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CASE REPORT

Unexpected prolonged extreme hypocalcaemia and an inadequate PTH response in a patient with metastatic breast carcinoma

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ABSTRACT

Although hypercalcaemia is often encountered during the course of malignant disease, hypocalcaemia appears to be rather rare. We describe a 37-year-old patient with metastatic carcinoma of the breast, who developed extreme hypocalcaemia (as low as 0.75 mmol calcium per litre) after chemotherapy. This is caused by a combination of hungry-bone syndrome and an insufficient parathyroid response. The latter may be the result of a direct toxic effect of chemotherapy on parathyroid hormone (PTH) synthesis possibly in combination with microscopic tumour infiltration in the parathyroid glands. Correction of the extreme hypocalcaemia over a period of 100 days by oral and intravenous calcium supplementation, corresponding to a total of 352 gram elemental calcium (1/3 of the total body calcium), resulted in gradual symptomatic relief. The possible mechanisms for these findings are discussed and the literature is briefly reviewed.

INTRODUCTION

Hypercalcaemia due to carcinoma metastatic to bone occurs frequently. In contrast, hypocalcaemia is a rare complication of breast and prostate carcinoma.[1-6] A number of factors may be implicated in the development of hypocalcaemia in cancer patients, including hypoalbuminaemia, surgical and infiltrative hypoparathyroidism, radiologically destructed parathyroid glands, osteoblastic metastases, hypomagnesaemia, vitamin D deficiency, renal failure, massive cell lysis, drug effect and sepsis. We describe a patient with advanced breast carcinoma who developed extreme hypocalcaemia due to the combination of osteoblastic metastases and an inadequate PTH response.

METHODS

The Vitros 950 analytical system (Ortho Clinical Diagnostics) was used for the determination of creatinine, calcium, magnesium, albumin, inorganic phosphorus, alkaline phosphatase (AP), blood urea nitrogen, γ-glutamyl transferase (γ-GT,), lactate dehydrogenase (LDH), aspartate aminotransferase, alanine aminotransferase in plasma, and for calcium in urine. Serum ionised calcium was measured with an ion-selective electrode on the Synthesis analyser (Instrumentation Laboratory). Thyroid-stimulating hormone, PTH and tumour markers were determined in serum on the Immuno I analyser (Bayer Diagnostics), the Immulite system (DPC) and IMx (Abbott), respectively. Cation exchange chromatography was used for the determination of hydroxyproline in urine. PTH-related peptide (PTHrP), calcitonin, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were determined by competitive radioimmunoassays. All instruments and assays were calibrated and operated according to manufacturer's recommendations.

CASE REPORT

A 37-year-old woman was admitted because of progressive mental instability and paresthesia of the distal extremities.

Her medical history included breast carcinoma ($T_2N_1M_0$) for three years, for which she had undergone a mastectomy, radiotherapy and chemotherapy (cyclophosphamide, methotrexate and 5-fluorouracil). Six months before admission, sacroiliac metastases were discovered and radiotherapy, goserelin and tamoxifen were given. Two months before admission, thoracic spine metastases were irradiated and pamidronate (90 mg iv) was administrated. Four days before admission, FEC chemotherapy (5-fluorouracil, epi-adriamycin and cyclophosphamide) was started because of progressive painful osteoblastic metastases and rising tumour markers (CA15-3 46 kμ/l and CEA 25.3 μg/l). On admission, physical examination showed multiple skin metastases, a heart rate of 90 beats/min and blood pressure of 100/70 mmHg. Plasma calcium and phosphate levels were normal (*figure 1* and *table 1*).

Four days later, she became profoundly hypocalcaemic (1.26 mmol/l) and oral calcium supplementation was started. An MRI scan of the parathyroid region did not show any abnormalities. Serum calcium levels dropped to 1.09 mmol/l on day 12 and intravenous calcium supplementation was added. Nevertheless, the calcium level decreased to 0.75 mmol/l at day 21. Around this time, she suffered from distal paresthesia, severe cramps in her face, arms, legs and abdomen, as well as chest tightness.

Other biochemical results were phosphate 2.61 mmol/l, ionised calcium 0.55 mmol/l, AP 1005 E/l and LD 1309 μ/l. Serum parathyroid hormone level was 1.1 pmol/l. Plasma albumin and magnesium, and serum PTHrP and calcitonin concentrations, as well as renal, liver and thyroid functions were normal. The concentration of 25-hydroxyvitamin D was normal. However, its active metabolite 1,25-dihydroxyvitamin D was elevated, indicating an adequate metabolism of vitamin D due to hypocalcaemia. Urinary calcium excretion was 0.72 mmol/day, hydroxyproline 0.20 mmol/day/m^2.
A second course of FEC chemotherapy was given at day 22. Despite the normal levels of both vitamin D and magnesium, calcitriol (5 μg oral) and magnesium sulphate (2 grams iv) were added from this moment. However, this did not result in a subsequent rise in calcium concentration. The PTH level fell even further (*table 1*). At day 50 a third course of chemotherapy was given in which epi-adriamycin was replaced by methotrexate.

