

Refractory hypercalcaemia secondary to parathyroid carcinoma: response to high-dose denosumab

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Abstract

Objective: Hypercalcaemia is an important cause of increased morbidity and mortality in patients with parathyroid carcinoma. Surgical resection is the mainstay of treatment but, equally, managing hypercalcaemia is of paramount importance. At present, few therapies have been shown to be effective in the most severe cases. This report describes the efficacy of denosumab in a patient with parathyroid carcinoma when conventional therapies had been shown to be relatively ineffective.

Subject, methods and results: A 50-year-old man presented with symptomatic hypercalcaemia 1 year after the surgery for his parathyroid carcinoma. Investigations revealed raised serum calcium and parathyroid hormone concentrations consistent with the recurrence of the disease. Imaging failed to localise any surgically remediable foci. Medical management with loop diuretics, calcimimetics and bisphosphonates failed to provide a sustained response. Denosumab, as a monthly injection, led to a gradual decrement in his peak calcium concentrations with the values now persistently below 3 mmol/l.

Conclusions: Denosumab, a fully human MAB that binds to the 'receptor activator of nuclear factor κ B ligand (RANKL)', was shown to have a profound effect in modulating malignant hypercalcaemia. This medication should be considered as an effective option in patients with refractory hypercalcaemia secondary to parathyroid carcinoma.

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Introduction

Parathyroid carcinoma is a rare disease, which occurs in <1% of all cases of hyperparathyroidism (1). Although it is difficult to distinguish between parathyroid adenoma and carcinoma clinically, parathyroid carcinoma is usually associated with profound hypercalcaemia and very high parathyroid hormone (PTH) concentrations. Compared with its benign counterpart, a palpable neck mass and concomitant renal and skeletal diseases are more common among patients with parathyroid carcinoma. A high degree of clinical suspicion is necessary in order to optimise the surgical outcome, as the first operation is the most important one: this should involve an *en bloc* resection of the tumour as well as all potential areas of

invasion at the initial operation (2). While parathyroid carcinoma has a relatively low potential for distant metastasis, it does tend to recur locally. These tumours may be very indolent, even when metastatic, and patients rarely die from tumour *per se*. It is therefore of paramount importance to control the hypercalcaemia, which may be lethal (3). However, at present, few therapies have been shown to be effective in the most severe cases.

Cinacalcet, a calcimimetic agent, has been used in these patients: under normal circumstances, PTH secretion is regulated by the calcium-sensing receptor on parathyroid chief cells and cinacalcet lowers PTH concentrations by increasing the sensitivity of these receptors.

It has been used to control the hypercalcaemia in parathyroid carcinoma, but its effectiveness in this situation depends on the tumour expressing the receptors, which may not always be the case. Furthermore, cinacalcet is often poorly tolerated at doses required for control (4). Bisphosphonates have shown some promise in the treatment of hypercalcaemia by inhibiting PTH-dependent osteoclast activation; pamidronate and zoledronate are widely used for such patients, although renal function needs to be monitored periodically (5).

Denosumab is a fully human MAB that binds to the 'receptor activator of nuclear factor κ B ligand (RANKL)' and inhibits osteoclast development, activation and survival. It has been shown to have a profound effect in modulating malignant hypercalcaemia (6). Very recently, the use of denosumab in the treatment of hypercalcaemia related to parathyroid carcinoma has been reported in two case reports (7, 8). We were contemporaneously using denosumab for a similar patient with hypercalcaemia and parathyroid carcinoma and report its high efficacy when all else had failed.

