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Successful Management of Humoral Hypercalcemia of Malignancy in A Patient with Ovarian Cancer

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We present here successful treatment with bisphosphonate pamidronate of a 54-year-old patient with advanced ovarian cancer and humoral hypercalcemia of malignancy, followed by cytoreductive surgery and postoperative chemotherapy. Concentration of serum calcium increased to 16.8 mg/dL and parathyroid hormone-related protein (PTHrP)-intact was remarkably elevated. Interestingly, the 1,25-dihydroxyvitamin D (1,25-DHD) was high in this case. Treatment with bisphosphonate pamidronate was effective for the improvement of hypercalcemia so that she could undergo optimal surgery followed by postoperative chemotherapy. The histochemical examination of PTHrP using anti-human monoclonal antibody showed positive staining in the cancer cells of the ovary.

Key words: bisphosphonate pamidronate; humoral hypercalcemia of malignancy; parathyroid hormone-related protein

Hypercalcemia is frequently associated with malignancy, and is often a major contributor to morbidity and complicates clinical management (Allan et al., 1984; Fujino et al., 1992). Humoral hypercalcemia of malignancy (HHM) is defined as hypercalcemia in malignant tumor patients without bone metastasis (Martin et al., 1991). Parathyroid hormone-related protein (PTHrP) is one main causative substance for HHM. HHM is commonly found in squamous cell carcinoma, renal cell carcinoma, and hematopoietic malignancies (Honda et al., 1988; Kitazawa et al., 1991; Gotoh et al., 1993). There are a few reports of HHM in patients with ovarian cancer (Kitazawa et al., 1997).

Bisphosphonate pamidronate strongly inhibits bone resorption, probably by exerting a cytotoxic effect on mature osteoclasts and impairing recruitment and maturation of osteoclast-precursor cells (Thiebaud et al., 1990). This agent has been considered effective for HHM, but there are few reports on the efficacy of HHM with ovarian cancer. Serum dihydroxyvitamin D (1,25-DHD) concentrations are commonly low in patients with HHM. However, the concentration of 1,25-DHD was high in this case.

We present an ovarian adenocarcinoma patient with HHM who underwent successful management with bisphosphonate pamidronate. Additionally, PTHrP metabolism including 1,25-DHD was investigated.

Patient Report

A 54-year-old postmenopausal woman, gravida 0, presented herself to Tottori University Hospital on August 30, 1995. She had a 4-week history of lower abdominal pain, constipation, nausea, general malaise and a loss of weight of 5 kg. Upon presentation, her weight was 43 kg, height, 148 cm, pulse rate, 72 beats/min and regular, and blood pressure, 106/70 mmHg. A

Abbreviations: DHD, dihydroxyvitamin D; HHM, humoral hypercalcemia of malignancy; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; TGF, transforming growth factor

Table 1. Biochemical data of bone and mineral metabolism before therapy

Laboratory findings			Measured values	Normal values
Serum	Calcium	(mg/dL)	16.8	8.6 – 11
	Phosphate	(mg/dL)	1.1	3 – 5
	Creatinine	(mg/dL)	0.7	0.6 – 1.6
	Alkaline phosphatase	(IU/L)	259	111– 295
	Alkaline phosphatase isozyme 3	(%)	28	29 – 62
	Osteocalcin	(ng/mL)	4.9	2.5 – 13
	PTH-intact	(pg/mL)	< 2.0	6.5 – 59.7
	PTHrP-intact	(pmol/L)	10	< 1.1
	1,25-DHD	(pg/mL)	104	20 – 60
	25-Hydroxyvitamin D	(ng/mL)	10	10 – 55
	24,25-DHD	(ng/mL)	1.2	1.8 – 3.8
Urine	Calcium	(mg/dL)	21.3	5.3 – 30
	Phosphate	(g/day)	0.72	0.3 – 2.2
	Nephrogeneous cyclic AMP	(μmol/day)	4.8	1.8 – 6.3
	Pyridinoline	(μmol/molCr)	120	13 – 36
	Deoxypyridinoline	(μmol/molCr)	16	< 7

DHD, dihydroxyvitamin D; PTH, parathyroid hormone; PTHrP, PTH-related protein.

