American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e923412
DOI: 10.12659/AJCR.923412

Received: 2020.02.10
Accepted: 2020.05.19
Available online: 2020.06.18
Published: 2020.08.05

# Hypercalcemia Resulting from Necrotizing Leiomyoma in a Pregnant Female

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDE 1 Jacqueline Kropf
CDE 2 Mai Vo
ABC 1 Sarah Cheyney
CDE 3 Omar Kayaleh
DE 4 Jeannie McWhorter
CDEF 5 Steve J. Carlan

1 Department of Internal Medicine, Orlando Regional Healthcare, Orlando, FL, U.S.A.
2 Division of Medical Critical Care, Orlando Regional Healthcare, Orlando, FL, U.S.A.
3 Division of Medical Oncology, Orlando Regional Healthcare, Orlando, FL, U.S.A.
4 Department of Obstetrics and Gynecology, Orlando Regional Healthcare, Orlando, FL, U.S.A.
5 Division of Academic Affairs and Research, Orlando Regional Healthcare, Orlando, FL, U.S.A.

**Corresponding Author:** Steve J. Carlan, e-mail: stevecarlan@gmail.com
**Conflict of interest:** None declared

**Patient:** Female, 38-year-old
**Final Diagnosis:** Hypercalcemia resulting from necrotizing leiomyoma in pregnancy
**Symptoms:** Pain
**Medication:** —
**Clinical Procedure:** Cesarean section
**Specialty:** General and Internal Medicine • Obstetrics and Gynecology

**Objective:** Rare disease

**Background:** Hypercalcemic crisis is defined as a serum calcium level >14 mg/dL in a symptomatic patient. While severe hypercalcemia during pregnancy is rare, it poses a life-threatening risk to both mother and fetus. Hypercalcemia in association with a benign tumor such as a leiomyoma is exceedingly rare.

**Case Report:** A 38-year-old primagravida at 31.2 week's gestation conceived by *in vitro* fertilization presented to the emergency department for complaints of nausea, vomiting, and epigastric abdominal pain. Her fetal monitor strip was reassuring. A complete metabolic panel on admission was significant for severely elevated calcium of 15.9 mg/dL (8.6–10.3 mg/dL) and an elevated lipase of 1457U/L (11–82 U/L). She was started on aggressive intravenous fluid resuscitation, but became confused and lethargic, unarousable to verbal stimuli, as a result of hypercalcemia. Computed tomography (CT) scan of the abdomen and pelvis revealed a heterogeneously enhancing, placental-appearing soft tissue mass extending posteriorly and to the right that measured 2414 cm. The patient subsequently underwent planned low transverse cesarean delivery and exploratory laparotomy for myomectomy with removal of a 2834-g benign leiomyoma measuring 19.018.514.0 cm. Her serum parathyroid hormone-related protein (PTHrP) was elevated to 9.6 pmol/L (<4.2 pmol/L). The patient's calcium normalized to 9.8 mg/dL (8.6–10.3mg/dL) immediately following surgery.

**Conclusions:** Leiomyoma as a cause of hypercalcemia should be included in the differential diagnosis because surgical removal of leiomyoma is curative. Particularly in pregnant patients, for whom medical therapies for hypercalcemia are limited and those available can result in complications, early identification and surgical resection can be life saving.

**MeSH Keywords:** Cesarean Section • Hypercalcemia • Leiomyoma

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/923412







Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

## Background

Hypercalcemic crisis is defined as a serum calcium level >14 mg/dL in a symptomatic patient [1]. Symptoms of hypercalcemic crisis include hypertension, confusion, vomiting, muscle weakness, pancreatitis, and coma [2]. Differential diagnosis includes malignancy, renal failure, milk alkali syndrome, and preeclampsia [1]. While severe hypercalcemia during pregnancy is rare, it poses a life-threatening risk to both mother and fetus [2,3]. Complications from sustained hypercalcemia in pregnancy include intrauterine growth restriction and fetal demise [3,4]. There are several mechanisms resulting in hypercalcemia complicating pregnancy, the most common being primary hyperparathyroidism [2,3]. Hypercalcemia associated with malignancies is a well-known and well-documented entity as it occurs in 20% to30% of malignancies [5]. However, hypercalcemia in association with a leiomyoma is exceedingly rare [5], with only seven reported cases to date [6]. The condition is even more unusual in pregnancy. We performed a MEDLINE search of the English language literature from January 1, 1966, to December 31, 2018, using the keywords "leiomyoma", "pregnancy", and "hypercalcemia". We could find three cases of hypercalcemia in the thirdtrimester in a woman with a degenerating myoma [1,2,6]. Our patient presented similarly to two of the three previously described cases, with vomiting and anorexia, and also had a similar clinical course, developing lethargy and confusion [1,2]. However, ours is the fourth and the earliest at 31 weeks and the only one complicated with concurrent preeclampsia. In this case, we present an early third-trimester 38-year-old female with hypercalcemic crisis due to a large necrotizing leiomyoma.

