Severe hypercalcaemia during pregnancy is rare and most cases are secondary to hyperparathyroidism. This is the first report of a parathyroid hormone related protein (PTHrP) secreting neuroendocrine tumour of the pancreas manifesting with severe hypercalcaemia during pregnancy. Measurement of PTHrP was useful in both the diagnosis and follow up of our patient and should be considered in the diagnostic workup of patients with unexplained hypercalcaemia. A raised PTHrP concentration is a strong indicator of malignancy.

CASE REPORT

A 25 year old woman presented at 29 weeks’ gestation with altered consciousness, headache, hypertension and proteinuria, and was initially thought to have pre-eclampsia. She was noted to have taken 1 g of mefenamic acid in divided doses during the two days before presentation.

Her initial investigations showed a serum calcium adjusted for albumin of 5.9 mmol/l (reference range 2.2–2.6). A retrospective measurement of calcium at 19 weeks’ gestation was obtained at 2.33 mmol/l. Her serum phosphate was raised to 2.07 mmol/l (reference range 0.7–1.2), probably as a result of her renal impairment. She had renal failure with a serum creatinine of 328 µmol/l (reference range 60–110) and her 24 hour urinary protein was 9.09 g. Parathyroid hormone was undetectable using a two site immunoradiometric assay (Diagnostic Product Corporation Immulite, Los Angeles USA).

Parathyroid hormone related protein (PTHrP) was first isolated in 1987 from cancer cell lines and a tumour associated with hypercalcaemia, and is now considered to be the main mediator of humoral hypercalcaemia of malignancy.\(^1\) The placenta (during pregnancy) and mammary glands (postpartum) are important physiological sources of PTHrP.\(^2\)

We report a case of extreme hypercalcaemia manifesting during pregnancy. The hypercalcaemia was associated with raised levels of 1,25-dihydroxyvitamin D\(_3\), \(25(\text{OH})D_3\), and was eventually found to be due to a PTHrP secreting pancreatic neuroendocrine tumour.

Severe hypercalcaemia during pregnancy is rare and most cases are due to hyperparathyroidism but there are fewer than 150 patients reported in world literature.\(^3\) There have been two reports of the milk alkali syndrome\(^4\) and four reported cases of parathyroid carcinoma during pregnancy.\(^6\) Other cases of malignancy related hypercalcaemia in pregnancy are very rare.

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Her early management consisted of an emergency caesarean section followed by transfer to the intensive therapy unit. She was given five intravenous doses of pamidronate 15 mg twice daily. In the postpartum period calcium decreased rapidly after pamidronate and she required calcium supplements for one month. The calcium decreased to a nadir of 1.9 mmol/l then subsequently steadily increased to 2.68 mmol/l at 12 months and 2.76 mmol/l at 15 months. Her renal function improved rapidly with serum creatinine decreasing to 99 µmol/l at 10 days but the proteinuria took six months to normalise.

Serum parathyroid hormone concentrations were undetectable on three occasions between three and 12 months postpartum while the patient remained significantly hypercalcaemic at the time (fig 1). Measurement of serum vitamin D metabolites showed a normal 25-hydroxyvitamin D\(_3\), \(25(\text{OH})D_3\), at 19 nmol/l (reference range 15–100) with a 1.25(\(\text{OH})_2D_3\) level in the upper end of the normal range at 97 nmol/l (reference range 20–120). Because of these results, extrarenal vitamin D production secondary to granulomatous disease or lymphoma was considered as a possible cause of the hypercalcaemia. Serum angiotensin converting enzyme was normal at 38 U/l (reference range 8–52 U/l) and chest radiography did not suggest sarcoidosis. An ultrasound of her abdomen was normal and isotope bone scans performed at one and eight months postpartum were both normal. A myeloma screen was negative. Transluminal biopsy showed increased osteoclastic activity but no evidence of lymphoma. A whole body computed tomogram at 14 months postpartum showed a 9 cm pancreatic mass and an ultrasound guided fine needle aspiration of this mass showed results consistent with a neuroendocrine tumour. An octreoscan showed increased uptake in this mass.

Figure 1 Summary of PTHrP (reference value <0.5 pmol/l) and serum calcium (reference range 2.2–2.6 mmol/l) concentrations over two years (PAM, pamidronate).

Abbreviations: \(1,25(\text{OH})_2D_3\), \(25(\text{OH})_2D_3\), 25-hydroxyvitamin \(D_3\), PTHrP, parathyroid hormone related protein

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uptake in the region of the distal pancreas with no evidence of metastases.

A vitamin D challenge test was performed by administering 2000 IU of 25-hydroxyvitamin D\(_{3}\) for 10 days with alternate day measurement of calcium and vitamin D metabolites (see table 1). This suggested inappropriate activation of vitamin D since the levels of 1,25(OH)\(_{2}\)D\(_{3}\) remained suppressed and the Parathyroid Hormone-related Protein (PTHRP) (DiaSorin Stillwater, USA) measured immediately and two months postpartum was 3.3 pmol/l and 3.9 pmol/l (reference value <0.5 pmol/l). A somatostatin challenge test was performed using octreotide 100 μg subcutaneously and the PTHrP decreased from 3.3 to 2.1 pmol/l in one hour followed by normalisation of the serum calcium.

The patient underwent laparotomy and removal of the pancreatic mass in November 1998. For effective tumour removal a splenectomy was also required. Histology and PTHrP immunostaining showed a neuroendocrine tumour with positive immunocytochemical staining using a PTHrP antibody. Staining for the \(\alpha\)-hydroxylase enzyme was negative.

