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Clinical case

Parathyroid hormone-related protein in metastatic breast cancer induced hypercalcemia: A case report

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Introduction

Hypercalcemia is associated with a variety of endocrine and metabolic diseases (Table 1), hyperparathyroidism and cancer being the two most common causes [1]. Patients presenting with asymptomatic hypercalcemia or chronic symptoms are most commonly affected by primary hyperparathyroidism, while on the other hand, patients with symptomatic hypercalcemia and weight loss of recent onset are more likely to suffer from an underlying malignant disorder. In general, the presence of an elevated serum calcium with a low or normal serum parathyroid hormone (PTH), especially when combined with an increase in serum parathyroid hormone-related protein (PTH-rP) is sufficient to exclude the diagnosis of primary hyperparathyroidism [2, 3].

Hypercalcemic patients may complain of a variety of symptoms affecting several systems. The most frequent clinical manifestations of cancer related hypercalcemia are: dehydration, weight loss, anorexia, pruritus, polydipsia, neuromuscular symptoms (fatigue, lethargy, muscle weakness, confusion, psychosis, coma), gastrointestinal problems (nausea, vomiting, constipation, ileus), urogenital (polyuria, renal insufficiency) and cardiac (bradycardia, wide T wave, atrial or ventricular arrhythmia) abnormalities.

Table 1. Classification of causes of hypercalcemia.

Endocrine
Primary hyperparathyroidism
Hyperthyroidism
Pheochromocytoma
Cancer
Renal insufficiency
Granulomatous disease
Sarcoidosis
Berylliosis
Infective
Tuberculosis
HIV
Diet and drug related
Vitamin D intoxication
Vitamin A intoxication
Retinoids
Thiazides
Lithium

Hypercalcemia is the most common life threatening metabolic disorder in patients with cancer: overall, it owns in about 5%–10% of cancer but it is most common in patients with squamous cell cancer of the lung, breast cancer, multiple myeloma, uroepithelial cancer, lymphoma and leukaemia.

The classic, mechanistic explanation that hypercalcemia was the result of direct tumour-induced bone resorption has been abandoned in favour of multiple, different pathogenic mechanisms which may be specfic for different tumour types.

Theoretically, three major mechanisms can be responsible for hypercalcemia:

1. increased calcium release from bone;
2. reduced renal calcium excretion;
3. excessive intestinal calcium absorption.

In tumour-induced hypercalcemia, chemical mediators produced by cancer cells increase bone resorption and impair calcium excretion by directly affecting renal tubular excretion (Figure 1).

Bone resorption may also be induced by TGF (transforming growth factor), TNF (tumour necrosis factor), IL-1, prostaglandins and other tumour factors [4].

Intestinal calcium absorption may be increased by vitamin D3.

PTH-rP, which is secreted by some tumour cells, enhances both tubular reabsorption and bone calcium resorption [4].

Case report

A 69-year-old woman with metastatic breast cancer had undergone a left radical mastectomy in April 1989 for invasive ductal carcinoma (pT3, pN+[2/14], M0) with

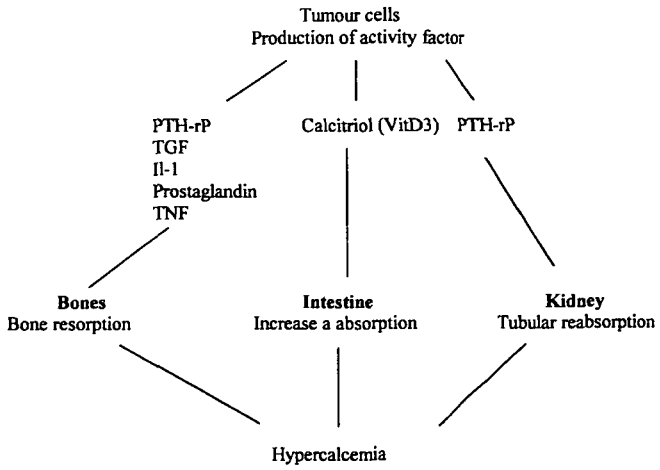

Figure 1. Pathogenesis of malignancy-associated hypercalcemia. Modified from H. Ludwing and E. Fritz, Oncological emergencies, Textbook of Medical Oncology (1997).

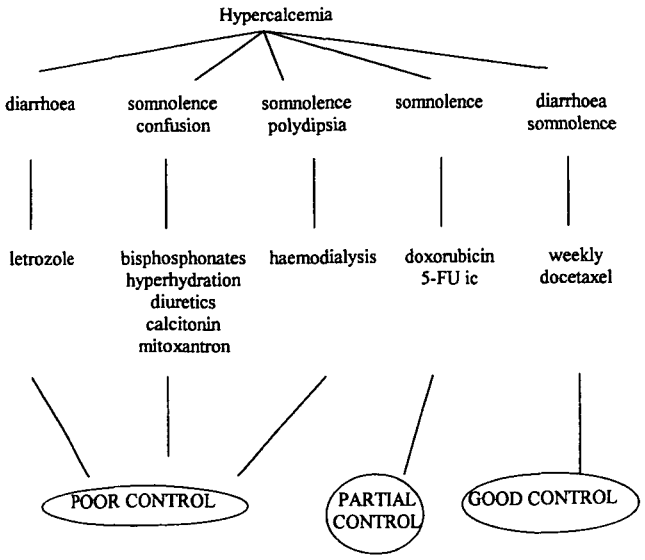

Figure 2. Treatment of patient's hypercalcemia.