## Case Report

A 38-year-old gravida 1 para 0 (G1P0) 31 weeks and 2 days status post frozen embryo transfer *in vitro* fertilization (IVF) female with a past medical history of 16-cm right posterior uterine fibroid and chronic hypertension and a past surgical history of cholecystectomy presented to the emergency department for complaints of nausea, vomiting, and epigastric abdominal pain. She reported no use of tobacco, alcohol, or illegal substances. Her family history was nonsignificant. Her symptoms had been present for approximately 1 week. Initial vital signs were within normal limits aside from two elevated blood pressure readings of 169/81 and 165/80 at 10 weeks' gestational age. The patient was admitted to rule out superimposed preeclampsia. At 24 weeks' gestation, she had an outpatient 24-hour urine protein study with normal results (240 mg) and was therefore being treated with labetalol 200 mg BID for chronic hypertension. Her admission 24-hour urine protein was 477 mg, indicating she had developed superimposed preeclampsia. At that point, she was started on magnesium sulfate seizure prophylaxis, intravenously. The fetal heart rate was reassuring in the 140s and reactive with moderate variability and her contraction pattern showed irritability. Her cervix was closed and there was no vaginal bleeding.

Physical examination was within normal limits with the exception of diffuse abdominal guarding without rebound and tenderness of uterus, without evidence of contractions. Basic laboratory studies revealed a normal platelet count of 350 (139–36110$^3$/uL) and normal liver function tests, aspartate aminotransferase (AST) of 11 (13–39 U/L) and alanine aminotransferase (ALT) of 14 (17–52 U/L). Laboratory studies were significant for severely elevated calcium of 15.9 mg/dL (8.6–10.3 mg/dL), an elevated lipase of 1457U/L (11–82 U/L), and an elevated amylase of 449 U/L (29–103 U/L). Because of her elevated lipase and clinical examination findings of persistent abdominal pain, nausea, and vomiting, she was diagnosed with acute pancreatitis secondary to hypercalcemia. Triglycerides were 234 mg/dL (<149 mg/dL), blood glucose of 104 mg/dL (65–100 mg/dL) and lactate was 1.1 mmol/L (0.5–2.2 mmol/L). She was started on intravenous (IV) lactated ringers and made strict nil per os and further studies were ordered to assess the reason for her hypercalcemia.

Shortly after admission, she became acutely encephalopathic with a Glasgow Coma Score 13, arousable to painful stimuli and following only intermittent commands. She was given two doses of betamethasone 12 mg intramuscularly 24 hours apart for fetal lung maturation. Further laboratory studies revealed that the patient had a parathyroid hormone (PTH) of 5 pg/mL (12–88 pg/mL), an elevated ionized calcium of 2.26 mmol/L (1.12–1.32 mmol/L), a decreased vitamin D 29.2 ng/mL (30.0–96.0 ng/mL), and an elevated vitamin D-1,25-dihydroxy of 121 pg/mL (18–78 pg/mL) indicating an ectopic production of calcium. Intravenous (IV) fluid resuscitation was continued with multiple electrolytes injection, Type 1, USP (Plasma-lyte A) at 200 cc/hr rate. Because of the patient's altered mental status, thought to be secondary to severe hypercalcemia, she was started on calcitonin 430 U subcutaneous every 12 hours for 48 hours.

Due to deteriorating mental status, the decision was made to undergo a computed tomography (CT) scan of the abdomen and pelvis to evaluate the pancreas and rule out necrotizing pancreatitis. CT revealed moderate acute pancreatitis, an intrauterine pregnancy in vertex presentation, and a heterogeneously enhancing, placental-appearing soft tissue mass extending posteriorly and to the right that measured 2414 cm. The findings were concerning for placenta percreta with possible acute hemorrhagic component; however, malignancy could not be excluded. She underwent a preoperative magnetic resonance imaging, which revealed a single intrauterine pregnancy, posterior placenta, and large mass posterior to the





Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

placenta, likely a large degenerating fibroid or leiomyosarcoma. The patient underwent planned low transverse cesarean delivery and a 2090-g female was delivered without complication. Afterward, exploratory laparotomy with removal of the leiomyoma, lysis of adhesions, and omental biopsy was performed.

