CASE REPORT

Refractory hypocalcaemia complicating metastatic prostatic carcinoma

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SUMMARY

A 72-year-old man with a background of ischaemic heart disease was referred to the accident and emergency department with a 1-week history of worsening dyspnoea and lethargy. A chest X-ray revealed a right-sided lobar pneumonia and a prolonged corrected QT interval was noted on his ECG at presentation. Laboratory investigations confirmed severe hypocalcaemia, significant vitamin D deficiency and relative hypoparathyroidism. A markedly elevated prostate-specific antigen was also identified. Bone scintigraphy demonstrated widespread osteoblastic bone metastases. Severe hypocalcaemia persisted despite treatment and he succumbed after 60 days of hospitalisation.

BACKGROUND

Carcinoma of the prostate is the fourth most common cause of cancer death in the UK, accounting for around 7% of all deaths from cancer and the second most common cause of cancer death among men in the UK.¹ A third of patients with prostatic carcinoma and bone metastases have low serum calcium concentrations,² and some have severe hypocalcaemia. Accounting for considerable morbidity and mortality, such metastatic deposits are predominantly blastic (bone-forming)³ and commonly cause increased serum levels of parathyroid hormone on account of calcium ions being transferred from serum into blastic bone.⁴ We report the case of a patient whose presentation with severe hypocalcaemia led to a diagnosis of metastatic prostatic carcinoma.

CASE PRESENTATION

A cachectic 72-year-old man was referred to hospital because of a 1-week history of worsening dyspnoea and lethargy. On physical examination he was febrile, appeared pale and had coarse crackles at the base of his right lung.

INVESTIGATIONS

Chest X-ray showed consolidation in the right lung. ECG showed a prolonged corrected QT interval (513 ms; [figure 1](#)). Initial laboratory investigations showed severe hypocalcaemia (corrected serum calcium=1.32 mmol/L (2.05–2.60)) in the setting of hyperphosphataemia (1.57 mmol/L (0.87–1.45)), hypomagnesaemia (0.43 mmol/L (0.65–1.05)), normocytic anaemia (haemoglobin 6.7 g/dL), renal impairment, (serum urea 8.0 mmol/L (1.7–8.3), serum creatinine 134 µmol/L (62–106)), (estimated-glomerular filtration rate 46 mLs/min/1.73 m³) and

elevated serum alkaline phosphatase concentrations (448 IU/L (40–129)). Subsequent investigations revealed relative hypoparathyroidism (parathyroid hormone only mildly elevated at 76 pg/mL (14–72)) and severe vitamin D deficiency (serum 25-hydroxyvitamin D 7.9 ng/mL (20–70)). There was no evidence of iron, vitamin B₁₂ or folate deficiency. A CT scan of the thorax and abdomen showed two nodular lung lesions, extensive bone metastases, hydronephrosis of the right kidney and a dilated right ureter. Serum prostate-specific antigen was markedly elevated at 14 889 ng/mL (0–4), suggesting a significant tumour load. Bone scintigraphy confirmed widespread osteoblastic bone metastases ([figure 2](#)). He was reviewed by a urology team. Digital rectal examination confirmed an enlarged irregular firm prostate, rendering a clinical diagnosis of metastatic prostatic carcinoma highly plausible. A review of the patient's previous medical records revealed that 3 months prior to this, his serum calcium levels were normal and that there was no prolongation of the QT interval on his ECG.

TREATMENT

The patient was initially treated with intravenous antibiotics and in view of the hypomagnesaemia and severe hypocalcaemia with QT prolongation on the ECG, he was also started on intravenous infusions of magnesium and calcium. Two doses of 8 mmol of magnesium sulfate were given over 2 days. Oral magnesium glycerophosphate (8 mmol three times daily) was also initiated at a later stage, with improvement in serum magnesium levels ([figure 3](#)). High-dose oral 1-α hydroxyvitamin D3 (initially 1 µg daily and subsequently increased to 3 µg) and oral calcium supplements were also added during his admission. The patient did not

Figure 1 ECG showing a prolonged corrected QT interval (QT_c) of 513 ms.

