Increased 1,25-(OH)₂D₂ Concentration in a Patient with Malignancy-Associated Hypercalcemia Receiving Intravenous Hyperalimentation Inadvertently Supplemented with Vitamin D₂

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A 55-year-old patient with hypercalcemic crisis due to gastric carcinoma with bone marrow metastasis was treated with bisphosphonate (pamidronate) and calcitonin. Urinary excretion of parathyroid hormone-related protein (PTHrP) was increased. When normocalcemia had been attained, intravenous hyperalimentation was started, in which 1,000 U vitamin D₂ was inadvertently supplemented on days 5–18. On days 15–18, hypercalcemia rapidly recurred, accompanied by markedly increased serum levels of 25-OHD₂ (9.1 ng/dl) and 1,25-(OH)₂D₂ (161 pg/ml). This clinical course suggests that PTHrP, like PTH, stimulated 1 α -hydroxylase activity and produced excessive 1,25-(OH)₂D₂. Vitamin D should not be administered to patients with malignancy-associated hypercalcemia, particularly that due to PTHrP-producing tumors. (Internal Medicine 32: 886–890, 1993)

Key words: hypercalcemic crisis, metastatic calcification, vitamin D, bisphosphonate, pamidronate

Introduction

Malignancy-associated hypercalcemia (MAH) is chiefly caused by excessive production of parathyroid hormone-related protein (PTHrP) (1, 2). Although PTHrP is capable of stimulating 25-hydroxyvitamin D-1 α -hydroxylase, serum 1,25-(OH)₂D levels are usually decreased in patients with MAH (3, 4). However, a few reports have indicated that the serum 1,25-(OH)₂D concentration is not decreased or in fact shows a distinct increase in some hypercalcemic patients with solid tumors (5, 6), suggesting that PTHrP may stimulate 1 α -hydroxylase, as shown in animal models bearing PTHrP-producing tumors (7, 8).

We report a patient with MAH, who was treated effectively with bisphosphonate and calcitonin. On day 5 when the serum calcium concentration had normalized, the patient received intravenous hyperalimentation, inadvertently supplemented with vitamin D₂, until day 18. On days 15–18, hypercalcemia recurred rapidly and worsened, and this was also treated with pamidronate and calcitonin. Since the onset of hypercalcemia was more rapid after the first treatment compared to that after the second, we investigated the serum concentrations of vita-

min D₂ and D₃ metabolites.

Case Report

Clinical course of the patient

On November 2, 1991, a 55-year-old male patient was admitted to our hospital because of severe hypercalcemia, dyspnea and consciousness disturbance (Fig. 1). In mid October, he had complained of anorexia and general malaise, and had been admitted to another hospital. The serum calcium level was markedly elevated (18.8 mg/dl) and the patient received saline infusion, glucocorticoid and calcitonin. However, the hypercalcemia persisted, and the patient was referred to our hospital.

On admission, he was drowsy, and complained of dyspnea. His height was 170 cm and weight 54 kg. There was no anemia. Blood pressure was 128/80 mmHg, pulse rate 108/min, with an increased respiration rate of 28/min. Heart sounds were normal. There was no pretibial edema.

A complete blood count revealed leukocytosis (21,000/mm³) and very slight anemia (Hb 13.3 g/dl, RBC 418×10⁴/mm³, Ht 40.6%, platelets 23.4×10⁴/mm³). Serum total protein