solid ovarian tumor with a diameter of 8 cm in its greatest dimension revealed by computed tomography was observed in the lower abdomen. Serum levels of CA125 and small cell cancer were slightly elevated to 120 U/mL (normal range < 35 U/mL) and 1.7 ng/mL (normal range < 1.5 ng/mL), respectively. The serum calcium concentration increased to 16.8 mg/dL. Biochemical examination revealed that her urinary calcium excretion, cyclic AMP, alcohol dehydrogenase and free T_3 were within normal ranges, but that the serum phosphate extremely decreased and the 1,25-DHD increased to 104 pg/mL. PTHrP-intact was elevated to 10.0 pmol/L (PTHrP C-terminal 442 pg/mL). On the other hand, parathyroid hormone (PTH)-intact fell to < 2.0 pg/mL, (PTH C-terminal < 0.6 ng/mL). Biochemical data are shown in Table 1. The bone mineral density of the spine measured by dual energy X-ray absorptiometry was in the normal range. Whole body computed tomography, X-ray, and bone scintigram revealed no evidence of bone metastasis.

The serum calcium concentration raised to 16.8 mg/dL and an abnormal electrocardiogram reading due to hypercalcemia (shortened QT) was observed. For the treatment of hypercalcemia, 45 mg of bisphosphonate pamidronate was injected intravenously over a 240-min period on October 25. After the treatment, serum calcium decreased to 8.5 mg/dL. As a result, her complaints, such as nausea, vertigo, drowsiness, arrhythmia and muscle pain, disappeared.

On October 31, laparotomy was carried out, but it was judged impossible to achieve optimal operation criteria, because of the presence of a residual tumor mass smaller than 2 cm, so an omentectomy was performed without bowel resection. A biopsy specimen from the left ovarian tumor revealed a grade-1 adenocarcinoma (Fig. 1). Under diagnosis of stage IIIb ovarian cancer, she underwent chemotherapy consisting of a combination of 50-mg/m^2 cisplatin, 40-mg/m^2 adriamycin and 400-mg/m^2 cyclophosphamide. Serum calcium was well controlled by bisphosphonate pamidronate, and hydration with 3000 mL/day of saline and furosemide. In spite of 2 courses of chemotherapy, the tumor increased to 166% in the size of the measurable lesion. We conducted 2nd surgery consisting of total hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymphadenectomy including the para-aortic nodes. On December 26, she underwent 2nd surgery and a segment of the sigmoid colon and the

rectum were removed to achieve optimal tumor resection. After this surgery, serum calcium, PTHrP and 1,25-DHD fell to normal limits without other therapy. PTH was recovered 2 months later (Fig. 2). Tissue diagnosis showed adenocarcinoma. The histochemical examination of PTHrP using the anti-human monoclonal antibody, 4B3, showed positive staining in tumor cells (Fig. 3) (Kitazawa et al., 1991).