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Figure 2 Isotope bone scan showing diffuse metastases and a 'superscan' appearance.

consent to tissue biopsy. Antiandrogen therapy was initiated by his consulting urologists.

OUTCOME AND FOLLOW-UP

Severe hypocalcaemia persisted despite treatment (figure 4). He sadly succumbed after 60 days of hospitalisation from sepsis.

DISCUSSION

An unusual feature of the case we report here is the severe hypocalcaemia at presentation in a patient with prostate cancer metastatic to the skeleton. In its terminal stages, hypocalcaemia is usually asymptomatic and incidental.⁵

Bone metastases from prostate cancer are predominantly blastic (bone-forming) and commonly cause increased serum levels of parathyroid hormone (PTH) as calcium ions are transferred from serum into blastic bone.

The 'hungry bone syndrome' is a well-recognised metabolic derangement in metastatic prostatic carcinoma.⁶ This is characterised by calcium entrapment in bone as a consequence of excessive osteoblastic activity, causing hyperparathyroidism.

In case series reported by Berruti *et al*,⁷ Buchs *et al*⁸ and Murray *et al*,⁹ the prevalence of secondary hyperparathyroidism in advanced prostate cancer ranged from 21 to 57%.

The observation that prostate cancer metastasis to the bone is associated with increased osteoblast activity is supported by the finding that serum levels of markers of osteoblastic proliferation, such as bone-specific alkaline phosphatase, are increased in patients with metastatic disease.¹⁰

The normal vitamin B₁₂ and folate concentrations in our patient are against a state of generalised malabsorption. Hypomagnasaemia may have contributed to the low serum calcium levels initially;¹¹ however, hypocalcaemia persisted even after the improvement and correction of serum magnesium

Figure 3 Graph showing serum magnesium levels.

Figure 4 Graph showing persistent hypocalcaemia.

levels, making it unlikely to have contributed significantly to its development. Administration of supraphysiological doses of 1, 25 dihydroxyvitamin D did not correct hypocalcaemia.

Alternative therapies that could have been considered include parenteral calcitriol as well as oral or parenteral calciferol in high doses.^{8 12}

The persistence of severe hypocalcaemia despite the improvement and eventual normalisation of serum magnesium concentrations renders functional hypoparathyroidism secondary to hypomagnesaemia unlikely. Other factors may, however, have contributed to a blunted parathyroid hormone response, such as circulating humoral factors secreted from the tumour cells or bone. This might also explain the modest increase of serum alkaline phosphatase in our patient.

In a case series by Murray *et al*,⁸ out of 146 patients with advanced prostate cancer, only 34% of all patients had increased levels of PTH. Even in patients with progressive disease and proven bone metastatic tumours, only 57% had high PTH values.^{13–16}

Two classes of antiresorptive agents, bisphosphonates such as zoledronic acid and denosumab, a fully human monoclonal antibody that inhibits osteoclastic bone resorption by specifically binding and inhibiting the receptor activator of nuclear factor- κ B ligand-RANKL, are often used for prevention of skeletal events and to reduce skeletal morbidity in patients with advanced prostatic malignancy. Both can cause or worsen hypocalcaemia, making it important to check and monitor calcium levels, as this may have a bearing on the use of antiresorptive agents.^{17 18}

We postulate that this man's hypocalcaemia was likely to be multifactorial, stemming from disseminated osteoblastic metastases complicating his prostatic carcinoma, in the setting of pre-existing vitamin D deficiency and relative hypoparathyroidism.

Learning points

- Hypercalcaemia is a relatively common complication of malignancy, particularly in its terminal stages. Clinically significant hypocalcaemia is much less common.
- Hypocalcaemia can be a manifestation of prostate cancer metastatic to the bone.
- Osteoblastic bone metastasis should be considered in the differential diagnosis of hypocalcaemia.
- An abnormal parathyroid hormone response may contribute to and worsen the hypocalcaemia in advanced prostate cancer.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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