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Case Study

Parathyroid hormone-related peptide induced hypercalcemia of pregnancy due to mammary hyperplasia

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Abstract

Maternal Parathyroid Hormone-related Protein (PTHrP) is involved in the placental transport of calcium. Autonomous overproduction of PTHrP is a rare cause of hypercalcemia in pregnancy. Prior cases of PTHrP-induced hypercalcemia in pregnancy have been managed with either dopamine agonists, fetal delivery, termination of pregnancy, or mastectomy. However, PTHrP level normalization following mastectomy has not previously been documented. Herein, we present a 39-year-old female hospitalized at 19 weeks of gestation for acute encephalopathy due to PTHrP induced hypercalcemic crisis (calcium 15.8 mg/dL, PTHrp 46.5 pmol/L [normal 0-3.4]). Mammary hyperplasia resulting in gigantomastia significantly impaired her ability to ambulate and perform activities of daily living. She remained hypercalcemic during hospitalization despite aggressive hydration, calcitonin, and 2 weeks of dopamine agonist treatment. Bisphosphonate therapy was not administered due to pregnancy and potential effects on the fetus. Our patient underwent bilateral mastectomy along with excision of a large axillary mass. The pathology of all three specimens revealed mammary stromal hyperplasia. PTHrP was undetectable on post-op day 2 and calcium normalized by post-op day 3. At discharge, she was able to ambulate independently. To our knowledge, this is the first reported case of PTHrP induced hypercalcemia related to gigantomastia, documenting resolution of hypercalcemia, and PTHrP levels following mastectomy. Mastectomy is a potential option in the second trimester for pregnant patients with PTHrP induced severe hypercalcemia due to gigantomastia, refractory to treatment with dopamine agonist therapy.

Keywords: hypercalcemia, PTHrP, pregnancy, gigantomastia, mastectomy, bromocriptine

Lay Summary

Parathyroid Hormone-related Protein (PTHrP) is important for transportation of calcium during pregnancy, facilitating fetal skeleton formation. Rarely, excess production of PTHrP can cause critically elevated calcium levels in pregnancy. We present a 39-yr-old female hospitalized at 19 wk of gestation for altered mental status, due to PTHrP-induced hypercalcemic crisis. She demonstrated profound breast enlargement and a left axillary mass, impairing her ability to walk and work. Despite aggressive hydration, and medical treatment targeted to lower calcium, her calcium remained significantly elevated. She underwent surgical removal of both breasts and excision of the axillary mass which each demonstrated mammary stromal hyperplasia. PTHrP levels became undetectable, and calcium quickly normalized. To our knowledge, this is the first reported documentation of resolution of hypercalcemia and PTHrP levels following surgical resection of the excess breast enlargement during pregnancy.

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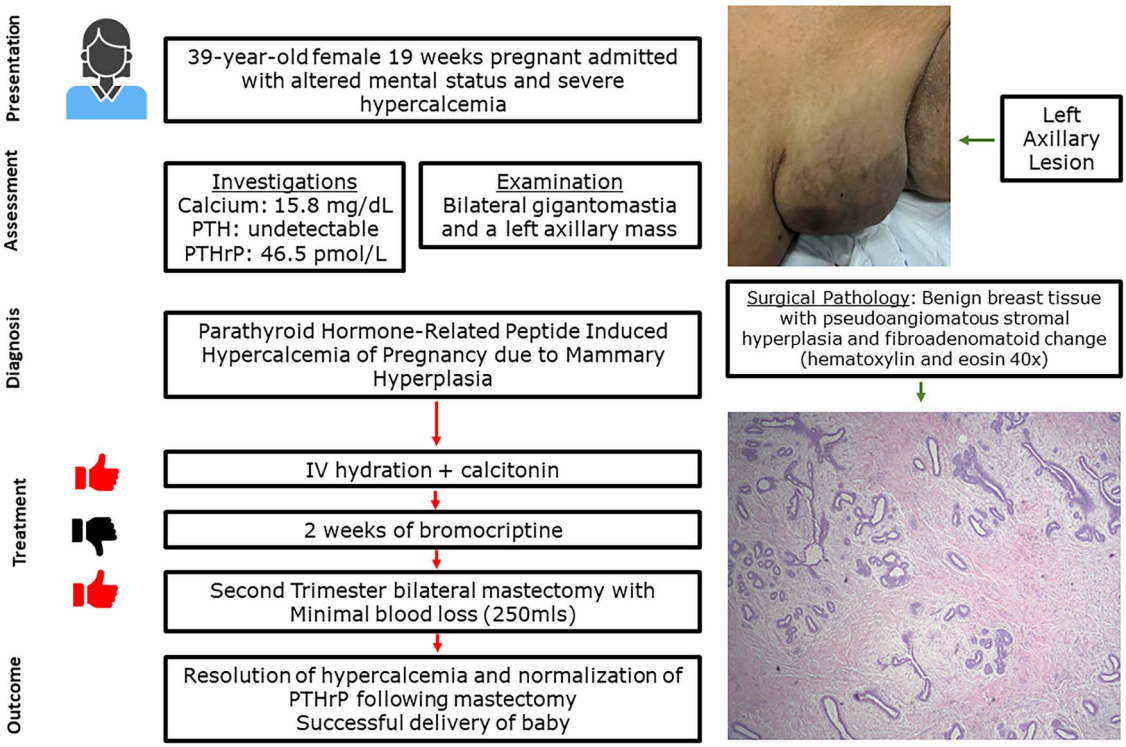
Graphical Abstract



