

A Case of Severe Humoral Hypercalcaemia of Malignancy Resistant to Bisphosphonate Therapy

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In January 2007 a 66-year-old lady with a 5-year history of depression presented to the local psychiatric unit following attempted suicide. She was found to have an elevated corrected calcium (cCa) of 3.74mmol/l (NR) and a low serum phosphate (PO_4) of 0.62 mmol/ (NR) but normal alkaline phosphatase (97 U/l). Renal and liver function, serum ACE, protein electrophoresis and a chest X-ray and mammogram were normal.

She was transferred for further investigation and management in March 2007. Her cCa was 3.51mmol/l, PO_4 0.75mmol/l, alkaline phosphatase 110mmol/l, creatinine 105micromol/l (NR) and 25-OH vitamin D 20.3 pmol/l (NR). Intact PTH was undetectable (<0.3 pmol/l) (NR 1.1-6.8), but PTH related peptide (PTHrP) was elevated at >30pmol/l; (NR <0.7pmol/l). Thus a diagnosis of humoral hypercalcaemia of malignancy (HHM) was made. Abdominal ultrasound revealed bilateral hydronephrosis secondary to a pelvic mass. MRI imaging identified a 10x14cm necrotic mass consistent with a subserosal leiomyosarcoma or ovarian carcinoma.

In the preceding two months treatment with 4 litres of 0.9% saline per day and a total of 210mg of intravenous pamidronate had resulted in only transient reductions of serum Ca, lasting less than 48 hours. Furthermore, a trial of SC calcitonin and IV glucocorticoids had no effect on the serum calcium. Due to her increasing resistance to IV pamidronate she was treated with 4mg of zoledronic acid. Within 4 days her cCa had fallen to 2.26mmol/l and she underwent a total abdominal hysterectomy and bilateral salpingoophorectomy. Histopathological analysis demonstrated an aggressive and invasive clear cell ovarian carcinoma (Grade III stage IIc). Post-operatively, she became hypocalcaemic, requiring intravenous and oral calcium supplementation. Post-operatively PTH levels rapidly increased to supra-physiological levels peaking at 10pmol/l whilst PTHrP was undetectable (<0.7pmol/l). Moreover, her depressive symptoms improved rapidly and she was discharged home on oral calcium and vitamin D supplements.

Physiologically PTHrP has a predominantly autocrine/paracrine role in regulating cell differentiation, proliferation and survival and circulating PTHrP is only detectable during pregnancy and lactation. In HHM, however, elevated PTHrP levels leads to renal and skeletal effects resulting in elevated serum calcium. This case demonstrates that resistance to pamidronate mediated inhibition of osteoclastic bone resorption may occur in HHM but treatment with the highly potent bisphosphonates zoledronic acid may still be of therapeutic benefit. In addition, PTHrP may be used as a sensitive tumour marker in monitoring tumour recurrence in this patient.