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CASE REPORT

A Rare Cause of Hypercalcemic Crisis in Pregnancy- “Uterine Leiomyoma”

ABSTRACT

Hypercalcemia in pregnancy is a rare condition and causes serious maternal and fetal outcomes. A 35-year-old woman presented with itching, nausea, and vomiting at 37 weeks of spontaneous pregnancy. Biochemical examination revealed hypercalcemia with a low parathyroid hormone (PTH) level and normal 25-hydroxyvitamin D level. An abdominal ultrasound (US) revealed a 158 × 151-mm intramural–subserosal myoma located in the left lateral wall of the uterus. Due to progressive hypercalcemia despite isotonic saline infusion, a single session of hemodialysis was performed. The patient underwent a cesarean section and myomectomy, and normocalcemia was achieved following removal of the placenta and myoma. Parathyroid hormone-related protein (PTHrP) secretion by benign tumors is rare and has been reported in association with intestinal and uterine leiomyomas, as well as renal adenomas.

Keywords: Hypercalcemia, Parathyroid Hormone-related Peptide, Leiomyoma, Uterine

Introduction

Hypercalcemia in pregnancy is a rare condition, with its incidence in women of reproductive age reported to be 0.03% (1,2). The most common cause of hypercalcemia in pregnancy is primary hyperparathyroidism. Other causes, similar to those in the general population, include hyperthyroidism, vitamin A or D toxicosis, familial hypocalciuric hypercalcemia, granulomatous diseases, and malignancies (3,4). Serious maternal outcomes (such as preeclampsia, nephrolithiasis, pancreatitis, and renal failure) and fetal outcomes (including intrauterine growth restriction, abortion, neonatal death, neonatal hypocalcemia, and, rarely, permanent hypoparathyroidism) may occur as a result of hypercalcemia during pregnancy (1,2).

Malignancy-associated hypercalcemia occurs in 20–30% of malignancies and develops through various pathogenetic mechanisms, most commonly due to the release of parathyroid hormone-related protein (PTHrP) (3,4). PTHrP release from benign tumors is quite rare and is referred to as benign tumor–related humoral hypercalcemia (1). Benign tumors that cause PTHrP-mediated hypercalcemia include intestinal and uterine leiomyomas, renal adenomas and benign pheochromocytomas (4). PTHrP release is also physiologically increased during pregnancy, originating from the placenta, breast tissue, and amnion (1).

Here, a 35-year-old pregnant woman was reported who developed hypercalcemic crisis during the third trimester.

Case Presentation

A 35-year-old primigravida at 37 weeks of spontaneous pregnancy was admitted to the gynecology clinic with complaints of itching, nausea, and vomiting for the past week. Her medical records showed Rh incompatibility, polyhydramnios, and a leiomyoma measuring 42 × 32 × 40 mm. On physical examination, vital signs were within the normal range, and there was no vaginal bleeding. Neurological examination revealed no pathological findings. The fetal heart rate was normal. Initial laboratory tests

Şule Canlar[1]
Murat Cinel[1]
Seyit Murat Bayram[1]
Hatice Şahin[2]
Hüseyin Demirci[1]
Erman Çakal[1]

[1]*Ankara Etlik City Hospital, Department of Endocrinology and Metabolism, Ankara, Türkiye*
[2]*Ankara Etlik City Hospital, Department of Nephrology, Ankara, Türkiye*

Corresponding author:
Şule Canlar
✉**sulejan82@gmail.com**

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revealed a total serum calcium level of 18.8 mg/dL, phosphorus level 2.6 mg/dl at the time of admission. The laboratory data obtained at the time of admission are summarized in Table 1. Retrospective review of the medical records showed that the only available calcium measurement, obtained at 33 weeks' gestation, was 9.03 mg/dl. Serum PTH was 4.4mg/dl. Serum amilase and lipase values were in normal ranges. Calcium oxalate crystals were detected in urine microscopy.

During the assessment for the differential diagnosis of PTH-independent hypercalcemia, we performed a chest X-ray, since organogenesis is completed by the third trimester, Abdominal ultrasonography revealed a 158 × 151 mm intramural–subserosal myoma in the left lateral wall of the uterus. Advanced imaging modalities were not performed because of pregnancy. Due to laboratory limitations, serum PTHrP level could not be measured.

The patient was admitted to the perinatology clinic and was consulted by both the endocrinology and nephrology departments for hypercalcemic crisis. Owing to the progressive increase in serum calcium levels, the patient required transfer to the medical intensive care unit for further evaluation and treatment. Isotonic saline was initiated at a rate of 200 mL/hour, with close monitoring to maintain urine output between 100 and 150 mL/hour.

