Hypercalcemia Induced by Parathyroid Hormone-related Protein from Lung Cancer Tissue*

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Most lung carcinomas with hypercalcemia are usually unresectable. However, this case was resectable and the serum calcium level was normalized after the operation. Messenger RNA of the precursor of PTH-related protein (PTHrP), a substance that may be one of the causes of hypercalcemia in malignant neoplasms, was identified in the tumor tissue of the patient. The patient was a 60-year-old man with squamous cell carcinoma originating from the posterior basal segment of the left lung and invading the main bronchus and left atrium. The serum calcium level was 14.3 mg/dl, preoperatively. Pneumonectomy with partial left atrium resection was carried out and the serum calcium level became normal postoperatively. Three months following the operation, this measurement was 9.4 mg/dl, but increased to 16.2 mg/dl at four months, at which time he experienced lumbago and chest pain. The patient died eight months following the operation from uncontrollable renal failure. In the tumor tissue, mRNA of PTHrP precursor was identified. To our knowledge, this is the first case of lung cancer that could be resected, and in which PTHrP was found present. (Chest 1991; 100:1451-53)

mRNA = messenger RNA; PTH = parathyroid hormone; PTHrP = PTH-related protein

Studies on the pathogenesis of hypercalcemia in patients with malignant tumors without bone metastasis direct attention at humoral factors such as ectopic parathyroid hormone (PTH), vitamin D metabolites, prostaglandins, transforming growth factors, interleukin 1, and PTH-related protein (PTHrP). Among these, PTHrP is one of the substances most likely responsible for this condition.

This article presents a case of hypercalcemia in a patient with lung cancer in which PTHrP mRNA was found present in the tumor tissue.

CASE REPORT

A 60-year-old Japanese man consulted his personal physician on April 27, 1985, because of a dry cough that had persisted for some months. A lesion of 6.5 x 7.0 cm in diameter was observed on his chest roentgenogram. A bronchogenic carcinoma was detected by fiberscopic biopsy in the lower lobe of the left lung. He was consequently transferred to Nagoya City University Hospital for further examination and treatment on May 16, 1985. At the time of hospital admission, the patient was emaciated with severe dehydration and anorexia. Body weight was 43 kg and height was 158 cm; laboratory data indicated hypercalcemia by as much as 14.3 mg/dl. Serum phosphate level was 2.7 mg/dl and calcitonin level was 16 pg/ml. However, serum PTH level determined by C-terminus radioimmunoassay was below 0.1 ng/ml. Urinary specific gravity was high at 1.026 and increased sodium, chloride, and calcium levels were evident.

The primary tumor originated from the posterior basal segment of the left lung (Fig 1) and invaded surrounding tissues such as main bronchus and left atrium. No abnormality except subperiosteal absorption of the finger tips could be found by plain roentgenographic examination of the bone. A bone scintigram failed to indicate any metastatic regions. The serum calcium level was reduced to 11.7 mg/dl by fluid transfusion and calcitonin administration preoperatively. Left pneumonectomy with partial resection of left atrium was conducted on June 11. The histologic diagnosis was moderately differentiated squamous cell carcinoma with regional lymph node metastasis. The serum calcium level resumed its normal value immediately following removal of the tumor tissue.

The postoperative course of the patient was uneventful up until December 1985. He experienced severe pain in his chest wall and lower back in January 1986. Serum calcium level was elevated to 16.2 mg/dl. The patient died February 11, 1986, due to uncontrollable renal failure resulting from hypercalcemia brought on by tumor regrowth (Fig 2).

ANALYSIS OF PTHrP mRNA

The procedure and analytical results have been reported
in detail elsewhere by Honda and coworkers. The results are thus given briefly here. Poly (A) RNA was extracted from the tumor tissue that had been stored at -80°C until assay. Agarose-formaldehyde gel electrophoresis and Northern blot hybridization were conducted as described previously. A 60-base oligodeoxyribonucleotide corresponding to the amino-terminal 20 amino acids of the PTHrP precursor was labeled with (γ-32P) ATP and used as the probe to identify PTHrP mRNA. Two or more hybridizing species corresponding to human PTHrP mRNA were detected in this preparation as also in the other RNA samples prepared from tumor tissues obtained from patients with hypercalcemia.

**DISCUSSION**

Stewart et al. reported a protein other than PTH capable of binding to the PTH receptor of the target cell membrane and designated it as a PTH-like substance in 1980. This molecule was first isolated by Suva et al. from the conditioned medium of a squamous cell lung carcinoma cell line established from the tumor tissue of a patient with hypercalcemia without bone metastasis. Two other groups studied purified identical proteins. It was found to possess 141 amino acid sequences in the molecular weight range of 17,000, according to analysis of the full length of cDNA encoding PTHrP.

Hypercalcemia is not rarely observed in patients with advanced malignant disease. It has also been found in some patients without bone metastasis. Studies on various pathogeneses of hypercalcemia have directed attention to humoral factors arising from the malignant tumor tissue itself. Among various humoral factors, including cytokines, PTHrP has been found to be one of the substances most likely responsible for this condition.