oestrogen receptor status positive. Adjuvant tamoxifen (20 mg daily) was given until 1994. In August 1997 the patient developed a left malignant pleural effusion and was treated by drainage and insufflation of sterilised talcum powder by thorascopy: at that time radiological screening for bone desease showed osteolytic metastatic involvement of the IX left rib only, her liver ultrasound was normal. Treatment with tamoxifen and bisphosphonates was started. In January 1998 the patient underwent surgical excision of a local recurrence on the left chest wall.

In February 1998 she presented with diarrhoea and hypercalcemia (Ca^{++} 3.3 mmol/l with normal values ranging from 2.10–2.70 mmol/l): alkaline phosphatase was 104 U/l (normal 31–108 U/l) and creatinine was within normal values. These results were judged as signs of biological activity of her breast cancer and a new hormonal treatment with letrozol was started without any improvement. Two months later the patient became somnolent and poorly oriented, her calcium was still 3.12 mmol/l, creatinine was raised to 83 micromol/l (normal 44–80 micromol/l), PTH and urinary c AMP were slightly below normal values and VitD3 was normal. These findings supported the hypothesis of a paraneoplastic syndrome which was confirmed by an increased level of serum PTH-rP (16.2 pmol/l with normal level <2 pmol/l). The hypercalcemia did not respond to bisphosphonates, hyperhydration with isotonic saline, diuretics (furosemide 40 mg e.v.), or prednisone (50 mg/daily, orally). Calcitonin (600 U/24 hours) was then added, with no apparent benefit. Letrozol was interrupted and chemotherapy with mitoxantrone (20 mg total) was initiated. After a few days she became more somnolent and developed polydipsia with serum calcium raising to 5.2 mmol/l and creatinine to135 micromol/l. Haemodialysis was immediately started with progressive decrease in the serum calcium levels, which returned within normal ranges in a few days, and slow improvement of patient's consciousness. One month later the patient became somnolent once again, her serum calcium increased to 3.63 micromol/l, creatinine was slightly increased (111 micromol/l) in presence of unchanged radiological images (ribs X-ray and bone scan). Low dose weekly doxorubicin (20 mg total) together with continuous infusion 5-fluorouracil (5-FU, 300 mg e.v./daily) was started. Gradually her neurological condition improved and the calcium level decreased and stabilised for a few months. In September 1998 she developed grade 4 diarrhoea and became somnolent, with a new increase in serum calcium (3.12 mmol/l) and creatinine (138 micromol/l), the serum PTH-rP level was again 16.3 pmol/l. Treatment with weekly docetaxel (60 mg total) was started with good control of hypercalcemia until today (Figure 2).

Discussion

Hypercalcemia is the most frequent metabolic complication of breast cancer and it has usually been attributed to skeletal metastases with local osteolysis by tumour-derived factors.

Hovever, this metabolic disorder can be also related to the effect of tumour-derived parathyroid hormone-like factors both on kidney and bone and the current hypothesis is that the pathogenesis of hypercalcemia in breast cancer is mediated humorally through PTH-rP. PTH-rP is secreted by some tumours cells and it is supposed to mediate malignant hypercalcemia by binding to the parathyroid hormone related peptide receptor and then stimulating osteoclastic bone resorption and renal tubular calcium reabsorption. Its role as a humoral factor in malignant hypercalcemia has been recently established by several authors [5, 6]: elevated serum PTH-rP levels have been found in 30%–50% of hypercalcemic patient with breast cancer, even though hypercalcemia was concomitant with bone metastases, and its concentrations were significantly higher in hypercalcemic than in normocalcemic patients with bone metastases [7].

In breast carcinoma with metastatic bone spread PTH-rP is elevated in 90% of cases, as compared with only 17% of cases with non-skeletal metastases. These observations have led to the hypothesis that PTH-rP might contribute to the growth of breast cancer cells in bone due to its ability to stimulate osteoclastic bone resorption [8]: experimental evidence is currently available to support this hypothesis [9].

Other growth factors, such as TGF-beta, which are abundant in the bone matrix, are released and activated by osteoclastic bone resorption and may enhance PTH-rP expression and tumour cell growth [8].

Other *in vivo* studies have demonstrated that local production of PTH-rP by breast cancer cells can cause bone destruction, even in the absence of hypercalcemia or increased circulating plasma concentrations of PTH-rP [10]. Neutralising antibodies to PTH-rP may reduce the development of destructive bone lesions as well as the growth of tumour cells in bone [10].

From the clinical perspective, very few controlled studies have addressed the issue of the optimal treatment of cancer-related hypercalcemia. Interpretation of clinical trial results is confounded by enormous variability in patient selection, underlying diagnoses, severity of hypercalcemia and by unique methods of reporting results [11].