After 100 days of excessive calcium supplementation, her symptoms gradually improved. The cumulative amounts of calcium administrated were: oral calcium carbonate 242 gram and intravenous calcium glubionate 1680 gram, corresponding to 352 gram elemental calcium (1/3 of the total body calcium). She was discharged from the hospital with a calcium of 1.43 mmol/l, decreasing tumour marker

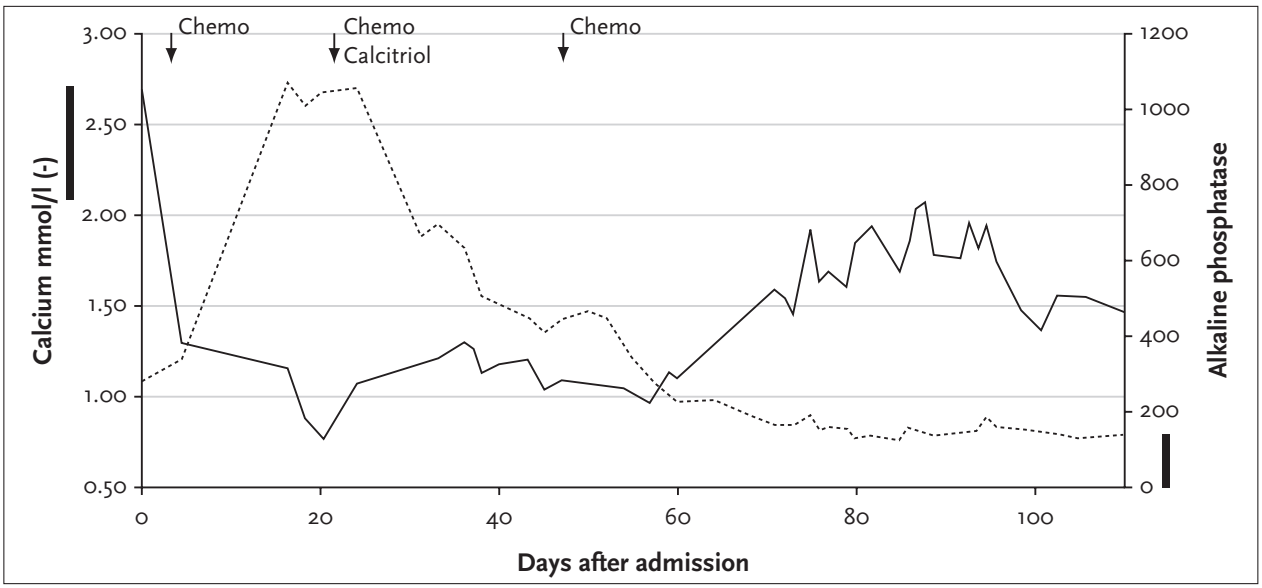

Figure 1
Time course of plasma calcium and alkaline phosphatase concentrations

Total calcium supplementation: 242 gram calcium carbonate orally and 1680 gram calcium glubionate intravenously corresponding to a total of 352 gram elemental calcium. With normal renal and liver functions alkaline phosphatase represents a marker of osteoblastic activity. Bars indicate normal ranges for calcium (2.10-2.70 mmol/l) and alkaline phosphatase (<120 μ/l). Arrows indicate chemotherapy and calcitriol administered. Chemo means the start of a course of chemotherapy.

