CASE REPORT

PTHrP-associated hypercalcemia of pregnancy resolved after delivery: a case report

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Abstract

A 35-year-old oriental woman, who was 32 weeks pregnant, was hospitalized with suspected preeclampsia. Subsequently, she developed stupor and lethargia. Biochemical assessment showed severe hypercalcemia (21 mg/dl) with undetectable parathyroid hormone (PTH) and markedly elevated PTH-related peptide (PTHrP) levels (26 pmol/l, normal values < 1.1 pmol/l). The patient was treated with i.v. fluid administration, which resulted in an unsatisfactory reduction in serum calcium. Therefore, a cesarean section was performed to deliver the baby. Serum calcium levels promptly normalized after delivery with undetectable PTHrP levels. She delivered a healthy infant only presenting with transient mild jaundice and slightly prolonged QT interval with serum calcium level of 7.8–8.4 mg/dl (corrected for albumin levels). In the subsequent days, the patient developed a transient ‘hungry bone’ syndrome (calcium 6.7 mg/dl, phosphorous 2.1 mg/dl, and PTH 100.4 pg/ml). In conclusion, this pregnant patient presented with PTHrP-associated hypercalcemia, presumably of placental origin. Delivery resulted in prompt reduction of serum calcium levels and a transient ‘hungry bone’ syndrome.

European Journal of Endocrinology 166 753–756

Introduction

Hypercalcemia is often a clue for the presence of unsuspected illness. The great majority of patients with hypercalcemia have either primary hyperparathyroidism (PHPT) or malignancy, although other rarer causes can be involved (1, 2). During pregnancy, hypercalcemia is uncommon and mostly associated with PHPT, even though in a minority of cases it can be due to malignancy (3, 4, 5, 6, 7, 8). The demonstration of suppressed/undetectable intact parathyroid hormone (PTH) levels, in particular, in the presence of high PTH-related peptide (PTHrP) levels, is generally considered as a clue for the presence of an occult malignancy. However, although very uncommon, PTHrP secretion occurs in benign tumors, leading to a syndrome called ‘humoral hypercalcemia of benignancy’ (9, 10, 11, 12, 13, 14). Moreover, PTHrP is produced physiologically in a number of fetal and maternal tissues, particularly in the placenta during pregnancy and in the mammary glands during lactation or in pregnant patients with mammary hyperplasia (15, 16, 17). If unrecognized or not treated properly, hypercalcemia may increase maternal and fetal morbidity and mortality. Up to now, few cases of hypercalcemia in pregnant women due to mammary hyperplasia have been described (18, 19) and

only one case of hypercalcemia, possibly due to PTHrP hypersecretion or release by placenta, has been reported (9). In this case report, we document a case of PTHrP-associated hypercalcemia during pregnancy.

Case history

A 35-year-old Philippine woman, who was 32 weeks pregnant with her first child, presented to the Accident and Emergency Unit of our Hospital with abdominal pain and suspected preeclampsia. The patient reported fatigue and constipation. She had been healthy and there was no familial history except for a uterine myoma of 15.0 cm in diameter, with regular follow-up during pregnancy. Physical examination revealed arterial hypertension (systolic/diastolic blood pressure, 165/100 mmHg) and polyhydramnios. The remaining clinical examination was normal and, in particular, mammary glands were not markedly enlarged. There was mild renal impairment with mild proteinuria (350 mg/24 h).

During hospitalization she became disoriented and stuporous and could not respond to simple questions. Subsequently, she developed acute renal insufficiency with oligoanuria and biochemical investigations

Table 1 Predelivery biochemical parameters.

Assay	Patient's value	Normal values
Ca _{alb adj} (mg/dl)	21.0	8.2–10.2
Phosphorous (mg/dl)	2.3	2.7–4.5
Creatinine _{serum} (mg/dl)	2.2	0.5–1.0
PTH (pg/ml)	<5.0	11.0–55.0
ALP (U/l)	139	35–104
PTHrP (pmol/l)	26.0	<1.1

Ca_{alb adj}, serum calcium level adjusted for albumin levels (Ca_{alb adj} (mg/dl) = total calcium + (4.4 – albumin mg/dl) × 0.8); PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide.

showed marked hypercalcemia (Table 1). Intact PTH levels were suppressed, whereas PTHrP levels were markedly elevated (Table 1). Vitamin D levels were normal (25-hydroxyvitamin D, 32 ng/ml). Markers of neoplasia (cancer antigen 125, carcinoembryonic antigen, carbohydrate antigen 19-9, and alpha-fetus protein) were negative.

