



## Metastatic carcinoma of the prostate with hypercalcemia

JAY H. AVASHIA, MD; T. DECLAN WALSH, MSC; ANTHONY J. THOMAS JR., MD; MITCHELL KAYE, MD; ANGELO LICATA, MD, PHD

■ A patient presented with advanced cancer of the prostate and underwent bilateral orchiectomy. After 2 years, hypercalcemia developed and was managed successfully with saline diuresis, furosemide, and oral glucocorticoid therapy. It is believed that the patient's hypercalcemia was caused by a metabolic complication of progressive, advanced disease.

□ INDEX TERMS: CARCINOMA, PROSTATE; HYPERCALCEMIA □ CLEVE CLIN J MED 1990; 57:636-638.

**H**YPERCALCEMIA is a known manifestation of malignancy. Malignant tumors commonly associated with hypercalcemia are cancer of the lung and breast, multiple myeloma, and squamous carcinomas.<sup>1</sup> Despite its propensity for skeletal metastases, prostate cancer is rarely associated with hypercalcemia.<sup>2,3</sup> In a review of prostate cancer with skeletal metastases, Raskin and associates<sup>4</sup> encountered hypocalcemia in 31 patients but hypercalcemia in none. When hypercalcemia develops, it may be a preterminal event or an indication of tumor recurrence in a patient with known prostatic cancer.<sup>2,3</sup> We report a case in which this rare association occurred.

### CASE REPORT

A 71-year-old man sought advice for hematuria and difficulty in micturition in April 1986. A well-differen-

tiated adenocarcinoma of the prostate (Gleason's score 6, stage D<sub>2</sub>) with metastases to the lumbar spine was diagnosed. He underwent bilateral orchiectomy during the same month.

The patient did well until April 1988, when he complained of midlumbar, localized, nonradiating pain. The appearance of new osteosclerotic bone lesions in the 12th thoracic and third lumbar vertebrae on plain films documented disease progression. Serum prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA) levels were 13.9 ng/mL (normal, 0 to 3) and 107 ng/mL (normal, 0 to 10), respectively. Magnetic resonance imaging was negative for extradural spinal cord compression.

Palliative radiotherapy, 3,000 rads over 2 weeks, was administered to the spine between the 10th thoracic and fifth lumbar vertebrae. Pain control was maintained with continuous use of oral opioids.

In December 1988, the patient was admitted with severe constipation, nausea, anorexia, weight loss of 10 pounds in 3 weeks, and constant back pain. Physical examination revealed a confused, cachectic male. There was no band keratopathy. Reflexes were normal and bowel sounds were diminished.

The rest of the examination was normal except for an

From the Department of Hematology and Medical Oncology (J.H.A., A.J.T.), the Palliative Care Service (T.D.W.), the Department of Urology (M.K.), and the Department of Endocrinology (A.L.), The Cleveland Clinic Foundation.

Address reprint requests to T.D.W., director, Palliative Care Service, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195-5236.

enlarged, hard, nontender prostate. Radiographic examination showed progression of osteosclerotic metastatic bone disease. A bone scan revealed multiple sites of asymmetric uptake in the thoracolumbar spine, ribs, and pelvis consistent with widespread metastatic disease.

The PAP and PSA were elevated to 52 ng/mL and 1,356 ng/mL respectively. Serum calcium was 15.4 mg/dL (normal, 8.5 to 10.5); phosphorus, 3.4 mg/dL (normal, 2.5 to 4.5); and albumin, 3.4 g/dL. Other test results included a chloride to phosphorous ratio of 34; blood urea nitrogen (BUN), 61 mg/dL; creatinine, 2.4 mg/dL; alkaline phosphatase, 245 IU/L (normal, 40 to 110). Serum protein electrophoresis electrolytes and thyroid function tests were normal. Serum intact immunoreactive parathyroid hormone (iPTH) level was 13 PG/mL (normal, 10 to 60). The concentration of urinary cyclic AMP (expressed as mmol cyclic AMP/g of creatinine) was 2.6 (normal, 1.39 to 4.13).

The patient's hypercalcemia was treated with saline diuresis, furosemide, and an oral glucocorticoid (dexamethasone, 16 mg/d in divided doses). The serum calcium decreased to 10.2 mg/dL and the BUN and creatinine improved to 18 mg/dL and 1.2 mg/dL respectively within 5 days. However, his general condition continued to deteriorate and patient died on December 31, 1988.

At autopsy, multiple histologic bone sections confirmed the presence of widespread, moderately well-differentiated metastatic adenocarcinoma consistent with the prostatic origin. Mixed osteolytic and osteoblastic bone changes were seen. Kidney examination revealed bilateral dystrophic renal tubular calcification. Only one parathyroid gland could be identified, and it was histologically normal.