Table 1
Laboratory parameters at day 0, 4, 21, 33, 72 and 101 after admission

	DAY 0	DAY 4	DAY 21	DAY 33	DAY 72	DAY 101	REFERENCE VALUES
Plasma							
Blood urea nitrogen	2.8	3.6	4.1		1.7	2.2	2.5-7.0 mmol/l
Creatinine	32	30	39		40	38	50-90 µmol/l
Alkaline phosphatase	275	323	1005	671	159	133	<120 U/l
γ-GT	80	64			43	32	<35 U/l
LD	1534	879	1309		714	504	<300 U/l
Calcium	2.58	1.26	0.75	1.18	1.50	1.32	2.10-2.70 mmol/l
Ionised calcium			0.40	0.64	0.74	0.85	1.15-1.35 mmol/l
Organic phosphate	1.36	1.49	2.61	1.67	1.98	2.23	0.60-1.60 mmol/l
Albumin		32	33	35	38	35	33-50 g/l
Magnesium			0.67	0.72	0.87	0.74	0.60-1.20 mmol/l
25(OH) Vitamin D			31				20-100 nmol/l
$1.25(OH)_2$Vitamin D			193				48-161 pmol/l
PTH			1.1	0.3	0.2	0.9	1.0-6.0 pmol/l
Calcitonin				0.08			<0.14 µg/l
TSH			2.19				0.3-4.0 mU/l
CEA		25.3		18			<5 µg/l
CA15-3		46		31			<30 kU/l
PTHrP			0.4				<2.6 pmol/l
24-hour urine							
Calcium			0.72	0.96	1.60	<0.61	2.5-10.0 mmol/24h
Hydroxyproline			0.20	0.28	0.36	0.28	0.05-0.17 mmol/24h/m^2

γ-GT = γ-glutamyl transferase, LDH = lactic dehydrogenase, PTH = parathyroid hormone, TSH = thyroid-stimulating hormone, CEA = carcinoembryonic antigen, CA 15-3 =a tumour marker for breast carcinoma, PTHrP = PTH-related peptide.

levels, disappearing osteoblastic metastatic activity on radiological investigation and reduction in number and severity of skin metastases. In the next months, her serum calcium and PTH concentrations returned to normal (2.11 mmol/l and 3.6 pmol/l, respectively) and calcium supplementation was discontinued.
Five months later, she presented with symptoms of hypercalcaemia. Her laboratory results showed a serum calcium of 3.00 mmol/l and an undetectable PTH level (<0.1 pmol/l). This time, X-ray investigation showed numerous new osteolytic metastases. Two months later, she died. Permission for autopsy was denied.

DISCUSSION

Hypercalcaemia is a common complication in patients with carcinoma metastatic to bone.[7] Hypocalcaemia is an uncommon but not unexpected finding in association with osteoblastic bone metastases, most commonly associated with metastases of prostate and breast carcinomas.[1-6,8-10] In 1984, Pepper *et al.* reported the first full endocrinology evaluation of a patient with osteoblastic metastases from a primary lesion in the breast.[11] This evaluation demonstrated that patients with osteoblastic metastases have an increased calcium resorption by the bone. The extreme hypocalcaemia in our patient is to our knowledge the lowest calcium concentration ever reported in this category of patients (*table 2*). From the possible causes of hypocalcaemia,[15,16] hypoalbuminaemia, renal insufficiency, hypomagnesaemia, pancreatitis and vitamin D deficiency could be excluded. Hypocalcaemia may be the result of the 'hungry-bone syndrome' after parathyroidectomy and/or hyperparathyroidism. In the first case, the PTH is low and in the latter case, PTH is increased. In case of osteoblastic bone metastases or acute mineralisation after tumour-lysis syndrome, a secondary hyperparathyroidism will develop. In our patient the PTH was low and remained low for a long time. Therefore, there must have been a primary hypoparathyroidism from the beginning, which could be a hypoparathyroidism caused by an autoimmune process, after parathyroidectomy or tissue destruction by infiltrating tumour cells or by irradiation. The last mentioned is a possible cause, because two months before admission the thoracic spine of the patient was irradiated. However, the radiation-exposure fields suggested that radiation injury

Table 2
Hypocalcaemia and hypoparathyroidism in patients with breast cancer

REFERENCE	SERUM CALCIUM (MMOL/L)	SERUM PHOSPHATE (MMOL/L)	BONE METASTASES	PARATHYROID EXAMINATION
Bouvier *et al.*[1]	2.20	1.20	Osteoblastic	Not done
Unger *et al.*[9]	1.68	1.20	Osteoblastic	Not done
Horwitz *et al.*, case 39[8]	1.62	2.25	Mixed	Parathyroid metastase
Hermus *et al.*[5]	1.57	1.42	Osteoblastic	Parathyroid metastases
Grieve *et al.*, case 2[12]	1.40	Not reported	Mixed	Not done
Mariette *et al.*[3]	1.36	3.06	Medullary metastases	Parathyroid metastases
Wantanabe *et al.*[13]	1.35	1.58	Osteolytic	Parathyroid metastases
Comlekci *et al.*[14]	1.32	1.96	Not reported	Not done
Wiegand *et al.*[4]	1.30	1.23	Osteoblastic	Not done
Horwitz *et al.*, case 41[8]	1.28	1.46	Mixed	Parathyroid metastases
Hall *et al.*, case 3[10]	1.26	2.20	Osteoblastic	Not found
Grieve *et al.*, case 3[12]	1.20	1.60	Mixed	Not done
Grieve *et al.*, case 1[12]	1.08	1.50	Mixed	Not done
Present case	0.75	2.61	Osteoblastic	Not done

