Hypertrophic Pulmonary Osteoarthropathy Associated with Non-small Cell Lung Cancer Demonstrated Growth Hormone-Releasing Hormone by Immunohistochemical Analysis


Abstract

Hypertrophic pulmonary osteoarthropathy (HPO) associated with non-small cell lung cancer in a 58-year-old man was accompanied by an elevated serum level of growth hormone (GH). HPO rapidly disappeared after resection of the primary tumor and the elevation of serum GH was resolved. Immunohistochemically the tumor contained growth hormone-releasing hormone (GHRH) but not GH. These findings suggest that the high serum GH level due to ectopic GHRH production in the tumor, was a contributing factor in HPO. This is the second reported case of non-small cell lung cancer which was immunohistochemically positive for GHRH associated with HPO.

Key words: growth hormone, clubbed fingers, bone scintigraphy

Introduction

Hypertrophic pulmonary osteoarthropathy (HPO) is a clinical syndrome presenting with osteitis of the long bones, arthritis, and clubbing of the fingers and toes. It is usually associated with lung cancer or other chronic pulmonary or pleural diseases. It has been found in about 3–10% of patients who have lung cancer (1, 2). The exact etiology of HPO in patients with lung cancer remains uncertain, however, vagal nerve stimulation or endocrine substances produced by tumors, such as estrogen, ACTH, GH and other vasodilative substances may be factors. To our knowledge, this is the second reported case of non-small cell lung cancer which was immunohistochemically positive for GHRH and showed high serum level of GH associated with HPO.

Case Report

A 58-year-old man was admitted to our hospital in March 1999 with chief complaints of two months of cough productive for hemoptysis and right pleuritic pain. Ten months before admission, he suffered severe arthralgia of both extremities and ankles. He was maintained on indomethacin therapy for relief of pain. Five months before admission, he developed clubbing of the fingers and toes. Medical history was unremarkable. He had smoked about one pack of cigarettes a day for the past 40 years. Physical examination on admission confirmed the bilateral swelling of legs and clubbing of the fingers (Fig. 1) and toes with a marked pretibial pain on palpation, but there was no acromegaly in his facial features. Lymphadenopathy and gynecomastia were not found. Initial investigation revealed an elevated serum level of alkaline phosphatase at 342 IU/l (normal range, 75–230 IU/l), C-reactive protein of 2.79 mg/dl (normal range, <0.40 mg/dl) and carcinoembryonic antigen of 5.6 ng/ml (normal range, 0.0–5.0 ng/ml). The fasting blood glucose level was 90 mg/dl and hemoglobin Alc level was 6.0% (normal range, 4.3–5.8%). The fasting serum GH level 0.74 ng/ml (normal range, 0.03–0.42 ng/ml) and all other serum hormone levels, including ACTH, antidiuretic hormone, parathyroid hormone, prolactin and human chorionic gonadotropin were within normal range. Anti-nuclear antibody, rheumatoid arthritis particle agglutination and transforming growth factor-β1 were negative.

Chest roentgenography and chest computed tomographic scan showed a mass lesion (6 cm in diameter) in the right upper lobe (Fig. 2A, B). Mediastinal, hilar lymphadenopathy and distant metastasis were not found. Bronchoscopic findings revealed complete obstruction at the orifice of the right B2 caused by tumor. A biopsy specimen confirmed the diagnosis of adenocarcinoma. The clinical TMN classification was T2 N0 M0, stage IB. Bone scintigraphy showed a pericortical concentration along the femoral and tibial shafts and ankles (Fig. 3 left).
Roentgenography of the tibia and fibula demonstrated subperiosteal proliferation. MRI of the pituitary gland did not show pituitary adenoma or hyperplasia.

Right upper lobectomy combined with mediastinal and hilar lymph node dissection was performed. Swelling and arthralgia of the lower extremities disappeared within a few days after operation, and the serum level of GH and hemoglobin A1c fell to the normal range. Bone scintigraphy showed nearly complete resolution of the activity two months after operation (Fig. 3 right). However, X-ray examination showed that periosteal changes and clubbing of the fingers remained. Six months later, the patient had no evidence of relapse.

