

Unusual hypocalcaemia in breast cancer relapse with multiple bone metastasis

Said Darawshi^{1,2}, Mahmoud Darawshi³ and Deeb Daoud Naccache^{1,2}

¹Department of Endocrinology, Rambam Health Care Campus, Haifa, Israel, ²The Faculty of Medicine, Technion, Haifa, Israel, and ³Clalit Health Services, Northern District – Arrabah, Israel

Correspondence
should be addressed
to S Darawshi
Email
m_darawshi@hotmail.com

Abstract

Severe hypocalcaemia in breast cancer with bone metastasis is a rare finding usually associated with an advanced stage of the disease. We report a case of a 45-year-old woman with a history of local ductal carcinoma *in situ* (DCIS) of the breast, who presented with muscle tremors and general weakness. Hypocalcaemia was evident, with a positive Chvostek sign and a serum calcium level of 5.9 mg/dL (1.47 mmol/L), phosphorus 5.9 mg/dL (normal range: 2.3–4.7 mg/dL) with normal levels of albumin, magnesium and parathyroid hormone. High oral doses of alpha calcitriol and calcium with i.v. infusion of high calcium doses were instituted, altogether sufficient to maintain only mild hypocalcaemia. A whole-body CT revealed bone lesions along the axial skeleton. A biopsy from a bone lesion revealed a metastasis of breast carcinoma. With this pathological finding, leuprolide (GNRH analogue) and chlorambucil (alkylating agent) were initiated, followed by prompt tapering of infused calcium down to full discontinuation. Serum calcium was kept stable close to the low normal range by high doses of oral alpha calcitriol and calcium. This course raises suspicion that breast metastases to the skeleton caused tumour-induced hypocalcaemia by a unique mechanism. We assume that hypocalcaemia in this case was promoted by a combination of hypoparathyroidism and bone metastasis.

Learning points:

- Severe hypocalcaemia can be a presenting symptom for breast cancer relapse.

Background

Hypocalcaemia is common in oncology, where it affects 10% of all inpatient oncologic cases somewhere along the course of their disease. In general, it is mild and has a better prognosis than hypercalcaemia (1), generally associated with prostate cancer (2). Causes of hypocalcaemia include malabsorption, treatment with bone anti-resorptive drugs, osteoblastic bone metastasis, tumour lysis syndrome and chemotherapeutic agents (3). In contrast to hypocalcaemia found in advanced cases (4, 5, 6), our case presents treatment-resistant hypocalcaemia in an otherwise fresh relapse of metastatic breast carcinoma. To our knowledge, no cases of relapsed breast cancer that presented as treatment-resistant hypocalcaemia were reported before.

Case presentation

A 45-year-old woman with a history of left breast malignant neoplasm staged:

T4b N0 M0 grade 2, in biopsy: invasive lobular carcinoma grade 2, ER (estrogen receptor)=POS+3 in 100% of cells, PR (progesterone receptor) – NEG, HER2/NEU – NEG, KI-67 = 2%.

She underwent a left mastectomy due to breast adenocarcinoma 2 years before her admission, preceded by adjuvant Adriamycin/Cytosan and followed by local chest radiotherapy.

The patient received tamoxifen post-op for a short while, but it was discontinued by her request due to side effects.



She reported no comorbid states nor chronic consumption of medications.

A month prior to her admission to our department, she started complaining of muscle aches and tremor. An outpatient works up revealed mild hypocalcaemia of 7.4 mg/dL and a new normocytic anaemia (8 g/dL), otherwise absent in previous blood tests. She started on oral iron and calcium supplements.

The patient's worsening symptoms led her to seek in-hospital care, where she was diagnosed with pronounced hypocalcaemia and evident relapse of breast cancer. We ascribed her resistant-to-treatment hypocalcaemia in the presence of normal serum parathyroid hormone (PTH) levels to hypoparathyroidism. The patient denied the use of any drug that might interfere with serum calcium homeostasis, she also denied using herbal, homeopathic or alternative preparations, neither had she received chemotherapy in the previous 2 years nor any bone anti-resorptive agent. Physical examination on admission elicited a positive Chvostek sign. The rest of the physical examination revealed no other relevant finding.