Postoperatively serum calcium (fig 1) and PTHrP levels normalised and remained normal after two years of follow up. Gut hormones were normal and vitamin D metabolites returned to reference values.

The baby was also noted to have hypercalcaemia immediately after birth (calcium 3.03 mmol/l) but subsequently became hypocaloicaemia over the next two days (calcium 1.59 mmol/l) and required calcium supplementation for about a month. The baby had other problems related to prematurity and required mechanical ventilation for four days along with surfactant. On discharge from the neonatal unit two months after the delivery all metabolic problems had settled, and on subsequent follow up a diagnosis of mild asymmetric cerebral palsy was made which was felt to be mainly due to prematurity.

**DISCUSSION**

This is the first reported case of a PTHrP secreting pancreatic neuroendocrine tumour manifestation with a hypercalcaemic crisis during pregnancy. The combination of non-steroidal anti-inflammatory drugs with hypercalcaemia combined to produce a severe acute renal failure and acute deterioration leading to her presentation during pregnancy.

The role of vitamin D metabolites in the pathogenesis of humoral hypercalcaemia of malignancy is a controversial area. While PTHrP binds to the parathyroid hormone type I receptor and mimics virtually all the biological actions of parathyroid hormone, serum levels of 1,25(OH)\(_{2}\)D\(_{3}\) in humoral hypercalcaemia of malignancy are frequently suppressed and much lower than in primary hyperparathyroidism.\(^8,9\) This has led many workers to suggest that PTHrP does not stimulate renal \(\alpha\)-hydroxylation activity in patients with humoral hypercalcaemia of malignancy.\(^7,11,12\) However Schweitzer et al,\(^6\) Sato and Takahashi,\(^1\) and Ralston et al\(^a\) have commented on the fact that 1,25(OH)\(_{2}\)D\(_{3}\) levels are frequently not suppressed in humoral hypercalcaemia of malignancy, consistent with a stimulatory effect of PTHrP on \(\alpha\)-hydroxylase activity. In keeping with this hypothesis, serum 1,25(OH)\(_{2}\)D\(_{3}\) levels are increased in various animal models of PTHrP mediated humoral hyperparathyroidism.\(^13,14\) Reasons that have been put forward to explain the lower levels of 1,25(OH)\(_{2}\)D\(_{3}\) in humoral hypercalcaemia of malignancy compared with primary hyperparathyroidism include the fact that humoral hypercalcaemia of malignancy is often associated with very severe hypercalcaemia and renal failure which can suppress \(\alpha\)-hydroxylase activity\(^8\) and that many patients with humoral hypercalcaemia of malignancy have low levels of the precursor 25(OH)\(_{2}\)D\(_{3}\).\(^15\)

Inappropriate activation of 1,25(OH)\(_{2}\)D\(_{3}\) production was found in our patient, which almost certainly represented a stimulatory effect of PTHrP on renal \(\alpha\)-hydroxylation activity. Increased production of 1,25(OH)\(_{2}\)D\(_{3}\) by the tumour itself was excluded by the fact that we found no evidence of \(\alpha\)-hydroxylation activity within the tumour.

The reduction in PTHrP and calcium after administration of the somatostatin analogue octreotide is interesting and has been documented previously in other neuroendocrine tumours.\(^7,16\) This may have therapeutic potential if surgical clearance is not possible. PTHrP measurements were useful in this case in clarifying the diagnosis of the hypercalcaemia and also in follow up as the PTHrP remained reassuringly normal over two years of follow up. PTHrP measurement should be considered in the diagnostic workup of hypercalcaemia of obscure aetiology. A raised PTHrP concentration is strong evidence for the presence of malignancy.

ACKNOWLEDGEMENT

The PTHrP was measured at the Department of Clinical Chemistry, Royal Liverpool University Hospital.

**REFERENCES**


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**Table 1** Vitamin D challenge test (performed by administering 2000 IU of 25-hydroxyvitamin D\(_{3}\) (25(OH)D\(_{3}\)) for 10 days with alternate day measurement of calcium and vitamin D metabolites)

<table>
<thead>
<tr>
<th>Calcium</th>
<th>25(OH)D(_{3})</th>
<th>1,25(OH)(<em>{2})D(</em>{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>(RR 2.3–2.6 mmol/l)</td>
<td>(RR 15–100 pmol/l)</td>
</tr>
<tr>
<td>1</td>
<td>2.13</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>2.66</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>2.89</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>2.97</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>2.68</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>3.08</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>3.15</td>
<td>97</td>
</tr>
</tbody>
</table>

1.25(OH)\(_{2}\)D\(_{3}\), 1,25-dihydroxyvitamin D\(_{3}\); RR, reference range.

**Table 2** Measurement of calcium and vitamin D metabolites (see table 1).

<table>
<thead>
<tr>
<th>Day</th>
<th>Calcium</th>
<th>25(OH)D(_{3})</th>
<th>1,25(OH)(<em>{2})D(</em>{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.66</td>
<td>41</td>
<td>239</td>
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<tr>
<td>2</td>
<td>2.89</td>
<td>66</td>
<td>208</td>
</tr>
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<td>2.97</td>
<td>80</td>
<td>187</td>
</tr>
<tr>
<td>5</td>
<td>2.68</td>
<td>75</td>
<td>212</td>
</tr>
</tbody>
</table>

5–10

1,25(OH)\(_{2}\)D\(_{3}\), 1,25-dihydroxyvitamin D\(_{3}\); RR, reference range.
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