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Severe hypocalcaemia associated with extensive osteoblastic metastases in a patient with prostate cancer

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ABSTRACT

A patient with an untreated carcinoma of the prostate was admitted with dehydration, stupor and a surprisingly deep hypocalcaemia. The severe hypocalcaemia was largely attributed to extensive osteoblastic activity due to widespread skeletal metastases although contributing factors to the severity of the hypocalcaemia were a relative vitamin D deficiency, hypomagnesaemia and renal impairment, preventing the mounting of an adequate homeostatic response. There was significant clinical and biochemical improvement after antitumour treatment using androgen deprivation, and supplementation with calcium and vitamin D.

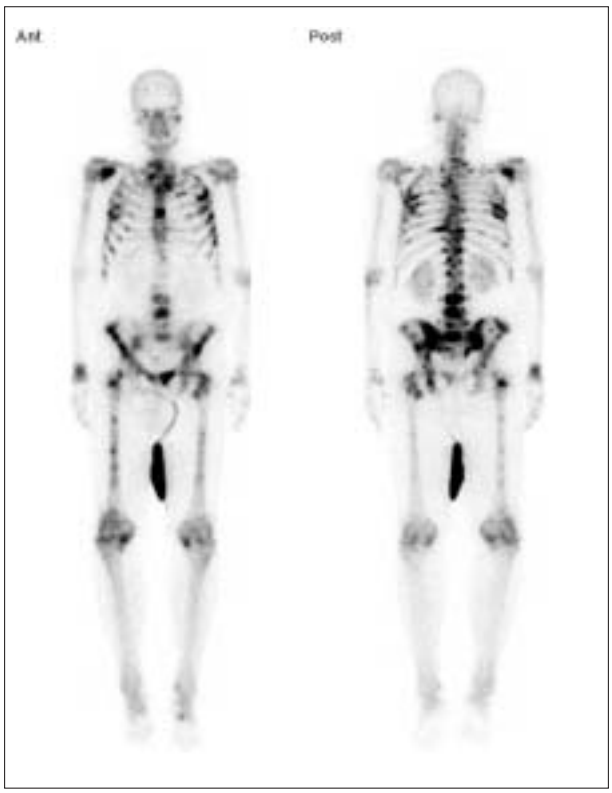
INTRODUCTION

Hypercalcaemia is a relatively common complication of malignancy, particularly in its terminal stages. Clinically significant hypocalcaemia is much less common. Reported causes of malignancy-associated hypocalcaemia are hypoalbuminaemia, vitamin D deficiency, tumour lysis syndrome usually following chemotherapy, and increased calcium utilisation by extensive osteoblastic skeletal metastases. This last cause of hypocalcaemia has mostly been reported in the advanced stages of prostate cancer. However, even in the terminal stages of this malignancy, hypocalcaemia is usually an asymptomatic, incidental finding. In this case report we present a patient with an untreated carcinoma of the prostate who presented with unusually severe, life-threatening hypocalcaemia. A combination of androgen deprivation, high doses of calcium and an active metabolite of vitamin D led to a significant clinical and biochemical improvement.

CASE REPORT

A 67-year-old patient was referred for admission because of progressive lethargy, anorexia and dehydration. An adenocarcinoma of the prostate had been diagnosed by transrectal biopsy three months previously, with Gleason score (4 + 4). ^{99m}Tc-hydroxymethylene-diphosphonate bone scintigraphy performed at the time of diagnosis showed evidence of limited metastatic involvement of the skeleton (*figure 1*). Besides a chest X-ray, no standard X-rays were taken.

The patient was then largely asymptomatic and it was decided not to start hormonal treatment as yet.
On admission, the patient was disorientated in time and place and in a semi-stupor state. He was apyrexial and showed signs of dehydration. Chvostek and Trousseau's signs could be clearly elicited. Results of initial laboratory investigations are shown in the *table 1* (first column). Renal function was significantly impaired. There was a severe hypocalcaemia associated with mild hyperphosphataemia, but an only moderately (fourfold) increased PTH concentration despite the severe hypocalcaemia, probably because of the prevailing significantly decreased serum magnesium concentration. Serum alkaline phosphatase activity was increased more than 20-fold and serum PSA concentration was markedly elevated suggesting significant tumour load. This was also suggested by bone marrow suppression as evidenced by the low haemoglobin concentration and the low white blood cells and platelets counts. 25-hydroxy vitamin D concentration was low and 1,25-dihydroxy-vitamin D concentration inappropriately normal for the degree of hypocalcaemia. No abnormalities were detected on plain radiographs of the chest.