Introduction

During pregnancy, fetal calcium demands are provided through maternal physiologic adaptations. Progressive increase in PTHrP levels, produced in both the breast and the placenta, enhances calcium release from the skeleton and also mediates placental transfer of calcium.[1,2] Other maternal changes to promote calcium availability for the fetus include increased 1,25-dihydroxyvitamin D production and resulting increases in gastrointestinal absorption.[3,4] Although such physiologic adaptation is designed to meet the nutritional needs of the fetus while maintaining maternal ionized calcium; perturbations resulting in hypercalcemia during pregnancy can occur with resultant adverse effects on the mother and newborn.

Hypercalcemia is uncommon in pregnancy, with an incidence of 0.03%, but can lead to hypertension, pancreatitis, nephrolithiasis, and renal failure in the mother,[5] and growth restriction, tetany, and death in the fetus.[6] Hypercalcemia in pregnancy is usually attributable to primary hyperparathyroidism[7] but rarely can also be caused by autonomous overproduction of PTHrP. Excess PTHrP stimulates osteoclast differentiation, thereby enhancing bone resorption, followed by hypercalcemia.

During pregnancy, physiologic PTHrP is produced by the placenta, breast, and uterus. During PTHrP-induced hypercalcemia of pregnancy, mammary hyperplasia, mammary hypersensitivity to prolactin, and placental overproduction of PTHrP have all been implicated as possible etiologies.[8-12] Therein, we present the first case of PTHrP-induced hypercalcemia, refractory to dopamine agonist, with documented resolution of PTHrP elevations and hypercalcemia after bilateral mastectomy and axillary mass resection.

Clinical vignette

A 39-yr-old female, 19 wk pregnant, presented to the emergency room with altered mental status. One week prior to presentation, she noted increasing fatigue, urination, and constipation. On examination, she was encephalopathic, tachycardic (122 bpm), and blood pressure was 112/65. Most notable on the exam was bilateral gigantomastia with significant excoriation and bleeding (Figure 1A) and a left axillary mass. Investigations revealed severe hypercalcemia (corrected calcium of 15.8 mg/dL [3.94 mmol/L]). With hydration mental status improved, the patient reported that her breasts had substantially increased in size with mild tenderness during pregnancy. She could no longer ambulate independently or perform many activities of daily living.

During her prior pregnancy with twins (4 yr earlier), the patient had experienced a dramatic increase in breast size and presented with bilateral breast discomfort and a left axillary mass. Mild incidental hypercalcemia (10.2 mg/dL normal range 8.1-10) was noted which increased to 12.2 mg/dL [3.04 mmol/L] on the day of delivery (32 wk and 5 d), but she remained asymptomatic. Postpartum, calcium levels normalized, and breast size returned to prepregnancy size over 2 mo, though the left axillary mass remained. Three months prior to the current presentation investigation of the left axillary mass with a core biopsy demonstrated breast tissue with fibroadenomatoid changes and pseudo-angiomatous stromal hyperplasia (PASH). Breast reduction or mastectomy was considered; however, the patient was already 13-wk pregnant.

Her medical history was notable for controlled human immunodeficiency virus infection, depression, and polycystic ovarian syndrome. Medications included prenatal multivitamin (containing cholecalciferol 400 units and calcium sulfate 200 mg), abacavir-dolutegravir-lamivudine, and escitalopram.

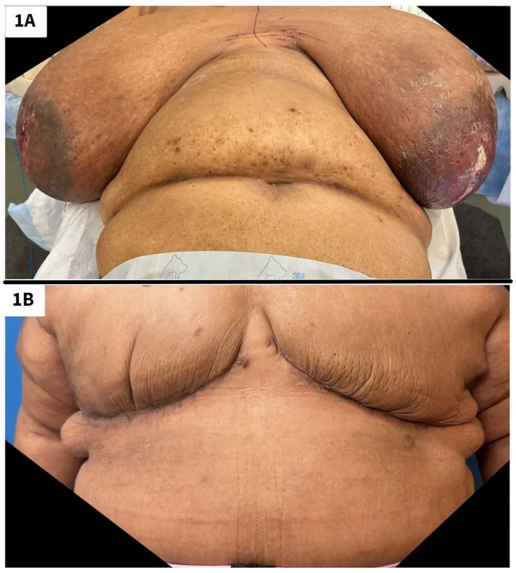


Figure 1. (A) Gigantomastia evident in both the right breast and left breast with erythematous periareolar changes, nipple excoriation, and sanguinous discharge. (B) Anterior view of chest status post bilateral total mastectomy at 4-mo outpatient surgical follow-up. Incisions are well healed.