Due to progressive hypercalcemia, a single session of hemodialysis with low-calcium dialysate was performed on the first day of admission. Following dialysis, the total calcium level decreased to 11.3 mg/dL but subsequently rose again to 17.2 mg/dL on the same day (Figure 1 shows the course of calcium levels).

As the patient was at term and calcium levels could not be stabilized, caesarean delivery and myomectomy were performed on the second day of admission. In the postoperative period, hydration was continued, and calcium levels returned to the normal range within 48 hours. Histopathological examination revealed leiomyoma with degenerative and pregnancy-related changes, without evidence of malignancy and the placenta showed no significant histopathological abnormalities (Figure 2-3). No PTHrP immunohistochemical staining could be carried out on placental or myoma tissue.

Following delivery, both the mother and the newborn remained stable. The newborn's serum calcium level was in normal range. The patient initiated breastfeeding, and the newborn required no medical intervention. They were discharged in the second postpartum week with normal serum calcium levels.

Discussion

We present a rare case of a giant uterine myoma, leading to a hypercalcemic crisis during pregnancy. In the context of pregnancy, the placenta and mammary glands represent the principal sources of PTHrP. Circulating maternal PTHrP concentrations gradually increase throughout gestation and reach their maximum in the third trimester (5). In addition, elevated PTHrP levels may also be observed in association with both malignant and benign tumors (6).

Estrogen and PTHrP contribute to myoma growth, and as the myoma enlarges, PTHrP release further increases (7). Five cases of hypercalcemia during pregnancy associated with leiomyoma have been reported in the literature. These cases are summarized in Table 2. In previously reported cases, PTHrP release was demonstrated either biochemically or by histological staining. In our patient, although PTHrP production could not be confirmed biochemically or histologically in the myoma, placenta, or amnion, serum calcium levels normalized following delivery and myomectomy. Furthermore, imaging studies revealed no alternative source of PTHrP production.

Treatment approaches in such cases are generally similar due to safety concerns during pregnancy. Loop diuretics are associated with placental hypoperfusion and are therefore considered relatively contraindicated (8).

Calcitonin is considered safe in pregnancy, as it does not cross the placenta. However, although fast-acting, it typically lowers serum calcium by only 1–2 mg/dL and is associated with a high risk of tachyphylaxis (9). Cinacalcet is effective only in cases of hypercalcemia associated with elevated PTH levels (7). Bisphosphonates are contraindicated during pregnancy, as they cross the placenta (10).

The cornerstone of treatment for PTHrP-associated hypercalcemia is elimination of the underlying disease. In our case, the probable sources of PTHrP were the myoma and placenta; therefore, their removal represented the main therapeutic approach. Normocalcemia was achieved following removal of the placenta and myoma. Given the advanced gestational age and young maternal age, maternal and neonatal well-being was ensured through successful caesarean section and myomectomy.

Conclusion

When evaluating hypercalcemia during pregnancy, humoral hypercalcemia should be included in the differential diagnosis, particularly in patients with a past medical history of uterine leiomyoma, as such tumors may represent a potential source of PTHrP secretion.

In such cases, aggressive hydration and low-calcium dialysis have been shown to be effective in the management of hypercalcemia, thereby preventing maternal and fetal complications. Dialysis is an effective treatment option for the interim period until delivery. Definitive management consists of myomectomy and delivery, which also reduce estrogen levels.

Although the inability to measure PTHrP represents a significant limitation in the management of this case, the rapid normalization of calcium levels after delivery and myomectomy, along with the clinical course, strongly suggests that the hypercalcemia was PTHrP-mediated and originated from the

placenta or uterine leiomyoma.

Author contributions

We declare that all authors have accepted the submission and that the manuscript has not been published in whole or in part or submitted elsewher

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Tables

Table-1 Laboratory findings at admission

Parameter	Value	Reference Range
Complete Blood Count		
Hemoglobin(Hb)	10.3 gr/dl	12-16 gr/dl
WBCs	16.7x10.000 mcL	4.5-10 x10.000 mcL
Platelets	160.000/mcL	150-450.000/ mcL
Serum Biochemistry Results		
SerumCreatinine	0,59 mg/dl	0.5-0.9 mg/dl
Serum Na	136 mmol/l	135-145 mmol/l
Total Calcium	18.8 mg/dl	8.6-10.2 mg/dl
Ionized Calcium	2.17mmol/L	1.12-1.29 mmol/L
Serum Phosphorous	2.6 mg/dl	2.5-4.5 mg/dl.
ALT/AST	10/15 U/L	8-34/8-31U/L
Alkaline phosphatase	136 U/L	35-104 U/L
Albumin	32 g/L	35–52 g/L
Parathormone	4,4 mg/dl	16-38 mg/dl
TSH	0.86 mIU/l	0.45-4.5 mIU/l
25-OH-vitamin D 1.25 (OH) vitamin D	25 mcg/L 22 ng/L	30-180 mcg/L 18-78 ng/L