Figuur 1
^{99m}Tc-HDP bone scintigraphy at time of the diagnosis of prostate carcinoma

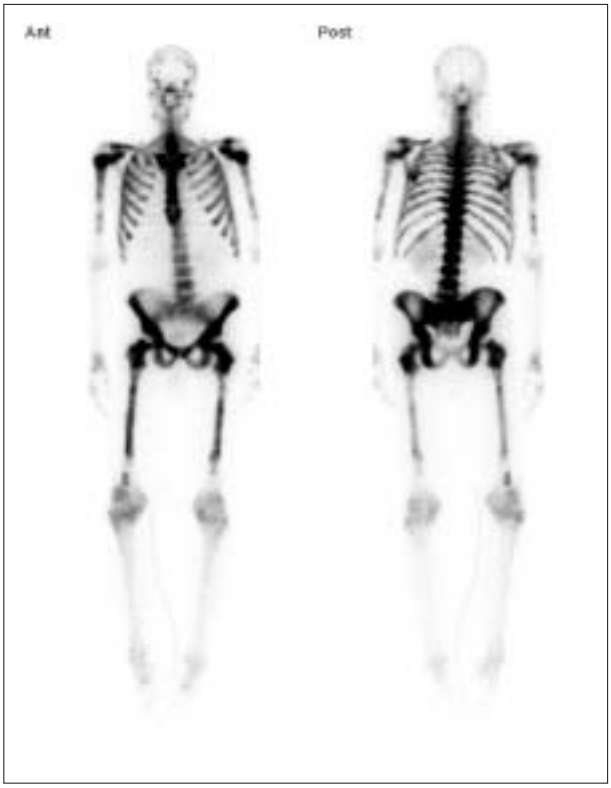


Figure 2
^{99m}Tc-HDP bone scintigraphy at time of the admission with hypocalcaemia

Table 1
Biochemical data on admission and 10 and 20 days after institution of therapy in a patient with prostate cancer and widespread skeletal metastases

	ON ADMISSION	10 DAYS LATER	20 DAYS LATER	NORMAL VALUES
Haemoglobin	4.5	6.6	6.3	7.2-9.8 mmol/l
White blood cell count	7.4	9.4	7.6	4.0-11.0 x 10^9/l
Platelets	75	113	179	150-400 x 10^9/l
Sodium	141	134	139	136-146 mmol/l
Potassium	5.7	4.7	4.8	3.5-4.5 mmol/l
Creatinine	306	92	105	62-106 µmol/l
$Calcium_{(total)}$	<1.0	1.56	1.95	2.10-2.60 mmol/l
Albumin	30	26	30	36-47 g/l
$Calcium_{(ionised)}$	0.46		0.99	1.10-1.35 mmol/l
Magnesium	0.56	0.80	0.83	0.70-1.0 mmol/l
Phosphate	1.65	1.69		0.70-1.40 mmol/l
Alkaline phosphatase	2430	1880	2090	<90 U/l
Lactate dehydrogenase	2110	940	760	<300 U/l
Prostatic specific antigen	946	156		<4 µg/l
25-hydroxy-vitamin D_3	21			30-100 nmol/l
1,25-dihydroxy-vitamin D_3	62			40-160 pmol/l
Parathyroid hormone	35.9	26.1	27.1	1.5-9.0 pmol/l
Testosterone	13.0		0.3	10-40 nmol/l

After exclusion of a post-renal cause for the renal impairment, the patient was intensively rehydrated together with intravenous supplementation with calcium gluconate and administration of calcitriol. Primary treatment of the prostate cancer by androgen deprivation was concurrently instituted using leuprolin, an LHRH analogue, and bicalutamide, an androgen-receptor blocker. Repeated ^{99m}Tc-HDP bone scintigraphy now showed the pattern of a 'superscan', indicating extensive skeletal metastases. Clear progression could be demonstrated compared with the bone scintigraphy performed at the time of diagnosis (*figure 2*).