The tumor was located posteriorly with multiple attachments that included the right retroperitoneum and posterior peritoneum and involvement of the sigmoid mesentery. The ureter was intimately attached to the lateral aspect of the mass. The bowel was free of any attachment. Duration of the operation was 3 hours, 15 minutes. The surgically resected mass (Figure 1) and omental biopsies were sent to pathology. Following resection of the mass, the patient's calcium improved dramatically from 11.8 to 9.8 immediately. Similarly, the patient's mental status returned to baseline. A repeat lipase following surgery was 168 U/L (11–82 U/L). The calcitonin injections were discontinued and calcium was trended every 12 hours. Further hematologic work-up was completed, including serum free light chains to rule out plasmacytoma, revealing mildly elevated kappa/lambda free light chain ratio of 1.86 mg/dL (0.2600–1.65 mg/dL), angiotensin 1 converting enzyme was 41 U/L (16–85 U/L), and significantly elevated PTHrP was 9.6 pmol/L (<4.2 pmol/L). Pathology of the surgical specimen revealed whorled smooth muscle tissue with a central hemorrhagic area, consistent with a benign smooth muscle neoplasm (leiomyoma) with ischemic and degenerative changes. The specimen stained positive for desmin, consistent with leiomyoma, and negative for calcitonin. The specimen weighed 2834 gram and measured 19.018.514.0 cm with smooth to rough surface which was focally congested and mild focal adhesions. The patient's hospital course was complicated by acute shortness of breath requiring oxygen therapy with 3L nasal cannula. She developed pulmonary edema due to volume overload from IV fluids, confirmed by pulmonary vascular congestion on chest radiograph. The patient recovered with parenteral diuretic judicious fluid adjustment, and was discharged on postoperative Day 9. The mother and baby continue to do well.

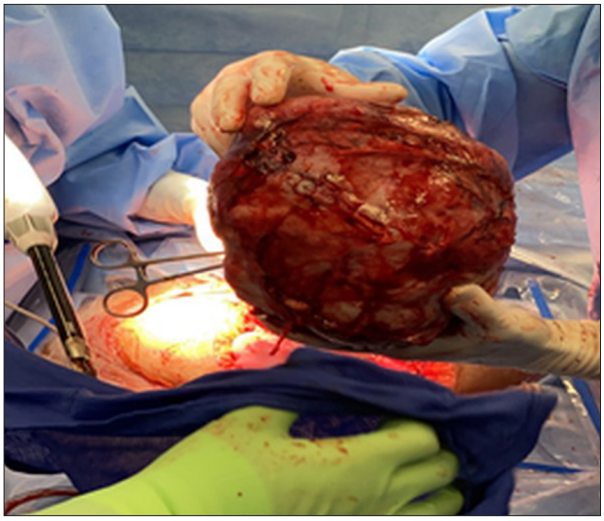

**Figure 1.** Surgical resection of 2834-g mass measuring 19.0×18.5×14.0 cm.

## Discussion

Leiomyoma is the most common tumor of the female genital tract [7]. They have characteristics similar to malignant tumors despite being benign growths. These shared characteristics include abnormal vasculature and unregulated growth. Like malignant tumors, it has been suggested that leiomyomas are a result of genetic mutation that leads to loss of integrity of the cell cycle resulting in inappropriate growth [1].

The increased hormonal state of pregnancy has variable effects on leiomyomas. While leiomyomas are particularly sensitive to the hormonal influence of estrogen and progesterone, most of them do not increase in size during pregnancy. Complications in pregnancy associated with leiomyomas include increased risk of preterm labor, fetal malpresentation, abnormal labor, potential placentation disorders, and requirement for cesarean delivery. Spontaneous abortions and infertility have also been linked to leiomyomas; however, this association is likely dependent on the location of the benign growth and not a result of the leiomyoma itself [1].

Hypercalcemia in pregnancy is rare and only occurs in approximately 0.03% of reproductive age women [3]. While there are many potential causes for hypercalcemia or hypercalcemic crisis in pregnancy, the most common are due to elevated parathyroid hormone (PTH). Malignancy should be considered as another cause of elevated calcium mediated through parathyroid hormone-related protein (PTHrP) [1,3].

Although classically seen with malignancies such as renal cell carcinoma, breast cancer, and squamous cell cancers, physiological PTHrP can be detected during pregnancy from the placenta and in the postpartum period from the breast during lactation. While mildly elevated levels of calcium can be noted during pregnancy due to these physiological adaptations, symptoms, if present, are typically mild [1,7].