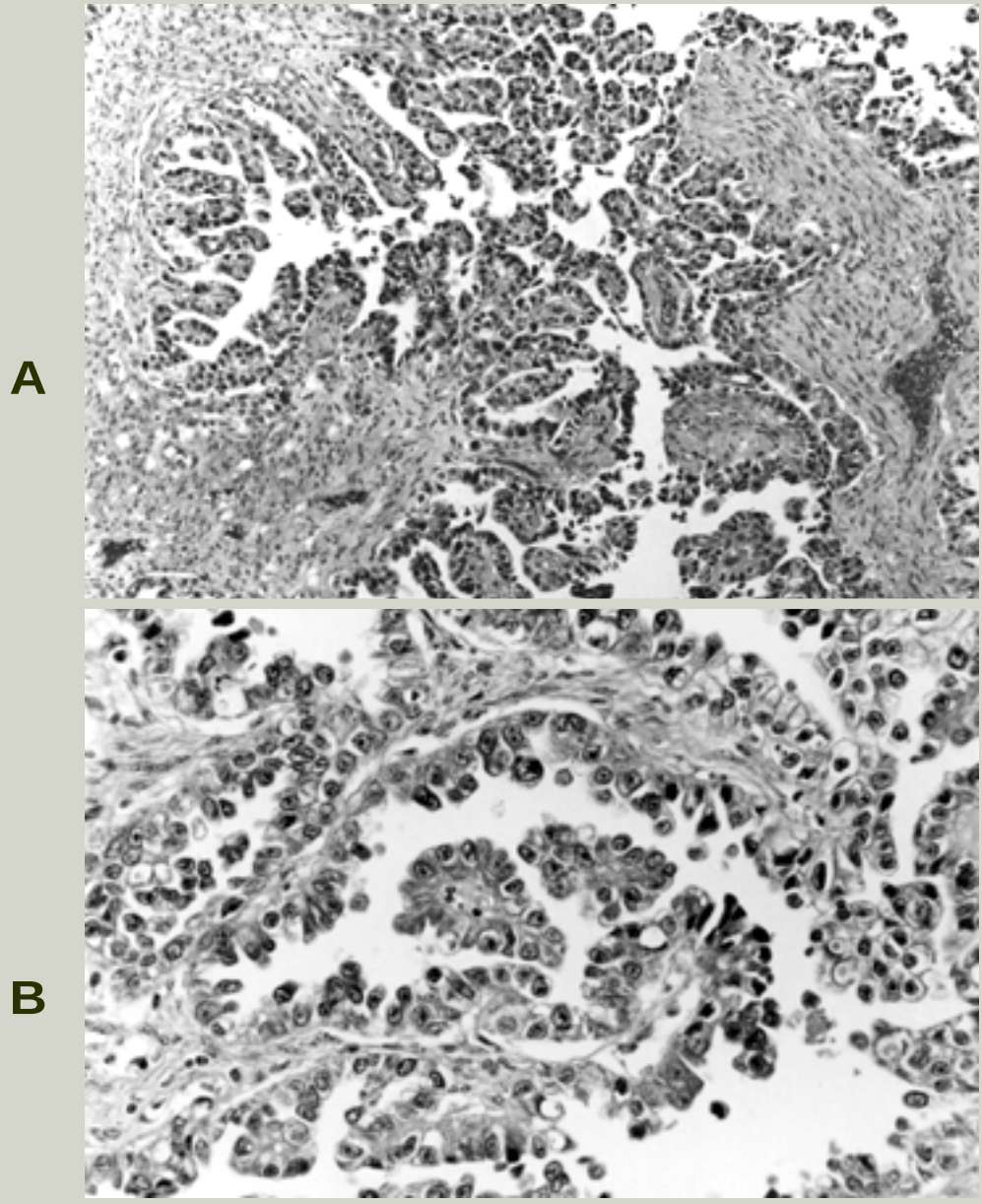

Fig. 1. Photomicrograph of cancer tissues. **A:** Low magnification. There is papillary proliferation of cancer cells (hematoxylin and eosin stain). Original magnification, × 40. **B:** High magnification (hematoxylin and eosin stain). Original magnification, × 200.

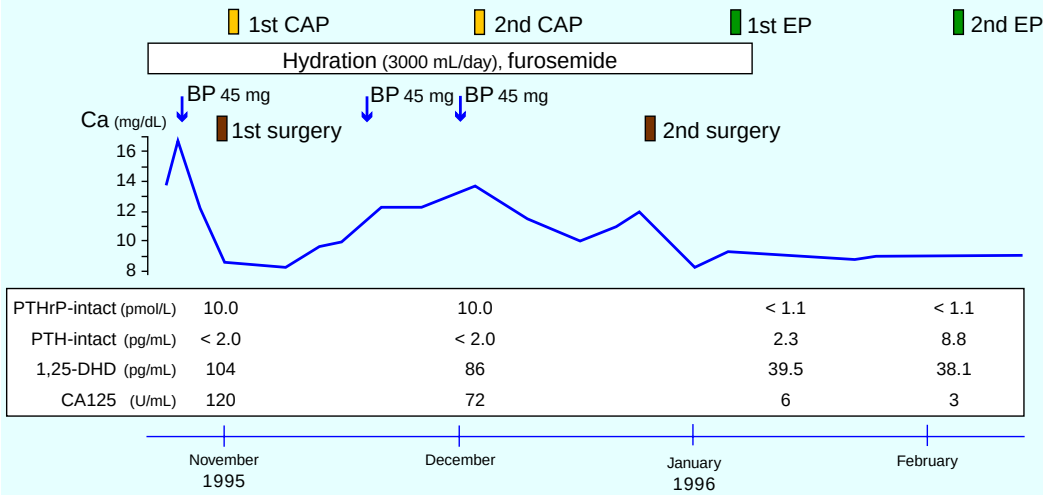

Fig. 2. Treatment and changes of calcium, PTHrP-intact, PTH-intact and CA125. BP, bisphosphonate pamidronate; CAP, cisplatin, adriamycin and cyclophosphamide; EP, etoposide and cisplatin.