Case presentation

A 50-year-old man was referred to the Endocrine Department with a recurrence of symptomatic hypercalcaemia. Two years earlier, he had been referred to a renal physician with subacute deterioration in his renal function. He had a history of significant weight loss, malaise, constipation and arthralgia. There was no radiation exposure or personal history of cancer. He had a family history of bowel cancer in his mother and sister, who had died at the age of 68 and 46 years respectively. One of his other sisters died from melanoma in her early 20s. On further investigation of his impaired renal function, he was found to have an elevated serum calcium concentration of 3.70 mmol/l (normal range 2.12–2.62 mmol/l: all values are 'albumin-adjusted' serum calcium concentrations) with a serum PTH concentration of 177 pmol/l (normal range 1.3–7.6 pmol/l). Plain radiography of his chest revealed a symmetrical periosteal reaction and subperiosteal bone resorption involving the distal clavicles, and he had medullary nephrocalcinosis on renal ultrasonography. A radiolabelled ^{99}Tm -sestamibi scan and neck ultrasonography both localised a left parathyroid tumour. The very high PTH concentration and markedly elevated calcium concentration with concomitant renal and bone involvement raised the suspicion of a parathyroid carcinoma. He was scheduled for emergency surgery for left thyroid lobectomy, parathyroidectomy and central

node dissection. At operation, a large mediastinal tumour measuring $\sim 3.0 \times 2.2 \times 1.5$ cm was found, requiring median sternotomy. Histology of the mediastinal mass consisted of a mixed population of cells, the majority of which resembled parathyroid chief cells with a smaller proportion of oncocytic cells. There were areas of necrosis and mitoses, and the lesion had an infiltrative margin (Fig. 1). In these infiltrative areas, the tumour looked frankly malignant, and there were foci suspicious of lymphovascular invasion. Overall, the tumour was suggestive of a parathyroid carcinoma, and at one edge, there remained a small area of convincing parathyroid tissue that had retained its original architecture. Immunohistochemistry showed patchy positivity with chromogranin and negativity for CEA, calcitonin, TTF1 and thyroglobulin. The tumour itself was negative for parafibromin staining (Fig. 2), confirming its status as a parathyroid carcinoma. The thyroid lobe showed no evidence of malignancy, while a small nodule adjacent to the thyroid was consistent with parathyroid tissue hyperplasia. Post-operatively, his staging imaging investigations were negative, including normal magnetic resonance imaging (MRI) of the neck and computed tomography (CT) scanning of the chest, abdomen and pelvis. Post-operatively, serum PTH concentrations dropped to 0.3 pmol/l immediately.

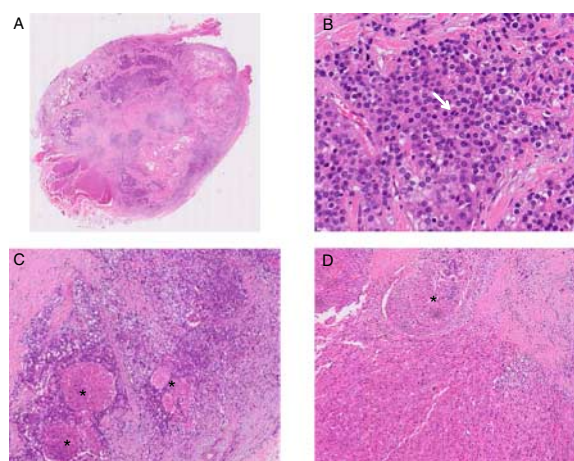


Figure 1

Parathyroid carcinoma. (A) Low image scan of H&E section showing circumscribed tumour with broad bands of fibrosis. (B) Tumour cells with an abnormal mitotic figure (200 \times) are indicated by the white arrow. The tumour is composed of lobules of chief cells (C, 40 \times) and oncocytes (D, 40 \times) with foci of necrosis (*). Immunohistochemical studies show chromogranin positivity, confirming its endocrine nature. Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-14-0166>.