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was 5.1 g/dl, and albumin 2.6 g/dl. Serum calcium was 13.3 mg/dl, phosphorus 3.1 mg/dl, and Mg 0.6 mEq/l. Liver function was normal. Renal function was slightly impaired (BUN 49 mg/dl, creatinine 2.3 mg/dl, creatinine clearance 30 ml/min). Serum Na, K, and Cl were 148, 3.9, and 108 mEq/l, respectively. Chest X-ray examination revealed a slightly enlarged heart, with hazy shadows in the bilateral lower lung fields. Ultrasonic examination of the neck and abdomen revealed no parathyroid gland abnormalities or changes in the liver, gallbladder, spleen, kidney, and pancreas. Blood gas examination, while the patient was breathing room air, revealed marked hypoxia (pH 7.589, PaO₂ 48.3 mmHg, PaCO₂ 33.9 mmHg, HCO₃ 32.8 mM), which was slightly improved by O₂ inhalation at a rate of 8 l/min (pH 7.525, PaO₂ 72 mmHg, PaCO₂ 35.4 mmHg, HCO₃ 29.4 mM, Sat 95.9%). Under a diagnosis of hypercalcemic crisis, with metastatic calcification in the bilateral lungs (9, 10), saline containing 3-amino-1-hydroxy-propylidene-1,1-bisphosphonate (AHPPrBP, or pamidronate, kindly supplied by Ciba-Geigy, Basel, Switzerland) (60 mg) was administered intravenously. Furthermore, elcatonin (a derivative of eel calcitonin, Asahi Kasei, Tokyo) was administered intramuscularly twice a day for 7 days.

The corrected serum calcium concentration (11) decreased to 11 mg/dl within 3 days, accompanied by a marked decrease

in urinary excretion of calcium (from 670 mg on day 1 to 130 mg on day 4). On day 2, respiration suddenly ceased and artificial ventilation was started. On day 3, pulmonary function improved. However, no spontaneous respiration occurred and the consciousness score of the patient was in the order of 200 (semicoma).

On day 5, intravenous hyperalimentation was started, without supplementation of calcium and phosphate, but a young physician inadvertently administered a multi-vitamin agent containing 1,000 U vitamin D₂ (MVI, Esu-esu Pharmaceutical Co., Tokyo). On day 14, hypercalcemia recurred, with a marked increase in urinary calcium and phosphorus excretion. On day 18, the serum calcium level increased to 16.3 mg/dl. Vitamin D₂ administration was discontinued and pamidronate (60 mg) was again administered intravenously, with a daily injection of elcatonin (80 U/day) for an additional 14 days. The serum calcium concentration rapidly decreased again. It remained below 12 mg/dl for 21 days as a result of the second treatment, which was a more prolonged decrease than that resulting from the first treatment (12 days) (Fig. 1).

At this time, a diagnosis of undifferentiated carcinoma of unknown origin was made after examination of a bone marrow biopsy sample from the iliac crest, which was compatible with a decreased serum intact PTH level (less than 5 pg/ml, normal

Fig. 1. Clinical course of the patient with hypercalcemic crisis treated with bisphosphonate and calcitonin. The hypercalcemia was treated with pamidronate (AHPPrBP) 60 mg and elcatonin (80 U/day) as indicated. On days 5–18, vitamin D₂ (1,000 U/day for 14 days) was inadvertently administered with intravenous hyperalimentation (■). Note that the corrected serum calcium concentration was below 12 mg/dl for 12 days after the first treatment and for 21 days after the second treatment.

Upper panel: ●—● Corrected serum calcium (mg/dl), ○---○ Total serum calcium level (mg/dl), ○—○ Serum phosphorus level (mg/dl), X---X Serum creatinine level (mg/dl)
Middle panel: Column: Urinary calcium excretion (mg/day), ● Urinary phosphorus excretion (mg/day)
Lower panel: Column: urine volume (l/day), X: Urinary creatinine excretion (g/day)

range 23–72 pg/ml, Nihon Medi-Physics, Tokyo) and increased urinary excretion of C-terminal fragments of PTHrP (5.6 µg/g Cr, normal range less than 1.57 µg/g Cr, Mitsubishi Yuka BCL, Tokyo) (12, 13). After this diagnosis had been made, no further examination was performed, and intensive treatments for MAH were withheld.

In December, the serum calcium concentration gradually increased, accompanied by severe anemia and hypoproteinemia. Disseminated intravascular coagulation developed and the patient died on day 66 after admission.