Table-2 Summary of the cases reported in the literature

	Case 1 (11)	Case 2 (6)	Case 3 (12)	Case 4 (13)	Case 5 (7)	Our Case
Maternal age	32	26	36	38	45	35
Gestational age	29 week	14 week	First month	31 week	31 week	37 week
Presentation	Lethargy, nausea and vomiting	Nausea and vomiting	Nausea and vomiting	Nausea and vomiting, Hypertension and acute pancreatitis	Dehydration with hypotension and tachycardia, delirium, and malnutrition	Itching, nausea and vomiting
Clinical progress	33 week, aspiration pneumonitis, vaginal delivery	D&C	34 week Emergency C/S	Emergency C/S	Emergency C/S	Emergency C/S
Max Ca level	20.8 mg/dl (8.8-11.2)	14.5 mg/dl (8.8-11.2)	19.2 mg/dl (8.8-11.2)	15,9 mg/dl (8.6-10.3)	17.92 mg/dL (8.8-11.2)	18,8 mg/dl (8.6 - 10.2)
Neonatal Period	IUGR	D&C	Not avaliable	No problem	Prematurity, temporary hypercalcemia	No problem
Surgery	Delivery+myo-mectomy	D&C-6 weeks later, surgery of fibroma	C/S-myo-mectomy	C/S-myomectomy	C/S- because of severe Hemorrhage without myomectomy	C/S-myomectomy
PTH level	Not avaliable	Not avaliable	0.3 pmol/L (1.6-6.9)	5 pg/ml (12-88)	<9,4 pg/nl (9.4-66.0)	4,4 ng/L (15-65)
PTHrP level	22 (<2)	46 (<15)	Not avaliable	9.6 (<4.2)	33 pmol/L < 3.4 pmol/L in pregnancy	Not avaliable
Treatment	Hydration, furosemid, pamidronat after delivery, dialysis	Hydration, furosemid, Cinacalcet, pamidronat	Hydration, Calcitonin, dialysis	Hydration, Calcitonin	Hydration, Calcitonin	Hydration, Dialysis
Histopathological Examination	23 cm diameter, benign, histological PTHrP staining (+)	Placenta PTHrP staining (+), fibroma staining (+)	23 cm diameter, benign, calcification (+)	19 cm diameter, benign		18 cm, benign

Figure 1 Mean serum calcium trend including 33rd week value

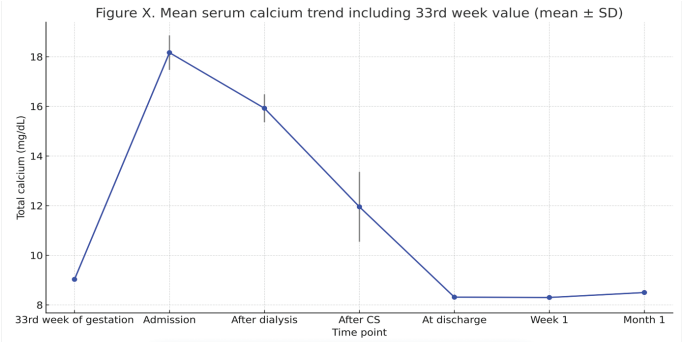

Figure 2 Microscopy of Myoma

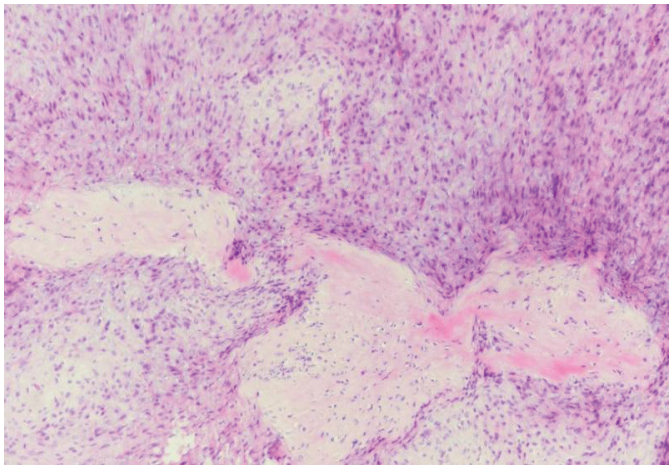

Figure 3-Macroscopy of of Myoma

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