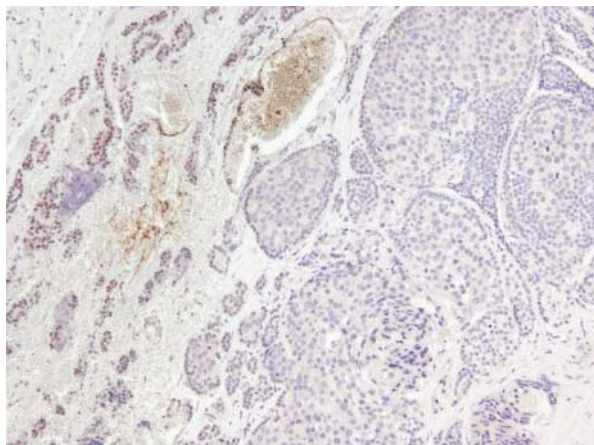


Figure 2

Parafibromin immunohistochemistry showing positive nuclear staining in the residual normal parathyroid gland tissue (left) with absent nuclear immunoreactivity in the malignant tumour cells (right). Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-14-0166>.

The levels had risen to 34.7 pmol/l at 1 month, but gradually showed a trend downwards to 20.2 pmol/l at 2 months and 8.2 pmol/l at 8 months after the surgery. His calcium concentration was 2.93 mmol/l immediately after surgery and dropped to 2.16 mmol/l at 1 month, which raised the possibility of hungry bone disease. He was commenced on vitamin D and calcium supplements, but this was stopped after 2 months when the calcium concentration was 2.45 mmol/l. He was asymptomatic with normocalcaemia for 8 months before his new presentation. Germline genetic testing was negative for any pathological variants in *MEN1*, *CDC73* (the *parafibromin* gene), *CASR*, *CDKN1A*, *CDKN1B*, *CDKN2B*, *CDKN2C* and *RET* oncogenes. Multiplex ligation-dependent probe amplification analysis (MPLA) of *MEN1* and *CDC73* did not show any deletion or duplication.

At presentation in our department, investigation revealed an elevated serum calcium concentration of 3.34 mmol/l and a PTH concentration of 73 pmol/l, suggesting recurrence of his parathyroid carcinoma. MRI scanning of his neck did not show any evidence of local recurrence, while FDG–positron emission tomography (PET)/CT and ⁹⁹Tm-sestamibi scanning also failed to localise surgically resectable lesions.

As there was no surgically remediable focus of the disease, we opted for medical management of his hypercalcaemia. He was commenced on cinacalcet at a

dose of 30 mg daily, the dose being gradually increased. Unfortunately, due to gastrointestinal side effects he was unable to tolerate a dose above 30 mg daily, on which his calcium concentration remained elevated at 3.6 mmol/l. At this point, he was admitted in hypercalcaemic crisis with a very high calcium concentration of 4.2 mmol/l: he was managed with fluids and i.v. bisphosphonates, initially pamidronate at a dose of 60 mg and then zoledronate at a dose of 5 mg. Following the treatment with zoledronate, his calcium concentration fell to 2.38 mmol/l but returned to 2.92 mmol/l at 6 days and to 3.54 mmol/l at 23 days after the infusion. Given the patient's failure to respond in a sustained manner to the above measures, we then trialled denosumab at a dose of 60 mg subcutaneously as a single dose, after consultation with the Chairman of the Hospital Drugs Committee.

His serum calcium concentrations decreased from 3.54 to 2.93 mmol/l at 10 days following the first dose of denosumab. However, by 4 weeks, it had risen to 3.38 mmol/l: 4 weeks later he received his second dose of denosumab 60 mg. This lowered his calcium concentration to 2.93 mmol/l. Following an application for an 'Individual Funding Requirement' from the local area Clinical Commissioning Group (CCG), in accord with UK NHS regulations, permission was obtained to continue treatment with denosumab. He was thereafter treated with denosumab at a dose of 120 mg subcutaneously every 4 weeks with a fall following each injection and then a return to an elevated level, but the peak calcium concentration gradually decreased (see Fig. 3). He remains on 4-weekly denosumab at a dose of 120 mg with serum calcium concentration persistently below 3 mmol/l. His PTH concentrations remain persistently elevated and are trending upwards; this may reflect the decreased feedback inhibition of serum calcium that has concomitantly declined with treatment, but we suspect this is mainly a progression of his carcinoma.