The patient was treated by continuous i.v. infusion of isotonic saline at an initial rate of 250 ml/h, which was subsequently adjusted to maintain the urine output at 100–150 ml/h. In addition, she was initially treated with methyldopa and furosemide to reduce blood pressure and serum calcium levels. However, 36 h later, considering the persistence of severe hypercalcemia (Fig. 1) and lethargy in spite of hydration and medical treatment, an emergency caesarean section was performed. The uterine myoma was not excised.

The patient delivered a healthy and normal for gestational age female infant (weight 1850 g, +0.3 SDS, length 42 cm), who presented only transient mild icterus and slightly prolonged QT intervals, with calcium levels corrected for serum albumin levels ranging between 7.8 and 8.4 mg/dl, phosphorous levels between 3.1 and 3.8 mg/dl, and normal creatinine levels (0.8 mg/dl). After delivery, the mother's PTHrP levels were undetectable, serum calcium levels promptly decreased and hypocalcaemia occurred (Fig. 1). At the same time, there was a prompt improvement in her lethargy (Table 2). Arterial hypertension persisted and was treated with doxazosin, amlodipine, and β-blockers. The patient denied taking any additional medication such as vitamin D, vitamin A, or calcium supplements.

A few days after delivery, she developed acute pulmonary edema, treated with continuous positive airway pressure and medical therapy. In the subsequent days, symptomatic hypocalcaemia (serum calcium level, 6.7 mg/dl; normal values, 8.2–10.2 mg/dl; Table 2 and Fig. 1) persisted, with raised serum alkaline phosphatase (ALP) and PTH levels, requiring intensive i.v. calcium and oral vitamin D supplements, consistent with the development of 'hungry bone' syndrome (Fig. 1). Hypocalcaemia was also complicated by a generalized epileptic seizure treated with diazepam.

During the subsequent months, the patient received oral calcium (1–2 g/day) and vitamin D (cholecalciferol, 1600 UI/day) supplementation, with relief of symptoms and normalization of calcium and phosphate levels (Table 2). During the subsequent 12 months, the child did not show any alteration of calcium and phosphorous levels.

The patient has been discharged with the diagnosis of 'hypercalcemic crisis due to a placental PTHrP hypersecretion'.

Methods

Serum and urinary samples were collected and stored at –20 °C until assayed. Serum calcium, albumin, 24 h urinary calcium, and ALP (reference interval, 35–104 U/l) were measured by standard colorimetric techniques. Total calcium was corrected for serum albumin (Ca_{alb adj}) according to the formula: Ca_{alb adj} (mg/dl) = total calcium + ((4.4 – albumin mg/dl) × 0.8), reference interval: 8.4–10.2 mg/dl. Serum intact PTH was measured by a chemiluminescent method (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA), with intra- and interassay CV of 5.1 and 8.2% respectively (reference interval: 10–60 pg/ml).

Figure 1 Modifications of the patient's biochemical parameters during medical therapy and after delivery. Ca_{alb adj}, serum calcium level adjusted for albumin levels (Ca_{alb adj} (mg/dl) = total calcium + (4.4 – albumin mg/dl) × 0.8); PTH, parathyroid hormone; Cr, creatinine; P, phosphorus. The gray area represents the normal range.

Table 2 Postdelivery biochemical parameters.