Squamous cell carcinoma is the most frequent type of lung cancer in patients having hypercalcemia. Radical resection is often difficult because of its location and growth characteristics. Coganshah et al. could not perform this operation on any of 67 patients with hypercalcemia. To date, they have reported only four resected cases, two cases of which did not show recurrent sign for 12th and 18th months following resection, respectively. Lately, Shigebara et al. reported a case of lung carcinoma accompanied by hypercalcemia in a patient who had lived for 26 months following resection.

The present patient gave no indication of hypercalcemia for four months following resection of the cancer tissue. Severe hypercalcemia following its recurrence could not be controlled. This may possibly be an indication of hypercalcemia induced by a humoral factor from the tumor tissue and in which PTHrP may be present.

Patients with humoral hypercalcemia of malignancy have more rapid progression of disease than those without this condition. Although the growth-promoting activity of PTHrP in tumor tissue has not been confirmed to date, PTHrP has recently been reported to possess transforming growth factor-like activity. Many malignant tumors secrete multiple cytokines along with various growth factors. Further study should be made to clarify completely the biologic role of PTHrP.

**REFERENCES**

Extrapulmonary Thoracic Restriction (Hidebound Chest) Complicating Eosinophilic Fasciitis*

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Eosinophilic fasciitis (EF) is an unusual disorder characterized by diffuse skin thickening and induration due to inflammation within the deep fascia; visceral involvement is generally mild or absent. A patient with biopsy-proven EF developed progressive respiratory limitation. Physical examination revealed marked induration of the thoracic integument with a severely limited chest wall excursion. Total lung capacity was 62 percent of predicted with a normal corrected Dco and maximal inspiratory force; a chest computed tomogram with thin sections showed no evidence of parenchymal lung disease. Extrapulmonary thoracic restriction (“hidebound chest”) has not been previously reported to complicate EF.

(CHEST 1991; 100:1453-55)

Since its initial description in 1974, more than 200 cases of eosinophilic fasciitis (EF) have been reported. The syndrome consists of symmetric thickening of the deep fascia between muscle and subcutis of the arms, legs, and torso, with full-thickness skin biopsy specimens typically showing a normal epidermis and an inflammatory infiltrate in the deep fascia. EF is notable for its lack of visceral involvement, and pulmonary complications of EF have only rarely been reported.

Extrapulmonary thoracic restriction not due to respiratory muscle weakness occurs following thoracic skin burns, in advanced ankylosing spondylitis, and in severe kyphoscoliosis; however, it has not been previously demonstrated in the setting of EF. We present herein a patient who developed progressive dyspnea and extrapulmonary thoracic restriction due to chest wall involvement by EF.

Case Report

A 71-year-old man was well until October 1988 when he noted progressive aching and stiffness in his shoulders and upper arms followed by the development of diffuse upper and then lower extremity swelling. He consulted a physician who noted tense brawny edema, primarily of the lower extremities. Laboratory studies showed a normal complete blood cell count (CBC) and leukocyte differential; the serum albumin, liver function tests, urinalysis, and electrocardiogram were also normal. An echocardiogram demonstrated normal left ventricular ejection fraction of 68 percent. Right heart catheterization revealed normal pressures and cardiac output.

The patient was initially treated with diuretics with some improvement, but over the next several months, he noted progressive dyspnea in addition to thickening and hardening of the skin of the upper and lower extremities and trunk. In June 1989, he underwent a full-thickness skin biopsy of the posterior calf (Fig 1). The biopsy specimen showed a normal epidermis, a reticular dermis thickened by increased collagen deposition, mild perivascular inflammation, and an intense inflammatory infiltrate within a markedly thickened deep fascial layer. Mild inflammation of the muscle layer with focal muscle atrophy was also noted. The patient’s clinical and pathologic picture was considered diagnostic of EF and he was begun on a regimen of prednisone (up to 80 mg/day); however, his symptoms worsened and he was referred to University Hospital.

His major complaint on presentation to University Hospital was progressive dyspnea on exertion. One year prior to hospital admission, he had no respiratory limitations; however, he was now dyspneic after walking 300 cm. He denied other pulmonary or cardiac symptoms. There was no history of weight loss, Raynaud’s phenomenon, heartburn, proximal muscle weakness, or ingestion of L-tryptophan. He had a 40 pack-year smoking history, but had stopped ten years prior.

Physical examination revealed a well-nourished man with a respiratory rate of 18 that increased with transfer from chair to bed. Temperature, blood pressure, heart rate, and jugular venous pressure were normal. Lungs had decreased air movement but were otherwise clear. Circumferential chest wall measurements with maximal exhalation/inspiration were 108/108.8 cm at nipple level and 108/108.5 cm at xyphoid level. Findings from cardiac, abdominal, and neurologic examinations were normal. Skin examination was remarkable for diffuse skin thickening with a “peau d’orange” appearance (Fig 2) especially marked on the upper arms.

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