Discussion

Parathyroid carcinoma is a rare disease: evidence to guide optimal treatment is therefore scarce. Surgical resection of the tumour is the mainstay of treatment, but more than two-thirds of patients will show recurrence after the initial operation. Adjuvant radiotherapy may play a role in the post-operative setting, but parathyroid carcinoma is generally resistant to radiation therapy (9). The published literature on medical therapy is limited due to the rarity of the disease, and there are no generally accepted regimens with proven efficacy using cytotoxic chemotherapy.

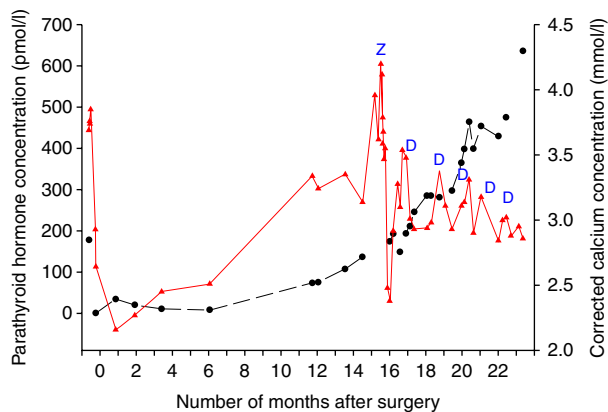


Figure 3

This graph illustrates the patient's calcium (solid line, closed triangles – scale on the right axis) and parathyroid hormone concentrations (interrupted line, closed circles – scale on the left axis) plotted against duration in months after surgery. This emphasises the relentless increase in PTH concentrations 12 months following surgery. In this graph, zoledronate (Z) follows an inpatient admission with severe hypercalcaemia (corrected calcium concentration >4 mmol/l), which was treated with aggressive i.v. fluids, furosemide and finally i.v. zoledronate (denoted as Z). This led to an impressive but short-lived drop in calcium (<4 weeks). Denosumab (denoted by D) was then given, first two doses at 60 mg s.c. and then 120 mg s.c. This led to gradual decrement in the peak calcium concentrations. Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-14-0166>.

Medical therapy is thus primarily focused on managing the hypercalcaemia, although this is often severe and may be highly resistant to conventional treatments, and is usually the cause of death in patients with metastatic disease. Calcimimetics and bisphosphonates have been used in controlling the hypercalcaemia, but with limited effectiveness, and calcitonin and octreotide use has also been reported in a few case reports (2). Rapid improvement in symptoms and calcium concentrations following immunisation with human and bovine PTH peptides was reported in one case (10), but this therapy is complex and not generally available.

Denosumab is a novel inhibitor of osteoclast function that is approved in many countries for the treatment of post-menopausal women with osteoporosis, for patients at a high risk for fracture, for the prevention of skeletal-related events in patients with bone metastases from solid tumours and unresectable giant cell tumours (11).

Two randomised trials have demonstrated a higher rate of hypocalcaemia with denosumab compared with zoledronic acid in patients with advanced malignancies (12, 13). Managing refractory hypercalcaemia remains a great challenge in patients with parathyroid carcinoma, and we report our experience in managing a patient with refractory hypercalcaemia due to parathyroid carcinoma using denosumab. Currently, the patient has his severe hypercalcaemia regulated to less critical levels by monthly s.c. injections of denosumab with no adverse events, and we may be able to space out his injections to longer intervals. We confirm recent case reports that denosumab should be considered as an option for this rare disease. In addition to its potent hypocalcaemic effect, it has other advantages: compared with bisphosphonates, it does not require dose adjustment in renal impairment and it is administered subcutaneously rather than intravenously. However, whether this response will be maintained over the long term remains to be seen.

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. The patient was fully informed about the medication and possible adverse effects and written consent was obtained before initiating this treatment. The patient has consented to the publication of his data.

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