At pathologic examination of the resected specimen, the tumor was well-demarcated and composed of well differentiated adenocarcinoma components showing papillary growth and undifferentiated components comprising round to oval shaped neoplastic cells with prominent nucleoli (Fig. 4A). Massive tumor necrosis and hemorrhage were intermingled in the lesion but no pleural invasion was seen. Neither osteoid, cartilage nor rhabdoid cells was found in the tumor. By immunohistochemical staining using the avidin-biotin complex method and diaminobenzidine as a chromogen, anti-alpha-sarcomeric actin (DAKO, Carpinteria, CA, USA), myoglobin (Nichirei, Tokyo), alpha-smooth muscle actin (DAKO) antibodies were negative in the tumor. So we diagnosed the lesion as not true carcinosarcoma but well differentiated adenocarcinoma with undifferentiated components. Immunohistochemical staining with anti-GH antibody (DAKO) was entirely negative in the tumor but that with anti-GHRH (Biogenesis Inc., Kingston, NH, USA) was positive in the undifferentiated components (Fig. 4B).

Discussion

About 80% of pulmonary lesions associated with HPO are lung cancers, pleural tumors make up 10%, and a miscellaneous group of intrathoracic malignancies account for 5% (2). Chronic suppurative pulmonary inflammatory disease and congenital cyanotic heart disease are non-malignant causes of HPO contributing to the remainder. HPO is usually detected before or at the time of diagnosis of the underlying disease, but occasionally is manifested years later. In this case, symptoms predated the diagnosis of primary lung cancer by ten months.

The appearance of radionuclide bone images are correlated...
with clinical signs and symptoms. Radionuclide studies are more sensitive than radiography in the detection of HPO (3–5). In the present case, the postoperative activity of bone scintigraphy in the area of HPO diminished markedly. However, radiographs still showed periosteal changes. This indicates that dynamic changes occurring in the bones are monitored more precisely by bone scintigraphy than by anatomical changes seen on the radiographs.

The pathogenesis of HPO is not fully understood. Opinions are divided between neurogenic and humoral mechanisms, though both could be simultaneously active (6). Responsible hormones are not entirely evident. Growth hormone produced by pulmonary tumors has also been implicated occasionally (7–10). Steiner and associates reported a patient who had typical osteoarthropathy, adenocarcinoma and high plasma GH levels (7). They found that the high level of GH returned to normal after resection of the tumor and that the patient had relief of clinical symptoms. Dupont et al reported that malignant tumor cells might be able to synthesize and secrete GH or GH-like substances (8). It is confirmed that lung tumor cells are capable of synthesizing immunoreactive GH. On the other hand, Beck and Burger claimed that plasma GH levels were labile and might become elevated in many different conditions and added that it was difficult to ascribe the pathogenic role to GH in HPO (9). Ectopic production of GH has been suggested as the cause of HPO associated with lung cancer, but there has only been one previous report of non-small cell lung cancer which was immunohistochemically positive for GHRH associated with HPO (10).

The present case had an elevated serum level of GH which was confirmed by immunohistochemical analysis of GHRH in the primary lesion. The high level of GH returned to normal after resection of the tumor, and the pain and swelling rapidly disappeared within a few days after operation. These findings suggest that the ectopically produced GHRH in the tumor stimulated secretion of GH from the pituitary body and that GH was
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a contributing factor in HPO. We did not recognize symptoms associated with the presence of high GH level except for HPO and mild abnormal glucose tolerance in the present patient. Several investigators report that not all patients with HPO have high GH levels, and the presence of high GH levels does not always lead to clinically detectable effects, such as HPO (9). It is therefore concluded that GH and GHRH can be some of the factors responsible for HPO in non-small cell lung cancer.

References