Investigation

Neck/thyroid ultrasound revealed a normal-sized thyroid gland without apparent nodules.

CT revealed multiple cerebral and cerebellar nodular lesions.

Diffuse heterogenic hyper-dense lesions of the axial skeleton suspected as bone metastasis appeared on whole-body CT. A biopsy from a sacral lesion showed a metastatic breast carcinoma. The most pertinent laboratory findings are listed in [Tables 1 and 2](#).

PTH measurements are listed in [Table 3](#).

Etiologic considerations

The differential diagnosis of hypocalcaemia included:

- (1) Vitamin D deficiency.

Table 1 Calcium values before admission.

Days prior to first admission	Serum calcium (8.4–10.2 mg/dL)
150 days	8.4
40 days	7.4*
20 days	7.6**
7 days	6.4
3 days	6.1

*Onset of hypocalcaemia symptoms. **Under calcium treatment

Table 2 Laboratory work-up available on admission.

Laboratory test (units)	Reference range	Baseline
Plasma calcium (mg/dL)	8.4–10.2	5.9
Plasma inorganic phosphate (mg/dL)	2.3–4.7	5.92
Plasma creatinine (mg/dL)	0.57–1.11	0.79
Magnesium (mg/dL)	1.6–2.6	1.94
Albumin (g/dL)	3.5–5.2	4.5
25(OH)vitamin D3 (nmol/L)	>50	27
Parathyroid hormone (ng/L)	15–65	36
Thyroid-stimulating hormone (mU/L)	0.4–4.2	2.58
24-h urine calcium collection (mg)	100–200	24
24-h urine phosphate collection (mg)	400–1000	47

- (2) Hypoparathyroidism due to normal PTH levels in the face of severe hypocalcaemia (inappropriately normal).

Mild hypovitaminosis D was an unlikely explanation due to elevated serum phosphate levels; unexpectedly, resistance to combined calcium and alpha calcitriol treatment underpins this notion. Low urine calcium excretion indicates a normal renal effect of in-range PTH levels.

Treatment

The treatment course and corresponding calcium levels are listed in [Table 4](#). The patient was started on oral high doses of alpha calcitriol and high-dose calcium with unsatisfactory results; high i.v. doses of calcium gluconate became a need in order to prevent further deterioration of calcium levels. Serum calcium levels, however, remained below target.

Upon histopathological discovery of a bone lesion, adjuvant treatment with chlorambucil and leuprolide were initiated. Three days later, the patient was weaned from i.v. calcium treatment, while calcium levels remained stable only on a high oral dose of alpha calcitriol and calcium.

The patient was discharged home with a stable and low near normal serum calcium level.

Discussion

The uniqueness of this case resides in its leading clinical presentation, which was a new severe hypocalcaemia on the background of a breast malignancy relapse, a disease rather often associated with hypercalcemia.

In a series of inpatient oncologic cases with concomitant hypocalcaemia and bone metastasis, 7% of all breast cancer patients exhibited mild hypocalcaemia. None of those with breast cancer had severe hypocalcaemia;



Table 3 PTH measurements.

Timing of PTH measurement	PTH value	Perspective calcium and albumin values at time of PTH measurement
8 months after admission	13 pg/mL (4.6–58)*	Calcium 8.46 (8.5–10.5 mg/dL) Albumin 4.7 (3.5–5.4)
During admission	36 ng/L (15–65)**	Calcium 7 (8.5–10.5 mg/dL) Albumin 4.1 (3.5–5.4 g/dL)
7 days before admission	46 pg/mL (4.6–58)**	Calcium 6.4 (8.5–10.5 mg/dL) Albumin 4.1(3.5–5.4 g/dL)

*The DiaSorin LIAISON® N-TACT® PTH II Assay. **ROCHE Diagnostics automated biointact PTH (1–84) assay.

interestingly, most cases with severe hypocalcaemia had metastatic prostate cancer to the skeleton (2).

The most common causes of hypocalcaemia in malignant diseases are malabsorption, bone anti-resorptive treatment, tumour lysis syndrome and chemotherapeutic treatment (3). Our patient did not exhibit signs of malabsorption and was not on any of the hypocalcaemia-causing treatments. Laboratory findings were inconsistent with tumour lysis syndrome.

