In the case of primary non-small cell lung cancer, clubbing and hypertrophic osteoarthropathy are presenting symptoms in 1% of all patients and, on careful review, 10% to 20% of all patients has various features of this disorder (1). Secondary hypertrophic osteoarthropathy is believed to be caused by a hormonal substance produced by the bronchial neoplasm. This substance has been suggested to be growth hormone (7), growth hormone-releasing hormone (8, 9), ACTH, beta MSH, calcitonin, gastrin, or a polypeptide related to the somatotrophins (10). Current knowledge supports that hypertrophic osteoarthropathy develops from the presence, in the systemic circulation, of one or more growth factors that are normally inactivated in the lungs. Recently, some cytokines, such as platelet-derived growth factor (11, 12) and vascular endothelial growth
factor (13), have been suggested to play an important role in the pathogenesis of hypertrophic osteoarthropathy. Hypoxia alone is not thought to be sufficient for the development of the syndrome. The present case, in which therapy with gefitinib showed normalization of the radionuclide uptake in the lower legs on bone scintigraphy and of the level of plasma growth hormone, suggests that growth hormone may cause secondary hypertrophic osteoarthropathy.

Gefitinib is an orally active, selective epidermal growth factor receptor tyrosine kinase (EGFR) inhibitor that blocks the signal transduction pathway implicated in the proliferation and survival of cancer cells (14). Although the mechanism is uncertain, the response rate was significantly higher in adenocarcinoma and female patients than in squamous cell carcinoma and male patients in a clinical trial with gefitinib for lung cancer (15). Further, the clinical effect is evident within the first few weeks if a sensitivity to gefitinib exists. Our observation suggests that the response in hypertrophic osteoarthropathy may be related to tumor cell death induced by gefitinib, subsequently reducing the level of plasma growth hormone.

In summary, we described a patient who was diagnosed with primary lung adenocarcinoma associated with secondary hypertrophic osteoarthropathy. Improvement of the osteoarthropathy, as well as primary lung lesions, occurred on administration of gefitinib as an EGFR inhibitor. These findings suggest that hypertrophic osteoarthropathy may be caused by primary lung cancer. To our knowledge, this is the first case in which gefitinib induced the successful treatment of secondary osteoarthropathy.

Figure 2. A. Bone scintigraphy showed a bilateral symmetrical and diffuse accumulation of radioisotope in the end of bone of the extremities. B. After treatment with gefitinib, the abnormal accumulation of radioisotope in the bone scintigraphy findings completely disappeared.
hypertrophic osteoarthropathy. The dramatic effect in our case indicates that gefitinib may be a promising option for hypertrophic osteoarthropathy occurring as a complication in advanced lung adenocarcinoma patients.

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