CASE REPORT

Hypercalcemia Caused by PTH-rP Associated with Lung Metastasis from Urinary Bladder Carcinoma: An Autopsied Case

Tetsuya Yoshida, Junji Suzumiya, Hideki Katakami*, Nobuhiro Kimura, Shusuke Hisano, Masahiro Kikuchi** and Makoto Okumura

We analyzed the parathyroid-related protein (PTH-rP) content in tissue specimens obtained from a 61-year-old man with hypercalcemia associated with lung metastasis from urinary bladder carcinoma using radioimmunoassay and immunohistochemistry. Radioimmunoassay showed that the PTH-rP content was higher in metastatic lung tumor tissue than in non-tumorous lung tissue. Immunohistochemical analysis revealed the presence of PTH-rP in tumor cells. Furthermore, proliferation of osteoclasts was found in bone marrow at autopsy. The results suggest that PTH-rP induced humoral hypercalcemia of malignancy in a patient with urinary bladder cancer.

(Internal Medicine 33: 673-676, 1994)

Key words: humoral hypercalcemia of malignancy, metastatic tumor

Introduction

The hypercalcemia of malignancy may be classified as either humoral hypercalcemia of malignancy (HHM) or local osteolytic hypercalcemia, depending on the etiology. Since Albright first proposed the clinical criteria for diagnosis of HHM (1), a number of factors that contribute to HHM, including parathyroid-related protein (PTH-rP), transforming growth factors, prostaglandin E2, interleukin-1, tumor necrosis factor (TNF)-α and TNF-β have been identified (2-6).

PTH-rP contributes to the hypercalcemia found in patients with lung cancer (7), breast cancer, renal cancer (8), myeloma, and adult T-cell leukemia (9). The NH2-terminal regions of PTH-rP and parathyroid hormone are homologous (8, 10, 11). Both proteins, which have 34-amino acid NH2-terminals, have similar effects on renal and osteoblast cell membranes in vitro and on calcium and inorganic phosphate flux in vivo (12-14).

We performed an autopsy in a patient who died of lung metastasis from urinary bladder carcinoma associated with hypercalcemia and investigated the presence of PTH-rP in cancer cells using radioimmunoassay (RIA) (15) and immunohistochemical studies.

Case Report

A 61-year-old Japanese man developed macrohematuria in March 1989. A cytoscopy revealed a tumor in the urinary bladder, which was histologically diagnosed as transitional cell carcinoma. In January 1990, he underwent total cystectomy. In October 1990, he complained of coughing and exertional dyspnea. A chest roentgenogram showed multiple tumors in the right lung field. A bronchofibroscopic examination showed that the bronchus of the right upper lobe was completely obstructed. A biopsy confirmed the presence of a pulmonary metastasis of transitional cell carcinoma of the urinary bladder. He underwent radiation therapy in November 1990. Radiation therapy (total 60 Gray) was administered to the right upper lung field. Radiation therapy improved atelectasis of the right upper lobe and eliminated the obstruction of the right upper bronchus. The patient was referred to our hospital on November 7, 1992 for evaluation of dyspnea on exertion and fever. On admission, his temperature was 37.5°C, pulse rate 90/min, respiratory rate 18/min, and blood pressure 122/60 mmHg. His performance status was grade 3. Physical examination revealed no masses in the head or neck, but respiratory sounds were diminished throughout the right lung field, and high pitched rales were audible in the left upper lung field.
Complete blood counts showed a red blood cell count of 400 x 10^4/μl, hemoglobin 11.9 g/dl, white blood cell count 14,200/μl, with 8% band form neutrophils, 81.5% segmented polymorphonuclear cells, 0% eosinophils, 6% monocytes, and 4.5% lymphocytes, and a platelet count of 26.6 x 10^4/μl. His erythrocyte sedimentation rate was 145 mm/hr. Serum calcium corrected by serum albumin measurements was 12.0 mg/dl (normal 8.5 to 10.2), and serum phosphatase was 2.9 mg/dl (normal 2.5 to 4.5). Hypercalciuria was present (urine calcium 770 mg/day; normal 100 to 250). Blood urea nitrogen was 14 mg/dl (normal 4 to 20), serum creatinine 0.9 mg/dl (normal 0.3 to 1.0), endogenous creatinine clearance was 72 ml/min (normal 62 to 108), and serum alkaline phosphatase was 140 IU/l (normal 90 to 230). Other biochemical parameters were within normal ranges. Oxygen saturation was 93.4%, arterial oxygen tension 62.4 mmHg, arterial carbon dioxide tension 44.5 mmHg, bicarbonate 34.0 mmol/l, base excess +9.4, pH 7.49, and serum chloride was 100 mEq/l (normal 98 to 108). The serum hypersensitive-parathyroid hormone (HS-PTH) level was 408 pg/ml (normal 180 to 560). Measures of thyroid and pituitary function were within normal limits. Uribalysis showed a specific gravity of 1.014. Tests for glucose and protein were negative and there were no casts. Several tumor markers were elevated, including B2-microglobulin (3.1 mg/l; normal 0.5 to 2.0), immunosuppressive acidic protein (1,100 μg/l; normal <500), squamous cell carcinoma antigen (13.4 ng/ml; normal <1.5), and tissue polypeptide antigen (>1,500 U/l; normal <110), but carcinoembryonic antigen and α-fetoprotein were within normal limits. A chest roentgenogram showed atelectasis of the right middle and lower lobes and an ill-defined tumor in the right upper lobe. A bronchofibroscopic examination confirmed that incomplete obstruction of the right main bronchus was caused by a metastatic tumor. After the patient was hospitalized, the corrected serum calcium level gradually rose to 19.2 mg/dl, and 24-hour urinary calcium excretion increased to 920 mg. Corrected serum calcium, serum phosphate and serum HS-PTH levels during this period are summarized in Table 1. Despite administration of large amounts of normal saline, furosemide, calcitonin (<40 to 160 U/day) and prednisolone (20 to 60 mg/day), the corrected serum calcium level continued to increase. The patient developed cardiac failure after receiving a large amount of isotonic saline for treatment of hypercalcemia. On December 2, 1991, he suddenly became apneic due to misswallowing. A tracheostomy was performed and the patient was maintained on a respirator until his death. He eventually developed renal failure caused by hypercalcemia and respiratory failure. He died on March 14, 1992.