The lowest calcium concentration of a case reported in the reference is noted.

of the parathyroid glands was unlikely. Neck surgery was not performed in our patient. The incidence of metastatic involvement of the parathyroid glands in cancer patients confirmed by autopsy is 6 to 12%.[8,9] However, parathyroid metastases will only lead to hypoparathyroidism when at least 70% of the parathyroid glandular tissue is replaced by metatastic tumour cells. So, diffuse metastatic infiltration of the parathyroid glands[3-5,13] could have led to the diminished PTH synthesis in our patient. Although she had several skin metastases, an MRI scan of the neck did not show any abnormalities of the parathyroid glands. Microscopic infiltration of the parathyroids, however, cannot be excluded because permission for autopsy was denied. However, if present, these micrometastases could have successfully responded to the chemotherapy as the skin metastases had done. Among the 13 published patients with breast carcinoma and documented hypocalcaemia and hypoparathyroidism (*table 2*), parathyroid metastases could be identified in only five patients. Autopsy did not disclose diffuse metastatic infiltration of the parathyroid glands in only one case. In the other seven cases parathyroid examination was not performed.[12] Grieve *et al.* described three patients with osteolytic metastases of breast cancer who initially had symptomatic hypercalcaemia, but after chemotherapy developed hypocalcaemia and an inappropriate PTH response.[12] In all three patients, the inadequate PTH response was transient as evidenced by a gradual normalisation of the PTH levels.
Tumour lysis can lead to the release of excessive amounts of phosphate with hypocalcaemia as a result.[16] This was, however, not the case in our patient because normal phosphate levels were found in the first stage of the hypocalcaemic episode. However, a contributory role of tumour lysis to the hypocalcaemia cannot fully be excluded, because hyperphosphataemia was found later on. Urinary calcium excretion was low, so we can only postulate that the patient's osteoblastic metastases rapidly absorbed calcium.
Ectopic secretion of calcitonin or PTHrP by tumour cells was unlikely in our patient because of normal calcitonin and PTHrP concentrations and normal calcium levels on admission.

The utility of biphosphonates is well established, not only in the treatment of tumour-associated hypercalcaemia,[17,18] but also to relieve pain in normocalcaemic patients with bone metastases. Severe hypocalcaemia has been described as a complication of pamidronate therapy in a hypercalcaemic[19] and in a normocalcaemic[14] patient with bone metastasis due to breast carcinoma. Although the PTH failed to rise after biphosphonate administration in these patients with subclinical hypoparathyroidism resulting in prolongation of the hypocalcaemia, no mechanism is known by which biphosphonates can cause a latent hypoparathyroidism, as was suggested to be the cause of hypocalcaemia in these case reports. Pamidronate is unlikely to be the cause of the hypocalcaemia in our patient because the effect of pamidronate is to be expected within two days after administration, and because the calcium level on admission was normal.
Epi-adriamycin and other chemotherapeutic agents might cause hypocalcaemia directly by suppressing PTH

secretion.[20,21] This could be the cause in our case of hypocalcaemia because the parathyroid glands proved to be able to excrete PTH up to normal levels three months after her last chemotherapy. Moreover, calcium concentration started to increase from day 60, ten days after her last chemotherapy in which epi-adriamycin was replaced by methotrexate. Furthermore, adequate calcium and calcitriol supplementations are capable of maintaining calcium levels in the presence of an inappropriate PTH concentration and will not result in a further decline in calcium level as chemotherapy is continued. Alternatively, aminoglycosides such as adriamycin can induce renal tubular dysfunction[20,21] leading to the loss of cations, such as calcium and magnesium. However, no hypomagnesaemia was found and calcium excretion was low.

In summary, we describe a patient with extensive osteoblastic metastases of breast cancer. We speculate that the combination of cytotoxic drugs, possible micrometastases present in the parathyroids and the 'hungry-bone syndrome' caused the extreme, prolonged hypocalcaemia and the inadequate PTH response in our patient. At the end of her admission, tumour load was decreased by chemotherapy, indicated by decreasing tumour markers, reducing skin metastases and disappearing osteoblastic metastatic activity on X-ray re-investigation. This resulted in decreased calcium utilisation by the metastatic process and improved clinical condition.

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