Autopsy findings

Autopsy was carried out one hour after death. At autopsy, a protruding tumor, measuring 3×5 cm, was found between the fundic portion of the stomach and the junctional portion of the esophagus, with deep infiltration to the gastric serosal membrane (Fig. 2). The tumor had widely metastasized to the liver, spleen, both kidneys, both adrenals, the small intestine, the pericardium, and massively to the bone marrow of distant bones (Fig. 3). Moreover, the bronchopulmonary lymph nodes were swollen with metastases. Microscopically, the tumor appeared as advanced adenoacanthoma, consisting of well or poorly differentiated tubular adenocarcinoma, and keratinized or non-keratinized squamous cell carcinoma. The pathohistological diagnosis of the tumor was compatible with adenoacanthoma of the stomach. In addition, calcium deposits were detected in the bilateral kidneys, small intestine, liver, and especially, the lung, in which multifocal calcium deposits were found in the alveolar walls and septa (Fig. 4). The patient had died of multiple organ failure resulting from disseminated carcinoma and bronchopneumonia.

Determination of serum levels of vitamin D metabolites

Blood was taken on day 5 when the serum calcium concentration had normalized (Table 1). A retrospective check of the nursing record revealed that intravenous hyperalimentation containing vitamin D₂ had been started on day 5, several hours before the blood sample had been taken. Another blood sample was taken on day 18, just before reinfusion of pamidronate. The serum was stored at –20°C until assay for vitamin D metabolites. Vitamin D₂, 25-OHD₂, 24,25-(OH)₂D₂, 1,25-(OH)₂D₂, and vitamin D₃ metabolites were measured as described elsewhere (14, 15). The results are shown in Table 1.

Discussion

In this patient with hypercalcemic crisis presenting with dyspnea, hypoxemia and hazy pulmonary shadows on a chest X-ray film, due probably to metastatic calcification in the lungs (9, 10), we were able to rapidly decrease the serum calcium concentration by simultaneous administration of the bone-resorption inhibitors, pamidronate and elcatonin.

Pamidronate, a newly synthesized bisphosphonate, is a potent bone-resorption inhibitor widely used in Europe as a first-choice treatment for MAH (16). Although alone it can ameliorate MAH for a prolonged period, we administered

Fig. 2. Protruding and advanced carcinoma of the stomach from an autopsy specimen. Left is low magnification (HE stain, ×60) and right is high-power view of the tumor. The tumor cells are distributed from the surface to deeper layers and show a tubular pattern with keratinized foci (right; HE stain, ×300).

Fig. 3. Bone marrow from lumbar vertebra showing cancer cell involvement. The tumor cells have spread throughout the entire bone marrow, resulting in reduction of the hematopoietic area (HE stain, ×430).

Fig. 4. Portion of the lung affected by calcium deposition. Many amorphous or crystallized deposits (arrows) are evident on the alveolar walls and the septa (HE stain, ×520).

Increased 1,25-(OH)₂D₂ in MAH

Table 1. Serum Levels of Vitamin D₂ and D₃

Date		Day 1 (Nov. 2)	Day 5 (Nov. 6)	Day 18 (Nov. 19)	Normal range
Serum	Albumin (g/dl)	2.6	2.1	2.8	3.8–5.1
	Ca (mg/dl)	13.3	7.6	15.1	8.8–10.5
	P (mg/dl)	3.1	1.4	4.5	2.5–4.3
Serum	D (ng/ml)				1–5
	D ₂	–	2.7	2.8	
	D ₃	–	2.5	2.8	
Serum	25-OHD (ng/ml)				10–40
	25-OHD ₂	–	1.9	9.1	
	25-OHD ₃	–	3.4	2.9	
Serum	24,25-(OH) ₂ D (ng/ml)				1–4
	24,25-(OH) ₂ D ₂	–	0.3	ND	
	24,25-(OH) ₂ D ₃	–	0.8	0.8	
Serum	1,25-(OH) ₂ D (pg/ml)				20–70
	1,25-(OH) ₂ D ₂	–	ND	160.6	
	1,25-(OH) ₂ D ₃	–	116.8	52.9	
Ratio of 1,25-(OH) ₂ D (pg/ml)/25-OHD (ng/ml)					
	D ₂		<5.2	17.6	
	D ₃		34.3	18.2	

–: not determined, ND: not detectable, 24,25-(OH)₂D: <0.1 ng/ml, 1,25-(OH)₂D: <10 pg/ml.

elcatonin simultaneously to rapidly decrease the serum calcium concentration (17, 18). In contrast to calcitonin, bisphosphonates elicit no escape phenomenon, and hypercalcemia can be treated effectively by readministration. In general, the period of hypercalcemia control is shorter following a second course of treatment than after a first course (19). However, this was not the case in the present patient (Fig. 1).