## DISCUSSION

Hypercalcemia is a rare complication of prostate cancer, despite the frequent association of prostate cancer with skeletal metastases. Hypercalcemia occurs in fewer than 1% of patients with prostate cancer metastatic to bone.<sup>3</sup>

### Humoral v direct-release mechanisms

The mechanism for hypercalcemia in prostate cancer is unknown. Of the 13 previously reported patients who had hypercalcemia associated with prostate cancer, 10 had extensive bone metastases. Four of these 10 had osteoblastic lesions and hypercalcemia, an unexpected association in view of the usual occurrence of hypocal-

cemia in this setting.<sup>3,4</sup>

Three of the 13 patients had hypercalcemia without any evidence of bone metastases. In these, one must postulate a paraneoplastic phenomenon mediated by humoral agents secreted by the neoplasm.

This mechanism contrasts with direct calcium release from bone secondary to osseous destruction. Ectopic production of PTH or PTH-like peptides, other osteoclastotropic peptides, prostaglandins and osteoclast-activating factor have been implicated.<sup>5-7</sup>

Another mechanism involves direct stimulation of osteolytic compounds in the bone by the neoplastic cells, leading to hypercalcemia. The relative frequency of the local osteolytic mechanism compared to the humoral mechanism is unclear.<sup>5</sup>

### Role of epidermal growth factor

Epidermal growth factor (EGF) is a powerful stimulator of osteoclastic bone resorption.<sup>8</sup> Fowler and associates, using immunohistochemical techniques, demonstrated increased levels of cytoplasmic epidermal growth factor in metastatic prostate cancer compared to localized cancer or benign prostatic hypertrophy<sup>8</sup>; they also found that an increased number of malignant cells stained for EGF after androgen deprivation.

Substances similar to EGF, produced by tumors associated with humoral hypercalcemia, are known as transforming growth factors.<sup>9</sup> Some transforming growth factors enhance the activity of  $\beta$ -EGF; while others competitively bind  $\alpha$ -EGF receptors.

A growth factor that acted specifically on MC3T3-E1 mouse osteoblasts was found in patients with prostatic cancer, but not in normal and benign hypertrophic prostates.<sup>10</sup> Platelet-derived growth factor (PDGF) may be expressed in hypercalcemic tumors but it probably plays only a synergistic role. Sitaras and colleagues<sup>11</sup> demonstrated the PDGF genes PDGF-1 and PDGF-2/SIS in human prostatic cancer cell lines DU-145 and PC-3.

Tumor mosaicism associated with ectopic hormone production has been reported in a patient with prostatic cancer and Cushing's syndrome; immunoperoxidase staining for adrenocorticotrophic hormone was limited to small, anaplastic cells admixed with adenocarcinoma.<sup>12</sup> Atypical tumor histological findings (anaplastic carcinoma or squamous differentiation) have been noted in prostate cancer and may relate to the apparent ectopic endocrine function manifested in these patients.<sup>5,13</sup>

### Metabolic complication

In the present case, hypercalcemia (uncorrected

serum calcium 15.4 mg/dL) was a preterminal metabolic complication of progressive, advanced disease. Normal levels of PTH and urinary cyclic AMP despite concomitant significant hypercalcemia rule out primary hyperparathyroidism. These findings suggest the possible production of an osteolytic compound other than parathyroid hormone by the neoplastic cells. Clinical

clues related to other possible causes were absent.

Extensive metastatic disease to bone was identified at autopsy. There was no evidence of abnormal histological differentiation in either the primary or the metastatic tumor sites. The absence of causes other than disseminated skeletal metastases suggests that the raised calcium level was secondary to metastatic bone disease.

REFERENCES.

1. Omenn GS, Roth SI, and Baker WH. Hyperparathyroidism associated with malignant tumors of nonparathyroid origin. *Cancer* 1969; **24**:1004-1011.
2. Olsson AM, JB(1r GCBXBunant disease. *Am J Med* 1974; **56**:821-826.
7. Powell D, Singer FR, Murray TM, Minckin C, Potts JT Jr. Nonparathyroid humoral hypercalcemia in patients with neoplastic diseases. *N Engl J Med* 1973; **289**:176-181.
8. Fowler JE Jr, Lau JLT, Ghosh L, Mills SE, Mounzer A. Epidermal growth factor and prostatic carcinoma: an immunohistochemical study. *J Urol* 1988; **139**(4):857-861.
9. Mundy GR, Ibbotson KJ, D'Souza SM. Tumor products and the hypercalcemia of malignancy. *J Clin Invest* 1985 **76**:391-394.
10. Nishi N, Matuo Y, Kunitomi K, et al. Comparative analysis of growth factors in normal and pathologic human prostates. *Prostate* 1988; **13**(1):39-48.
11. Sitaras NM, Sariban E, Bravo M, Pantazis P, Antoniadis HN. Constitutive production of platelet-derived growth factor-like proteins by human prostate carcinoma cell lines. *Cancer Res* 1988; **48**(7):1930-1935.
12. Vuitch MF, Mendelsohn G. Relationship of ectopic ACTH production to tumor differentiation: a morphologic and immunohistochemical study of prostatic carcinoma with Cushing's syndrome. *Cancer* 1981; **47**:296-299.
13. Mahadevia PS, Ramaswamy A, Greenwald ES, Wollner DI, Markham D. Hypercalcemia in prostatic carcinoma—report of eight cases. *Arch Intern Med* 1983; **143**:1339-1342.