She received 5 courses of post operative chemotherapy consisting of 100-mg/body etoposide daily from days 1 to 5 and 50-mg/m^2 cisplatin on day 5. She has had no evidence of recurrence for 24 months.

Discussion

Several agents, such as prostaglandin, interleukin 1, transforming growth factor (TGF)-α, TGF-β and colony stimulating factor, have

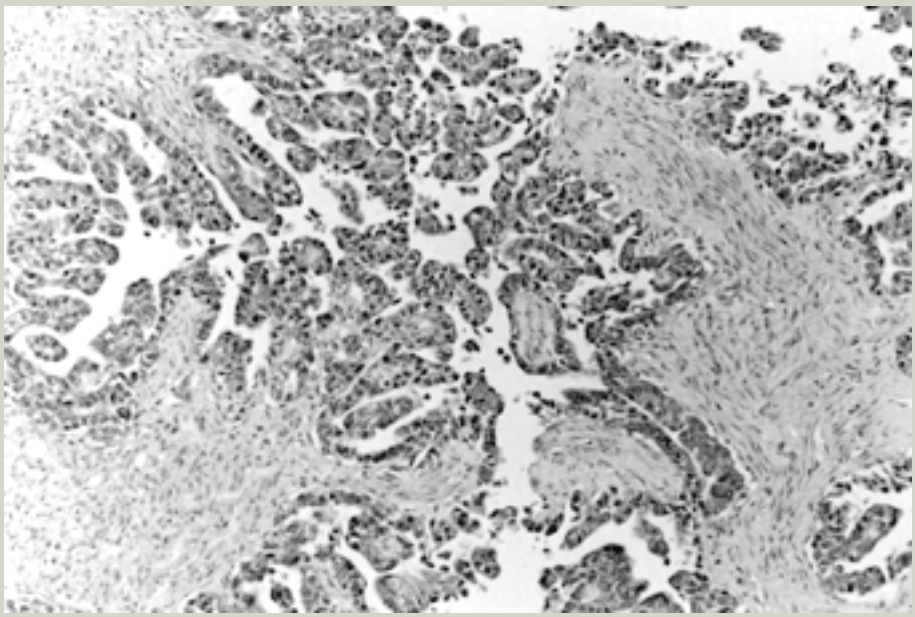

Fig. 3. Immunohistochemical demonstration of PTHrP production by the tumor. Positive staining is shown in the cytoplasm of the cancer cells. Original magnification, × 100.

been reported as inducing HHM factor (Bringhurst et al., 1986; Tashjian et al., 1986; Sato et al., 1987; Linkhart et al., 1989). These are considered to be local factors of osteolytic hypercalcemia. In this case, since immunohistochemistry revealed the production of PTHrP, PTHrP was causative for HHM.

PTHrP acted very similarly to the PTH, but the clinical syndrome of HHM has distinct differences from primary hyperparathyroidism. For example, in HHM, an increase in bone resorption is not coupled with increased bone formation as in primary hyperthyroidism. In our case, bone mineral density and serum osteocalcin were in the normal range and urine pyridinoline and deoxypyridinoline were high. Additionally, serum 1,25-DHD concentrations are commonly low in patients with HHM (Schilling et al., 1993). However, 1,25-DHD concentration was extremely high in this case. The concentration of 1,25-DHD is considered to relate to renal function. Most cases of HHM have damage in renal function because of long-standing hypercalcemia and so 1,25-DHD concentrations are low (Hoekman et al., 1991). In contrast, this case might have been in its early stages and had normal renal function. There was some possibility that several cytokines produced by cancer cells and the low serum phosphate may stimulate the renal 1α-hydroxylase activity.

Since HHM has been commonly observed in the end stages of malignancy, the prognosis of this disease is poor. Additionally, appropriate management for HHM has been not established. Bisphosphonate pamidronate was effective in normalizing the serum calcium level of hypercalcemic patients with malignancies (Harinck et al., 1987). However, the efficacy for HHM was transient. In our case, bisphosphonate pamidronate reduced serum calcium levels, but the serum level of PTHrP did not decrease. The management of HHM with bisphosphonate pamidronate is not easy, i.e., hydration is necessary to maintain urine flow and a proper level of sodium chloride. Our patient needed hydration with 3000 mL/day of saline and furosemide.