By measuring serum vitamin D₂ and D₃ metabolites separately, we demonstrated that the serum 25-OHD₂ level on day 5 (1.9 ng/ml) increased to 9.1 ng/ml on day 18 after 14,000 U vitamin D₂ had been infused. More interestingly, serum 1,25-(OH)₂D₂, which was undetectable (<10 pg/ml) on day 5, increased markedly to 160.6 pg/ml on day 18, when severe hypercalcemia recurred. Since intact PTH was not detectable and the serum phosphorus concentration was increased at this time, the increased conversion of 25-OHD₂ to 1,25-(OH)₂D₂ was probably due to PTHrP produced by the tumor.

Usually, serum 1,25-(OH)₂D levels are decreased in patients with MAH (3, 4). In the present patient, blood samples for assay of serum 1,25-(OH)₂D were not obtained on admission (day 1). On day 5, when normocalcemia had been attained, serum 1,25-(OH)₂D₃ was markedly elevated (Table 1). This was not an unexpected finding, since the PTH secretory threshold during the correction of MAH lies in the upper part of the normal calcium range (20), and serum intact PTH was evidently increased on day 5. Furthermore, administration of calcitonin (21) and bisphosphonate (22, 23) also contributed to the elevation of 1,25-(OH)₂D₃.

It should be pointed out that the ratio of serum 1,25-(OH)₂D₂ (pg/ml)/25-OHD₂ (ng/ml) on day 18 [17.6] was not different from that of serum 1,25-(OH)₂D₃/25-OHD₃ [18.2] (Table 1), suggesting that 1 α -hydroxylase did not discriminate D₂ and D₃ metabolites (24). In contrast, the ratio of serum 1,25-(OH)₂D₂/25-OHD₂ on day 5 was very low [less than 5.2] in comparison with that of serum 1,25-(OH)₂D₃/25-OHD₃ [34.3], suggesting that D₂ infusion had just started and that vitamin D₂ metabolism (conversion of vitamin D₂ to 25-OHD₂ and 25-OHD₂ to 1,25-(OH)₂D₂) had not reached the equilibrium stage after several hours.

Several hypotheses have been proposed to explain why 1,25-(OH)₂D is not elevated in patients with MAH (25). First, hypercalcemia per se is an inhibitor of 1 α -hydroxylase, resulting in suppression of the serum 1,25-(OH)₂D level. These findings have also been demonstrated in some patients with primary hyperparathyroidism, in whom the serum calcium concentration is markedly elevated (26, 27). However, even when serum 1,25-(OH)₂D levels were compared in patients with MAH and those with primary hyperparathyroidism, who were matched for total and ionized serum calcium concentrations, the former showed a decreased serum 1,25-(OH)₂D concentration (3, 25). Second, inhibitors of 1 α -hydroxylase are present among tumor products (28). Although this theory is attractive, no further biochemical characterization has been performed. Another hypothesis is that 1 α -hydroxylase is relatively refractory to PTH and/or PTHrP in patients with malnutrition. In contrast to a recent report (29), our clinical data suggest that 1 α -hydroxylase is indeed activated in patients with MAH receiving intravenous hyperalimentation supplemented with 1,500 cal of energy.

In summary, in a hypercalcemic patient with PTHrP-producing gastric carcinoma, who was inadvertently administered vitamin D₂ by intravenous hyperalimentation, we have demonstrated that 25-hydroxyvitamin D-1 α -hydroxylase was stimulated, probably by PTHrP, and that the elevated 1,25-(OH)₂D [1,25-(OH)₂D₂ + 1,25-(OH)₂D₃] certainly aggravated the recurrence of hypercalcemia. Needless to say, administration of vitamin D is contraindicated in hypercalcemic patients with MAH, particularly that due to PTHrP-producing tumors.

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