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.

**Presentation of a PTHrP-secreting pancreatic neuroendocrine tumour, with hypercalcaemic crisis, pre-eclampsia, and renal failure**

P Abraham, S H Ralston, M Hewison, W D Fraser, J S Bevan

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

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. The placenta (during pregnancy) and mammary glands (postpartum) are important physiological sources of PTHrP.

We report a case of extreme hypercalcaemia manifesting during pregnancy. The hypercalcaemia was associated with raised levels of 1,25-dihydroxyvitamin D$_3$, (1,25(OH)$_2$D$_3$) and was eventually found to be due to a PTHrP secreting pancreatic neuroendocrine tumour.

**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 at 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).

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(OH)D$_3$) at 19 nmol/l (reference range 15–100) with a 1,25(OH)$_2$D$_3$ 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 8–52U/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. Transilical bone 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 of the tumour.

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.

Abnormal presentations of pregnancy are very rare. Severe hypercalcaemia is rare during pregnancy. Most cases are due to hyperparathyroidism but there are fewer than 150 patients reported in world literature. There have been two reports of the milk alkali syndrome and four reported cases of parathyroid carcinoma during pregnancy. Other cases of malignancy related hypercalcaemia in pregnancy are very rare.

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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 D3 (25(OH)D3) 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)2D3 remained raised despite the hypercalcaemia. 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 1α-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 normal. PTHrP measurement should be considered in the diagnostic workup of hypercalcaemia of malignancy.

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The reduction in PTHrP and calcium after administration of the somatostatin analogue octreotide is interesting and has been documented previously in other neuroendocrine tumours. 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 Hospital.

Table 1 Vitamin D challenge test (performed by administering 2000 IU of 25-hydroxyvitamin D3 (25(OH)D3) for 10 days with alternate day measurement of calcium and vitamin D metabolites)

<table>
<thead>
<tr>
<th>Calcium Day</th>
<th>25(OH)D3 (RR 2.3–3.0 mmol/l)</th>
<th>25(OH)D3 (RR 15–100 pmol/l)</th>
<th>25(OH)D3 (RR 20–120 pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.13</td>
<td>62</td>
<td>160</td>
</tr>
<tr>
<td>0</td>
<td>2.66</td>
<td>41</td>
<td>239</td>
</tr>
<tr>
<td>2</td>
<td>2.89</td>
<td>66</td>
<td>208</td>
</tr>
<tr>
<td>4</td>
<td>2.97</td>
<td>80</td>
<td>187</td>
</tr>
<tr>
<td>6</td>
<td>2.68</td>
<td>75</td>
<td>212</td>
</tr>
<tr>
<td>8</td>
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<td>85</td>
<td>205</td>
</tr>
<tr>
<td>10</td>
<td>3.15</td>
<td>97</td>
<td>231</td>
</tr>
</tbody>
</table>

1,25(OH)2D3, 1,25-dihydroxyvitamin D3, RR, reference range.

REFERENCES


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