In our case, the patient could undergo tumor resection after the management of hypercalcemia with bisphosphonate pamidronate and then have a good prognosis.

These results suggest that bisphosphonate pamidronate may be useful for the management of hypercalcemia, but this management should be followed by radical treatment for HHM such as tumor reduction for improving prognosis, including the quality of life of patients with HHM.

References

1 Allan SG, Lockhart SP, Leonard RCF, Smyth JF. Paraneoplastic hypercalcaemia in ovarian carcinoma. Br Med J 1984;288:1714–1715.

2 Bringhurst FR, Bierer BE, Godeau F, Neyhard N, Varner V, Segre GV. Humoral hypercalcemia of malignancy: release of prostaglandin-stimulating bone-resorbing factor in vitro by human transitional-cell carcinoma cells. J Clin Invest 1986; 77:456–464.

3 Fujino T, Watanabe T, Yamaguchi K, Nagasaki K, Onishi E, Iwamoto I, et al. The development of hypercalcemia in a patient with an ovarian tumor producing parathyroid hormone-related protein. Cancer 1992;70:2845–2850.

4 Gotoh A, Kitazawa S, Mizuno Y, Takenaka A, Arakawa S, Matsumoto O, et al. Common expression of parathyroid hormone-related protein and no correlation of calcium level in renal cell carcinomas. Cancer 1993;71:2803–2806.

5 Harinck HIJ, Bijvoet OLM, Plantingh AST, Body JJ, Elte JWF, Sleeboom HP, et al. Role of bone and kidney in tumor-induced hypercalcemia and its treatment with bisphosphonate and sodium chloride. Am J Med 1987;82:1133–1141.

6 Hoekman K, Tjandra YI, Papapoulos SE. The role of 1,25-dihydroxyvitamin D in the maintenance of hypercalcemia in a patient with an ovarian carcinoma producing parathyroid hormone-related protein. Cancer 1991;68:642–647.

7 Honda S, Yamaguchi K, Miyake Y, Hayashi N, Adachi N, Kinoshita K, et al. Production of parathyroid hormone-related protein in adult T-cell leukemia cells. Jpn J Cancer Res 1988;79:1264–1268.

8 Kitazawa R, Kitazawa S, Matui T, Maeda S. In situ detection of parathyroid hormone-related protein in ovarian clear cell carcinoma. Hum Pathol 1997;28:379–382.

9 Kitazawa S, Fukase M, Kitazawa R, Takenaka A, Gotoh A, Fujita T, et al. Immunohistologic evaluation of parathyroid hormone-related pro-

tein in human lung cancer and normal tissue with newly developed monoclonal antibody. Cancer 1991;67:984–989.
10 Linkhart TA, Mohan S, Jennings JC, Baylink DJ. Copurification of osteolytic and transforming growth factor-β activities produced by human lung tumor cells associated with humoral hypercalcemia of malignancy. Cancer Res 1989;49: 271–278.
11 Martin TJ, Moseley JM, Gillespie MT. Parathyroid hormone-related protein: biochemistry and molecular biology. Crit Rev Bioc Mol Biol 1991;26:377–395.
12 Sato K, Fujii Y, Ono M, Nomura H, Shizume K. Production of interleukin 1α-like factor by a squamous cell carcinoma of the thyroid (T3M-5) derived from a patient with hypercalcemia and leukocytosis. Cancer Res 1987;47:6474–6480.
13 Schilling T, Pecherstorfer M, Blind E, Leidig G, Ziegler R, Raue F. Parathyroid hormone-related protein (PTHrP) does not regulate 1,25-dihydroxyvitamin D serum levels in hypercalcemia of malignancy. J Clin Endocrinol Metab 1993; 76:801–803.
14 Tashjian AH, Voelkel EF, Lloyd W, Derynck R, Winkler ME, Levine L. Actions of growth factors on plasma calcium-epidermal growth factor and human transforming growth factor-alpha cause elevation of plasma calcium in mice. J Clin Invest 1986;78:1405–1409.
15 Thiebaud D, Jaeger P, Burckhardt P. Response to retreatment hypercalcemia with the bisphosphonate AHPrBP (APD): respective role of kidney and bone. J Bone Miner Res 1990;5:221–226.

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