Assay	Patient's value	Normal values
7 days after delivery		
Ca _{alb} adj (mg/dl)	6.7	8.2–10.2
Phosphorous (mg/dl)	2.1	2.7–4.5
Creatinine _{serum} (mg/dl)	0.8	0.5–1.0
24 h urinary Ca (mg/kg)	0.11	1–4
PTH (pg/ml)	100.4	11.0–55.0
ALP (U/l)	124	35–104
PTHrP (pmol/l)	<1.1	<1.1
4 months after delivery		
Ca _{alb} adj (mg/dl)	9.3	8.2–10.2
Phosphorous (mg/dl)	3.0	2.7–4.5
Creatinine _{serum} (mg/dl)	0.8	0.5–1.0
24 h urinary Ca (mg/kg)	1.6	1–4
PTH (pg/ml)	45	11.0–55.0
ALP (U/l)	84	35–104
PTHrP (pmol/l)	<1.1	<1.1

Ca_{alb} adj, serum calcium level adjusted for albumin levels (Ca_{alb} adj (mg/dl) = total calcium + (4.4 – albumin mg/dl) × 0.8); 24 h urinary Ca, urinary calcium in 24 h collection; PTH, parathyroid hormone; ALP, alkaline phosphatase; PTHrP, parathyroid hormone-related peptide.

Reference intervals for Ca_{alb} adj and PTH are derived from a normal population recruited in our laboratory. PTHrP levels were measured immunoradiometrically (Nichols Institute Diagnostic).

Discussion

This is the first case, to our knowledge, of a PTHrP-associated hypercalcemic crisis during pregnancy, which promptly recovered after delivery, and which resulted in a transient 'hungry bone' syndrome. It is important to note that the infant was healthy and normal for gestational age with low normal calcium and normal phosphorous levels. The relatively low calcium levels of the infant might be explained by the partial inhibition of the parathyroid glands exerted by the high calcium levels in the maternal blood (20).

The patient had a voluminous uterine myoma, which was not excised during emergency delivery in consideration of the precarious condition of the woman. It is highly unlikely that the uterine myoma was the cause of the PTHrP hypersecretion because calcium levels normalized after delivery, even though the uterine myoma was not excised. On the other hand, the normality of the breast sizes permitted us to exclude the hypersecretion of PTHrP by the hypertrophic mammary tissue. Unfortunately, placental tissue was not examined for PTHrP. However, as PTHrP levels normalized following the discharge of the afterbirth, this further rules out a possible responsibility of hyperplastic breast tissue and indirectly but strongly indicates that the placenta was the only source of PTHrP.

The amnion in the human uteroplacental unit shows the highest expression of *PTHrP* mRNA, and the PTHrP concentration in amniotic fluid is 20–40 pmol/l from the third trimester of pregnancy (15, 16, 17). Therefore,

it is tempting to hypothesize that PTHrP was abundantly produced in the placenta and that a large amount of it was spilled into the systemic circulation, possibly by the compression exerted by the uterine myoma on the placenta. Alternatively, it is possible that the large uterine myoma induced a derangement of the intrauterine and placental circulation, in turn allowing a higher delivery of PTHrP to maternal blood. These mechanisms could have increased PTHrP in the blood of our patient approaching a level that is attainable in patients with humoral hypercalcemia of malignancy.

Our patient was treated by hydration and furosemide to reduce serum calcium levels, which, however, persisted above 15 mg/dl. We did not use bisphosphonates, because the safety of bisphosphonates in pregnancy is still not known, although some reports suggest that i.v. administration of pamidronate is effective in ameliorating hypercalcemia during pregnancy without any apparent effect on the newborn (21). On the other hand, in the presence of PTH-independent hypercalcemia, emergency delivery, if feasible, is indicated, whereas the use of bisphosphonates represents the last resort.

Finally, the patient developed pulmonary edema immediately before the appearance of acute hypocalcemia. In this respect, it must be considered that a reversible form of dilated cardiomyopathy has been described in association with severe hypocalcemia, especially of brisk onset (22).

In conclusion, this pregnant patient presented with PTHrP-associated hypercalcemia. Delivery resulted in prompt resolution of hypercalcemia and the development of a transient hungry bone syndrome. The elevated PTHrP levels present before delivery, which normalized after delivery, and placental discharge indicate that excessive placental synthesis and/or release of PTHrP into the maternal circulation was the most likely cause of hypercalcemia.

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.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Acknowledgements

The authors acknowledge Dr Alfredo Scillitani for the suggestions and advice for the discussion of the case.

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Received 6 December 2011

Revised version received 12 January 2012

Accepted 12 January 2012