The best treatment for cancer-related hypercalcemia should be directed at the underlying disease but hypercalcemia most commonly occurs in patients with advanced disease in whom cytotoxic therapy has failed. The usual therapies for hypercalcemia aim at decreasing serum calcium by increasing urinary excretion or decreasing bone resorption by inhibition of osteoclastic function.

Treatment with vigorous intravenous saline hydration (3000–6000 ml daily) represented the historical approach to hypercalcemia through restoration of the extracellular fluid deficit and induction of calcium diuresis. This procedure may reduce calcium levels by 0.3–0.5 mmol over the first 48 hours by itself, but most patients need additional combination with high doses of loop diuretics (furosemide 80–100 mg/day) to induce a sodium-linked calcium diuresis. This therapy can be excessively toxic as it frequently causes fluid overload and occasionally life-threatening pulmonary oedema [12].

In recent years hydration with isotonic saline, with or without diuretics, and bisphosphonates have been established as standard treatment of cancer associated hypercalcemia [12]. Bisphosphonates are chemical analogues of pyrophosphate that adsorb to the surface of crystalline hydroxyapatite and inhibits calcium release from bone by interfering with the metabolic activity of osteoclasts [13]. Three the bisphosphonates are currently available: etidronate, pamidronate and clodronate. Of these, pamidronate is probably the most potent and has become the most widely prescribed drug for the treatment of hypercalcemia [14]. A single-dose, (60–90 mg over two to four hours) has been reported to induce normalisation of serum calcium concentration in 70%–100% of treated patients [14, 15]. Pamidronate binds to bone and reduces resorption, but has no effect on the renal tubule [16]: patients with cancer-related hypercalcemia who have a detectable renal component have therefore usually a poor response to bisphosphonates [17].

An Australian report of 44 patients with tumour-induced hypercalcemia suggested that a poor response to bisphosphonates could be due to high concentrations of PTH-rP. PTH-rP was the best predictor for response, with high PTH-rP levels inversely correlating with response [16]. In poor response patients a post-treatment calcium clearance estimation showed that pamidronate effectively inhibited bone resorption but did not correct the tubular defect. This implies that the failure to inhibit the renal mechanism of hypercalcemia is probably the main cause of a poor response.

The development of drugs that inhibit tubular reabsorption of calcium [18], specifically inhibit PTH or PTH-rP action [19], or PTH-rP secretion or new antibodies against PTH-rP [20], could provide a better control of hypercalcemia in these patients when used in combination with the available inhibitors of osteolysis.

Other treatment options for hypercalcemia are calcitonin, corticosteroids, intravenous phosphate infusion, mithramicycin, gallium nitrate and prostaglandin inhibitors.

Calcitonin is the most useful drug; it effectively inhibits osteoclastic bone resorption as well as renal tubular calcium reabsorption and can lower serum calcium levels within two hours after treatment [21]. Calcitonin's effect on bone resorption is transient because of down regulation of receptors on osteoclasts, but it has a more sustained influence on the renal tubular calcium excretion, which accounts for its ability to control hypercalcemia for long periods of time. A recent Japanese study combined the rapid hypocalcemic effect of calcitonin together with the delayed effect of pamidronate in five patients with malignant hypercalcemia: no toxicity was reported and the combination allowed a rapid, long term control of hypercalcemia, possibly representing the treatment of choice in severe hypercalcemia [22].

Treatment with corticosteroids in patients with hypercalcemia and solid tumours has been disappointing [23]. Nevertheless, a recent randomised study performed in patients with metastatic breast cancer showed some beneficial effect [24]. The fact that response to corticosteroids may be observed after at least one week or more makes it imperative that more effective and rapid means of lowering serum calcium levels be used in symptomatic patients.

Intravenous phosphate infusion, mithramycin, gallium nitrate and prostaglandin inhibitors have significant disadvantages. Intravenous phosphate infusion may lead to renal precipitation of calcium-phosphate complexes and subsequent acute renal failure [25]. Mitramycin, a potent osteoclast inhibitor, may be associated with serious toxicity: thrombocytopenia, hepatic dysfunction, renal tubular damage and gastrointestinal side effects [26]. Gallium nitrate has been successfully used for treatment

of cancer associated hypercalcemia but its drawback lies in the requirement for a continuous intravenous infusion over five days [27]. Inhibitors of prostaglandin synthesis are effective only in an unpredictable 5% of patients with cancer related hypercalcemia [28].

Conclusions

The present case underlines the potential importance of PTH-rP as cause of severe, refractory hypercalcemia in patients with metastatic breast cancer. Its determination, whenever possible, can add useful information and lead to a better and more rational treatment strategy.

Hydration with diuretics and bisphosphonates are the first steps in the management of hypercalcemia but chemotherapy seems to be the fundamental tool in the long-term control of this paraneoplastic syndrome. The addition of calcitonin and corticosteroids can contribute to the optimal control of hypercalcemia but their specific role in the management of this patient cannot be clearly established.

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