Within a few days of starting treatment, a marked improvement was noted in the patient's general condition including his mental status. This clinical improvement was paralleled by a significant improvement in all biochemical parameters measured including PSA concentrations (*table 1*). After ten days of intravenous substitution, calcium was given orally at a daily dose of 1000 mg and calcitriol was continued at the same dose of 1 μg a day. The patient could be discharged home in a relatively good condition with significantly improved renal function although still demonstrating mild hypocalcaemia (ionised serum calcium 0.99 mmol/l). Serum magnesium had normalised but secondary hyperparathyroidism persisted probably due to the combination of persistent hypocalcaemia and still impaired renal function.

Within the following three months, the patient's clinical condition deteriorated significantly with the development of extensive liver metastases. The patient developed a clear Cushing's syndrome in this phase (24 hour cortisol >5000 nmol/l), suggesting a neuro-endocrine component. A biopsy of one of the liver metastases showed a small cell anaplastic carcinoma. Since there were no signs of tumour on the chest X-ray, the liver metatases had originated in the prostate.

NSE and chromogranin A levels were not determined. Although there was no recurrence of hypocalcaemia, there was a rapidly downhill clinical course and the patient died a few weeks later. An autopsy examination was not undertaken.

DISCUSSION

An unusual feature of the case we report here is the severe symptomatic hypocalcaemia at presentation in a patient with prostate cancer metastatic to the skeleton. In a survey of more than 7000 patients with cancer, hypocalcaemia was indeed found to be present in only 1.6% of cases.[1] In malignant diseases, the most common cause of hypocalcaemia is vitamin D deficiency associated with the malignant state. Rare reported causes of hypocalcaemia in cancer are hypoparathyroidism due to destruction of parathyroid glands by metastases from a breast carcinoma,[2,3] severe hypomagnesaemia due to paraneoplastic renal loss of magnesium described in ovarian carcinoma,[4] renal impairment, or a tumour lysis syndrome following the use of various chemotherapeutic agents.[5] The presence of bone metastases increases the prevalence of true hypocalcaemia to 5 to 13%, depending on the formula used to correct for serum albumin concentrations.[6] Osteoblastic metastases have been reported to be associated with hypocalcaemia in patients with breast carcinoma,[2,7] but the most frequently encountered tumour causing hypocalcaemia is prostate cancer metastatic to the skeleton.[8] In the study by Riancho *et al.*, 75% of cases of hypocalcaemia were due to prostate cancer.[6] In prostate cancer metastatic to the skeleton, hypocalcaemia is more likely because of the predominantly osteoblastic nature of the metastatic process leading to an increased influx of calcium into bone due to increased bone formation. Hypocalcaemia is usually mild and clinical signs are rare. In a study of 112 patients with metastatic prostate cancer only 0.9% of the patients were actually found to have symptomatic hypocalcaemia[8] although cases of severe hypocalcaemia have also occasionally been reported.[9-12]

In our patient, the marked tumour load and the subsequent rapid disease progression despite adequate androgen deprivation point to increased utilisation of calcium by avid osteoblastic metastases as playing a central role in the pathophysiology of the hypocalcaemia observed. It is of note, however, that our patient was also vitamin D deficient, with inappropriately normal 1,25-hydroxyvitamin D concentrations, probably due to impairment of the synthetic capacity of the kidney for 1,25-hydroxyvitamin D production and to the inappropriate increase in PTH concentrations because of the prevailing hypomagnesaemia.

The cause of the significantly decreased magnesium concentration, particularly in the presence of renal impairment, is not clear although probably paraneoplastic as the disturbance spontaneously reverted following institution of hormonal therapy. Reversal of renal impairment by successful rehydration and supplementation with calcium and an active metabolite of vitamin D resulted in a significant and rapid clinical and biochemical improvement with near normalisation of serum calcium concentrations. These, however, remained below the normal laboratory reference range and were associated with persistently elevated serum PTH concentrations suggesting that, in retrospect, higher doses of calcitriol may have achieved a more complete correction of calcium homeostasis than the dose used in our patient. The significant decrease in PSA concentration following androgen deprivation points to a decrease in tumour load with the decreased skeletal utilisation of calcium also contributing to correction of the hypocalcaemia.

This case underlines the fact that in malignant diseases, a probably otherwise common vitamin D deficiency may hold significant clinical consequences, particularly when calcium homeostasis is already jeopardised by the presence of skeletal metastases.

In summary, we present a patient with prostate cancer and severe symptomatic hypocalcaemia, predominantly due to extensive osteoblastic metastases, in whom primary treatment of the tumour and supplementation with calcium and vitamin D resulted in a significant clinical and biochemical response.

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