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Parathyroid hormone-related protein as a tumour marker in humoral hypercalcaemia associated with occult malignancy

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Summary: The tumour-derived factor PTH-related protein (PTHrP) is the primary humoral factor responsible for hypercalcaemia in patients with solid tumours. In a woman presenting with anaemia and hypercalcaemia, the finding of raised plasma PTHrP and undetectable serum PTH concentrations led to further investigations and the subsequent identification of a uterine tumour. No evidence of tumour spread was found at operation, and removal of the tumour resulted in normalization of both serum calcium and plasma PTHrP. Expression of PTHrP by the tumour was shown by immunohistochemistry and *in situ* hybridization. We conclude that the identification of an occult tumour in a patient with hypercalcaemia and raised plasma PTHrP provides evidence of the diagnostic utility of PTHrP immunoassays in the investigation of patients with hypercalcaemia and suspected malignancy.

Introduction

Hypercalcaemia is a common biochemical complication in patients with both solid and haematological malignancies. In the case of solid

tumours, there is overwhelming evidence that the tumour-derived factor parathyroid hormone-related protein (PTHrP) is an important humoral mediator of hypercalcaemia,¹ and is elevated in the plasma of the majority of hypercalcaemic patients.^{2,3} Here we report a patient identified during an assessment of the clinical roles of two-site immunoradiometric assays (IRMA) for parathyroid hormone (PTH) and PTHrP,⁴ in whom

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increased plasma PTHRP concentrations led to the diagnosis of humoral hypercalcaemia of malignancy associated with an occult uterine tumour.

Case report

The patient, a woman of 59 years, presented initially for repair of a para-umbilical hernia, and was found to have an iron-deficiency anaemia. An upper abdominal laparotomy at the time of hernia repair, and a gastroscopy and barium enema, failed to show any cause for this anaemia. Treatment with ferrous sulphate was unsuccessful, and after 5.5 months she was reviewed by a haematologist. At this time she complained of anorexia and constipation. Biochemical investigations showed a serum corrected calcium of 3.48 mmol/l (corrected calcium = measured calcium in mmol/l + $[40 - \text{albumin in g/l} \times 0.02]$). Physical examination and a chest X-ray were normal. Serum PTH measured by 'N-tact' IRMA, INCSTAR, Wokingham, Berkshire, UK, was < 0.5 pmol/l (reference range 0.9–4.0 pmol/l). Plasma PTHRP measured on two occasions by in-house IRMA³ was 2.8 and 2.6 pmol/l (range in normocalcaemic controls, < 0.25 pmol/l), and suggested non-haematological malignancy as the probable cause of the hypercalcaemia. Computerized tomography of the abdomen revealed a pelvic tumour. Neither a bone scan nor a hepatic ultrasound scan showed any evidence of metastases.

Pre-operatively, the hypercalcaemia was treated with intravenous disodium pamidronate (15 mg) which produced a fall in serum calcium to 2.70 mmol/l over 6 days, without any significant change in plasma PTHRP. Prior to operation, the corrected calcium rose again to 3.10 mmol/l. At laparotomy, a resectable uterine tumour was found, with no evidence of local spread, peritoneal seedlings or hepatic metastases. Histology showed the tumour to be a clear-cell adenocarcinoma.

Figure 1 Immunostaining for PTH-related protein in clear cell adenocarcinoma of uterus ($\times 10$ magnification).

Production of PTHRP by the tumour was confirmed by immunohistochemistry using an antiserum to PTHRP 37–67⁵ (Figure 1), and PTHRP mRNA was detected by *in situ* hybridization using a ³⁵S-labelled riboprobe⁶ (Figure 2).

Plasma PTHRP measured 48 hours after tumour resection was undetectable (< 0.25 pmol/l) and serum corrected calcium fell to a nadir of 2.10 mmol/l 5 days postoperatively before returning to the reference range. Nine months postoperatively, the patient was in good health, with no evidence of recurrence of the malignancy. Plasma

Figure 2 *In situ* hybridization of PTH-related protein mRNA. Sections of uterine tumour hybridized with 'antisense' probe seen by bright field (upper panel) and dark field (middle panel), and dark field 'sense' control (lower panel).

PTHrP was <0.25 pmol/l, and serum calcium and PTH were within their respective reference ranges.

Discussion

In this patient with severe symptomatic hypercalcaemia, the findings of undetectable PTH and raised PTHrP suggested the presence of a non-haematological malignancy.⁴ The site of the tumour was identified only after extensive investigations. Normalization of serum calcium and plasma PTHrP post-surgery, and localization of PTHrP in tumour tissue by immunohistochemistry and *in situ* hybridization provide convincing evidence that the hypercalcaemia was mediated humorally by PTHrP.

While solid malignancy is clinically apparent in the majority of patients with cancer-associated hypercalcaemia, occult tumours can prove a difficult diagnostic problem. Before the recent development of assays for plasma PTHrP, the finding of a suppressed or low-normal PTH concentration in a patient with hypercalcaemia provided indirect evidence for the presence of

malignancy. However, hypercalcaemia may be associated with a suppressed PTH level in a number of other conditions, such as vitamin D toxicity, sarcoidosis, thyrotoxicosis, and haematological malignancy; furthermore, a significant proportion of patients with malignant disease have high circulating PTH levels indicative of coexistent hyperparathyroidism.⁴ These factors account for the lower diagnostic sensitivity and specificity of a suppressed PTH compared with that of a detectable PTHrP in the identification of patients with solid tumours.

As demonstrated by this case and elsewhere,⁷ PTHrP may also be useful as a tumour marker in monitoring response to therapy or assessing completeness of surgical resection. It remains to be established whether detectable plasma PTHrP levels in normocalcaemic patients with malignancy can predict the subsequent development of hypercalcaemia.²

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