Rare causes include hypoparathyroidism and osteoblastic bone lesions. Hypoparathyroidism among breast cancer patients has been attributed to a direct toxic effect of:

- chemotherapy on the parathyroid glands (low PTH: 0.3, 0.2, 0.9 pmol/L; reference range: 1.0–6.0),
- malignant cells infiltrating the PT glands (in post-mortem autopsies) (4),
- an autoimmune mechanism (7), and
- a calcitonin-like peptide secretion by malignant cells (8).

Osteoblastic bone lesions can cause severe hypocalcaemia by depleting calcium stores; those lesions are associated with prostate cancer (9, 10) and rarely with breast cancer (4, 5, 6).

A sharp drop in serum calcium is expected to elicit compensatory PTH secretion until calcium levels are restored. Since the PTH level was in the normal range, the PTH response was not adequate to fully correct serum calcium levels. This inadequate response raises the question of whether a confounding factor had prevented an adequate increase in PTH (11), such as tumour-derived calcio-mimetic factors, supposed to offset the hypocalcaemia-induced PTH increase.

As to PTH effects on target tissues, low urinary calcium excretion indicates an intact PTH effect on the kidneys. Hence, severe hypocalcaemia under a normal renal PTH effect confines the defect of PTH action to the bone. Is it a mere primary PT gland inherent failure?

Relative hypoparathyroidism does not account for all findings. Respective treatment of primary PT gland failure (high oral doses of alpha calcitriol and calcium) failed to resolve severe hypocalcaemia.

Is it via a paraneoplastic factor that undermines the skeletal PTH effect? The improvement demonstrated in calcium levels following administration of antineoplastic therapy alludes to a tumour-related mechanism of severe hypocalcaemia. Whatsoever, this does not directly support

Table 4 Calcium and inorganic phosphate throughout the hospital stay.

Inpatient day no.	Lab results		Treatment				
	Calcium (mg/dL)	Phosphate (mg/dL)	Oral		Intravenous		
			1,25(OH)D3 (µg)	Calcium carbonate (g)	Calcium gluconate 10% (100 mg/mL)	Leuprolide 3.75 mg SC	Chlorambucil 3.5 mg i.v.
1	5.9	5.92	1 + 1	0.6 tid	1000 mg	×	×
2	6.1	6.25	1 + 1	1.2 tid	1000 mg	×	×
3	6.5		1 + 1	1.2 tid	2000 mg	×	×
5	7.0	5.71	1 + 1	1.2 tid	10 000 mg	×	×
7	6.8	5.61	1 + 1	1.8 tid	10 000 mg	✓	✓
8	6.5	6.1	1 + 1	1.8 tid	10 000 mg	×	×
9	6.9	5.26	1 + 1	1.8 tid	10 000 mg	×	×
10	7.8		1 + 1	1.8 tid	5000 mg	×	×
11	8.4	4.88	1 + 1	1.8 tid	None	×	×
12	7.5	4.46	1 + 1	1.8 tid	None	×	×
13	7.4	4.84	1 + 1	1.8 × 4/day	None	×	×
15 (end of stay)	7.9	5.53	1 + 0.5	1.8 × 4/day	None	×	×

SC: subcutaneous tid: three times per day



the notion of blunted skeletal PTH effects. Therefore, the mechanisms potentially involved in hypocalcaemia in our case are the following:

- A paraneoplastic factor that undermines the PTH effect on bone.
- High calcium consumption by osteoblastic lesions.
- Inadequate parathyroid gland function.
- A tumour-related calcio-mimetic factor.

The ongoing need for alpha calcitriol and calcium substitution after chemotherapy underpins the notion of combined aetiologies, since neither of them solved the hypocalcaemia alone.

Conclusions

Our case depicts the complexity behind breast cancer-induced hypocalcaemia and the lack of information and clinical understanding that hampers knowledge acquisition. It is therefore mandatory to carry out a comprehensive workup of parathyroid hormone as well as calcium haemostasis, to understand the precise mechanism underlying this rare entity and respectively evaluate the adequate treatment modality. In hope that similar reported cases help plot the detailed alterations that underly this phenomenon.