PTH and PTHrP share an identical amino terminus, and thus work to both activate the same receptor. This activation causes an increase in serum calcium levels due to decreased secretion of calcium from the renal system as well as increased bone reabsorption [2,3,8].

Humoral hypercalcemia of malignancy is a paraneoplastic syndrome commonly associated with elevated levels of PTHrP and subsequent hypercalcemia. While it is commonly associated





Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

with malignancies, few cases have reported associations with benign tumors such as leiomyomas. These rare cases of benign tumors releasing PTHrP have inspired the term "humoral hypercalcemia of benignancy" [1,8].

Prompt intervention in a hypercalcemic crisis during pregnancy is necessary due to potential life-threatening risk. Treatments include adequate hydration and normalization of electrolytes, as in non-gravid patients. Because calcitonin does not cross the placenta, it has been used safely to treat hypercalcemia during pregnancy. Calcitonin mechanism of action lowers the serum calcium levels by inhibiting osteoclastic activity as well as increasing renal excretion of calcium. Use of calcitonin is limited, however, as it only decreases serum calcium levels by 1.1–1.9 mg/dL [3]. Due to side effects such as diarrhea, hypokalemia, and soft tissues calcifications, use of oral phosphates is limited. Due to teratogenicity, bisphosphonates and mithramycin are contraindicated for hypercalcemia in pregnancy [2]. In our case, the leiomyoma, which had previously been chemically inactive, was likely stimulated by the increased hormonal state of pregnancy [1,3]. The elevated PTHrP was believed to be secreted by the activated leiomyoma and resulted in the hypercalcemic crisis.

Preeclampsia is a state of elevated blood pressures associated with proteinuria after 20 weeks' gestation. It occurs more frequently in women who begin pregnancy with chronic hypertension. It is fundamentally a condition of constricted intravascular compartment and should have no effect on leiomyoma or critical level serum calcium. However, it could have contributed to the development of flash pulmonary edema.

Removing a necrotic myoma at the time of cesarean delivery can be difficult depending on clinical findings including the size and location of the myoma. In many cases, unless the myoma is on a stalk, the uterus must also be removed. Therefore, unless there is a clinical indication, such as in this case, most myomas are left undisturbed at cesarean. Removing a necrotic myoma that is not on a stalk and continuing the pregnancy is highly likely to result in a maternal-fetal mishap and should only be attempted when medical management is unsuccessful.

## Conclusions

Because leiomyomas are exceedingly common in both gravid and nongravid patients, PTHrP secretion from a leiomyoma should be considered in the differential diagnosis in a patient presenting with severe hypercalcemia. Because medical treatment options for hypercalcemia are limited for gravid females and aggressive IV fluid resuscitation can result in complications, surgical resection of the leiomyoma should be considered, as it is the most definitive treatment for hypercalcemia from a leiomyoma.

## References:

1. Tarnawa E, Sullivan S, Underwood P et al: Severe hypercalcemia associated with uterine leiomyoma in pregnancy. Obstet Gynecol, 2011; 117: 473–76
2. Rahil A, Khan FY: Humoral hypercalcemic crisis in a pregnant woman with uterine leiomyoma. J Emergency Trauma Shock, 2012; 5(1): 87–89
3. Rey E, Jacob C-E, Koolian M, Morin F: Hypercalcemia in pregnancy – a multifaceted chal-lenge: case reports and literature review. Clin Case Rep, 2016; 4(10): 1001–8
4. Kolnick L, Harris BD, Choma DP, Choma NN: Hypercalcemia in pregnancy: A case of milk-alkali syndrome. J Gen Intern Med, 2011; 26(8): 939–42
5. Garcha AS, Gumaste P, Cherian S, Apurv K: Hypercalcemia: An unusual manifestation of uterine leiomyoma. Case Rep Med, 2013; 2013: 815252
6. Sobey N, Raubenheimer L: Cystic pelvi-abdominal mass in pregnancy: An uncommon presentation of a subserosal leiomyoma. SA J Radiol, 2019; 23(1): 1683
7. Herring R, Laji K: Humoral hypercalcaemia of benignancy. A case report. QJM, 2008; 101(4): 329–30
8. Dagdelen S, Kalan I, Gurlek A: Humoral hypercalcemia of benignancy secondary to parathy-roid hormone-related protein secreting uterine leiomyoma. Am J Med Sci, 2008; 335(5): 407–8





Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]