Autopsy was performed 12 hours after death. The right upper lung was occupied by a whitish-gray tumor showing necrosis. Histological examination of a specimen from the lung tumor showed nests of transitional cell carcinoma in the necrotized tissue. Visceral involvement was observed in the right pleura, the diaphragm, the left adrenal gland and the right hilar lymph nodes. No metastatic lesions were detected in vertebral bones or in the sternum. Histological examination showed hypocellular bone marrow. Partial proliferation of osteoclasts was observed (Fig. 1). Metastatic calcification was observed in the kidneys, lungs and pancreas. The parathyroid glands showed no hyperplastic changes or tumor formation. Foreign body granulomata resulting from food residue were observed in both lungs, indicating aspiration pneumonia.

Materials and Methods

Specimens of the metastatic lung tumor from the right upper lobe and of lung tissue free of tumor involvement from the left lobe were immediately frozen at -80°C until assay. The PTH-rP content in the patient’s serum and in the tumorous and non-tumorous lung tissue was measured by RIA using a specific antibody for PTH-rP according to a previously described method (15). Anti-PTH-rP rabbit serum was raised against synthetic PTH-rP-[1-34] (Peninsula Laboratories, Belmont, CA, USA) conjugated with bovine serum albumin according to a previously described method (16). The PTH-rP antibody has no significant cross-reactivity with human PTH-[1-34] or PTH-[1-84] (15). Synthetic PTH-rP-[1-34] was used as the standard. The specimen of metastatic lung tumor was examined immunohistochemically using the avidin-biotin complex method (Vectorstain; Vector Laboratories, Burlingame, CA, USA) according to the manufacturer’s instructions.

Results

Analysis of serum showed hypercalcemia and a PTH-rP...
level of 38 pg/ml (normal <16 pg/ml). The PTH-rP tissue content was 107 ng/g wet weight in the metastatic tumor specimen and 589 pg/g wet weight in the specimen without tumor involvement.

Immunohistochemical analysis showed a positive reaction for the antibody specific for PTH-rP in transitional cancer cells (Fig. 2).

Discussion

A variety of mechanisms are involved in the pathogenesis of hypercalcemia associated with malignancies (3), especially when carcinomas of the breast, lung or pancreas, metastasize to bone. Osteolysis may be caused by direct tumor invasion of bone or by the production of factors that act locally to produce bone resorption, such as prostaglandins and/or osteoclast-activating factor. However, many patients with hypercalcemia associated with malignancy show no bony destruction caused by a metastatic tumor.

The serum PTH levels have been reported to be low or low normal in HHM because the high serum calcium levels in HHM usually suppress PTH release from the normal parathyroid gland via the negative feedback mechanism. In the present case, despite the presence of hypercalcemia of malignancy, serum levels of PTH were not suppressed when assessed by the HS-PTH RIA which recognized a mid-region of PTH molecule. Excretion of a mid-region fragment of PTH from general circulation is decreased by impaired renal function. Although the exact mechanisms causing the HS-PTH elevation in the present case are unknown, the reason why the serum level of HS-PTH was not suppressed in the present patient might be caused by a decreased renal function which was associated with the terminal stage of the disease. The other possibility is that the HS-PTH RIA used in the present study might cross-react with the undetermined substance or substances which were produced from the bladder cancer.