Hypocalcaemia in our case was mainly a result of relative hypoparathyroidism, increased calcium consumption by osteoblastic lesions, not excluding potential paraneoplastic confounders. To our best knowledge, this is the first case to report severe hypocalcaemia as a presenting finding in breast malignancy relapse.

Supplements

PTH measurement

In our medical centre, we use the ROCHE Diagnostics automated Biointact PTH (1–84) assay- third generation.

The PTH measurement before and after the admission were conducted by an outpatient health provided with The DiaSorin LIAISON® N-TACT® PTH II Assay.

Normal ranges are described in [Table 4](#).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent

Written informed consent was obtained from the patient for publication of this report.

Author contribution statement

All the authors have contributed to the writing and editing of this manuscript and the physician responsible for the patient is one of the authors.

References

- Schattner A, Dubin I, Huber R & Gelber M. Hypocalcaemia of malignancy. *Netherlands Journal of Medicine* 2016 **74** 231–239.
- Gonçalves JAF, Costa T, Rema J, Pinto C, Magalhães M, Esperança A & Sousa L. Hypocalcemia in cancer patients: an exploratory study. *Porto Biomedical Journal* 2019 **4** e45. (<https://doi.org/10.1097/pbj.0000000000000045>)
- Riancho JA, Arjona R, Valle R, Sanz J & González-Macías J. The clinical spectrum of hypocalcaemia associated with bone metastases. *Journal of Internal Medicine* 1989 **226** 449–452. (<https://doi.org/10.1111/j.1365-2796.1989.tb01423.x>)
- Bergkamp FJ, van Berkel AM, van der Linden PW & Gorgels JP. Unexpected prolonged extreme hypocalcaemia and an inadequate PTH response in a patient with metastatic breast carcinoma. *Netherlands Journal of Medicine* 2003 **61** 371–375. (<https://pubmed.ncbi.nlm.nih.gov/14768721/>)
- Özçelik S, Ferhatoglu F, Çelik M, Özçelik M, Baş S, Cengiz H & Gözü HI. Metastatic breast carcinoma with treatment-resistant hypocalcemia. *Advancements in Case Studies* 2019 **1** AICS.000523.2019. (<https://doi.org/10.31031/AICS.2019.01.000523>)
- Watanabe T, Adachi I, Kimura S, Yamaguchi K, Suzuki M, Shimada A & Abe K. A case of advanced breast cancer associated with hypocalcemia. *Japanese Journal of Clinical Oncology* 1983 **13** 441–448. (<https://pubmed.ncbi.nlm.nih.gov/6887561/>)
- Farolfi A, Ferrario C, Aquilina M, Cecconetto L, Tartaglia A, Ibrahim T, Serra L, Oboldi D, Nizzoli M & Rocca A, Oboldi D, Nizzoli M & Rocca A. Paraneoplastic hypocalcemia-induced heart failure in advanced breast cancer: a case report and literature review. *Oncology Letters* 2015 **10** 773–777. (<https://doi.org/10.3892/ol.2015.3326>)
- Hall TC, Griffiths CT & Petranek JR. Hypocalcemia – an unusual metabolic complication of breast cancer. *New England Journal of Medicine* 1966 **275** 1474–1477. (<https://doi.org/10.1056/NEJM196612292752605>)
- Fokkema MI, De Heide LJ, Van Schelven WD & Hamdy NAT. Severe hypocalcaemia associated with extensive osteoblastic metastases in a patient with prostate cancer. *Netherlands Journal of Medicine* 2005 **63** 34–37. (<https://pubmed.ncbi.nlm.nih.gov/15719851/>)
- Kukreja SC, Shanmugam A & Lad TE. Hypocalcemia in patients with prostate cancer. *Calcified Tissue International* 1988 **43** 340–345. (<https://doi.org/10.1007/BF02553276>)
- Grant FD, Conlin PR & Brown EM. Rate and concentration dependence of parathyroid hormone dynamics during stepwise changes in serum ionized calcium in normal humans. *Journal of Clinical Endocrinology and Metabolism* 1990 **71** 370–378. (<https://doi.org/10.1210/jcem-71-2-370>)

Received in final form 27 August 2021

Accepted 15 November 2021