It is also possible that tumor-producing substances exert a systemic action on bone, stimulating osteoclastic resorption even in the absence of bone metastasis. The exact nature of most of these substances remains uncertain, but PTH-rP has been found to induce hypercalcemia in association with some malignant tumors (17–19).

Hypercalcemia of malignancy is commonly observed in patients with breast cancer, lung cancer and renal cancer (3), and there have been some reports of cases of HHM associated with bladder carcinoma, including 11 patients with squamous cell carcinoma (20–30), 6 with transitional cell carcinoma (26, 28, 31–33), 2 with mixed transitional and squamous cell carcinoma (26), 1 with spindle and giant cell carcinoma (34), 2 with small cell carcinoma (35) and 4 with unspecified malignant tumors (36–38). However, those reports did not provide PTH-rP measurements or discuss its association with HHM. Goddall and his colleagues (39) detected elevated levels of nephrogenic cyclic adenosine monophosphate in 6 patients with bladder cancer with HHM and suggested that HHM was induced by PTH-like cytochemical bioactivity.

Autopsy findings in the present patient revealed proliferation of osteoclasts in bone marrow but no bone metastasis. The serum PTH level was normal. These findings indicated that hypercalcemia was produced by a humoral factor. The serum PTH-rP level was elevated after hypercalcemia developed. The PTH-rP content was about 200 times higher in metastatic lung tumor tissue than in non-tumorous lung tissue. RIA and immunohistochemistry showed that PTH-rP was produced by urinary bladder cancer cells. The present findings suggest that PTH-rP induces HHM in patients with urinary bladder cancer, as it does in patients with solid tumors and hematolymphoid malignancies (7–11).

Acknowledgments: The authors thank Ms. Midori Sugihara for her excellent immunohistochemical technique.

References

5) Dewhirst FE, Stashenko PP, Mole JE, Tsurumachi T. Prostaglandins and/ or osteoclast-activating factor. However, many patients with hypercalcemia associated with malignancy show no bony destruction caused by a metastatic tumor.

The serum PTH levels have been reported to be low or low normal in HHM because the high serum calcium levels in HHM usually suppress PTH release from the normal parathyroid gland via the negative feedback mechanism. In the present case, despite the presence of hypercalcemia of malignancy, serum levels of PTH were not suppressed when assessed by the HS-PTH RIA which recognized a mid-region of PTH molecule. Excretion of a mid-region fragment of PTH from general circulation is decreased by impaired renal function. Although the exact mechanisms causing the HS-PTH elevation in the present case are unknown, the reason why the serum level of HS-PTH was not suppressed in the present patient might be caused by a decreased renal function which was associated with the terminal stage of the disease. The other possibility is that the HS-PTH RIA used in the present study might cross-react with the undetermined substance or substances which were produced from the bladder cancer.

It is also possible that tumor-producing substances exert a systemic action on bone, stimulating osteoclastic resorption even in the absence of bone metastasis. The exact nature of most of these substances remains uncertain, but PTH-rP has been found to induce hypercalcemia in association with some malignant tumors (17–19).

Hypercalcemia of malignancy is commonly observed in patients with breast cancer, lung cancer and renal cancer (3), and there have been some reports of cases of HHM associated with bladder carcinoma, including 11 patients with squamous cell carcinoma (20–30), 6 with transitional cell carcinoma (26, 28, 31–33), 2 with mixed transitional and squamous cell carcinoma (26), 1 with spindle and giant cell carcinoma (34), 2 with small cell carcinoma (35) and 4 with unspecified malignant tumors (36–38). However, those reports did not provide PTH-rP measurements or discuss its association with HHM. Goddall and his colleagues (39) detected elevated levels of nephrogenic cyclic adenosine monophosphate in 6 patients with bladder cancer with HHM and suggested that HHM was induced by PTH-like cytochemical bioactivity.

Autopsy findings in the present patient revealed proliferation of osteoclasts in bone marrow but no bone metastasis. The serum PTH level was normal. These findings indicated that hypercalcemia was produced by a humoral factor. The serum PTH-rP level was elevated after hypercalcemia developed. The PTH-rP content was about 200 times higher in metastatic lung tumor tissue than in non-tumorous lung tissue. RIA and immunohistochemistry showed that PTH-rP was produced by urinary bladder cancer cells. The present findings suggest that PTH-rP induces HHM in patients with urinary bladder cancer, as it does in patients with solid tumors and hematolymphoid malignancies (7–11).

Acknowledgments: The authors thank Ms. Midori Sugihara for her excellent immunohistochemical technique.

References


Fig. 2. Immunohistochemistry (×100). Positive reaction for PTH-rP was observed in the cytoplasm of tumor cells (arrows).