Evaluation revealed hypercalcemia with suppressed parathyroid hormone (PTH) (<6.5 pg/mL), low normal 1-25-dihydroxyvitamin D level (79.6 pg/mL, normal in second trimester 72-160), normal serum protein electrophoresis, and elevated PTHrP (46.5 pmol/L, normal 0-3.4, as measured by liquid chromatography, mass spectroscopy at ARUP (Associated Regional and University Pathologists) Laboratories, UT). Infectious testing, specifically, blastomyces antigen, histoplasma capsulatum antigen, and QuantiFERON were negative. Angiotensin converting enzyme level was 38 U/L (normal 16-85 U/L). A 24-h urine collection for calcium showed hypercalciuria (539.2 mg/day). Prolactin measured twice was 6.5 and 10.3 ng/mL, (nonpregnant normal range 2.8-29.2). CT chest, abdomen, and pelvis performed for concerns of malignancy demonstrated mammary enlargement but showed no distinct masses, lymphadenopathy, or granulomatous disease. Engorged subcutaneous vessels were detected in the breasts; however, the breasts were incompletely visualized, as they were larger than the field of view of the study.

Given the patient's increased PTHrP and gestational increase in breast size in the absence of alternative etiologies, the patient was diagnosed with PTHrP-induced hypercalcemia due to gestational gigantomastia.

Treatment included aggressive hydration with intravenous normal saline, calcitonin (dosed at 4 units/kg × 4 doses), and close monitoring of calcium levels (Figure 2). Vitamin D and calcium supplements were withheld. By day 2 of hospitalization, her mental status had improved. To reduce prolactin-mediated breast stimulation, bromocriptine 2.5 mg daily was attempted and advanced to 5 mg daily on day 6 without significant improvement in calcium or PTHrP levels. The patient experienced significant bleeding from the breast requiring multiple transfusions. Following multidisciplinary discussion, due to persistent hypercalcemia despite saline, calcitonin, and bromocriptine, the need for multiple transfusions, and resultant limited mobility due to gigantomastia, definitive therapy with bilateral total mastectomy was performed. Intravenous bisphosphonates were not attempted, as bisphosphonates cross the placenta and could lead to fetal or neonatal hypocalcemia, as well as other perinatal complications.[13]

Previous reports of mastectomy for gigantomastia have been complicated by significant blood loss, upward of 15 units of blood loss intraoperatively.[12,14] A number of surgical advancements made the operation much safer. A "no vertical scar" breast reduction incision pattern was used to allow for future breast reconstruction and to avoid additional bleeding from additional incisions. The use of a tumescent solution (30 mL of 1% lidocaine with epinephrine diluted in 1 L of Lactated Ringers) and careful control of dilated veins including the use of the Impact Ligasure energy-based vessel-sealing device (Medtronic, Minneapolis) was crucial. Furthermore, maintenance of dissection outside of the parenchyma (which was hypervascular and engorged with blood) was critical. Of note, the largest vessels encountered were the perforators from the pectoralis major, measuring over 1 cm in diameter (Figure 3A). Such measures in this case limited the estimated intraoperative blood loss to only 250 mL. Each mastectomy specimen weighed ~13.5 kg each. An additional left accessory breast was also removed, weighing 760 g.

Results

Surgical pathology from the right and left breasts and the left axillary mass all demonstrated PASH and fibroadenomatoid changes and were negative for malignancy (Figure 3B). PTHrP immunostaining was not available. However, serum PTHrP levels decreased from 39.7 pmol/L prior to mastectomy to undetectable levels 2 d after mastectomy (Figure 2). She was discharged home 8 d after surgery ambulating independently and total calcium levels remained normal. Pre- and postoperative fetal ultrasound scans indicated appropriate fetal development; however, genetic screening revealed mosaic trisomy 21. The baby was delivered at 36 wk via caesarean section and is doing well, and 4 mo after surgery, the patient was ambulating well and reported no pain. Examination showed healed incisions (Figure 1B), no evidence of recurrent mammary hyperplasia, and her albumin-corrected calcium remained normal at 9.6 mg/dL.

Discussion

Autonomous overproduction of PTHrP is a rare cause of hypercalcemia in pregnancy. Hypercalcemia accompanying breast enlargement in both her current and prior pregnancies highly suggests mammary hyperplasia induced PTHrP excess. This is the first reported case of PTHrP-induced hypercalcemia related to gigantomastia that has documented the resolution of hypercalcemia and PTHrP levels following bilateral mastectomy. Furthermore, surgical advancements allowed the mastectomy to be performed efficiently and safely, both to mother and child.

This is also the first hypercalcemia case reported to be associated with 3 pathologic sites of PASH (both breasts and the left axillary mass). PASH is a benign lesion, most often seen in premenopausal women, histologically defined as network of slit-like spaces lined by spindle shaped myofibroblasts against a background of dense fibrous stroma. Unique to this

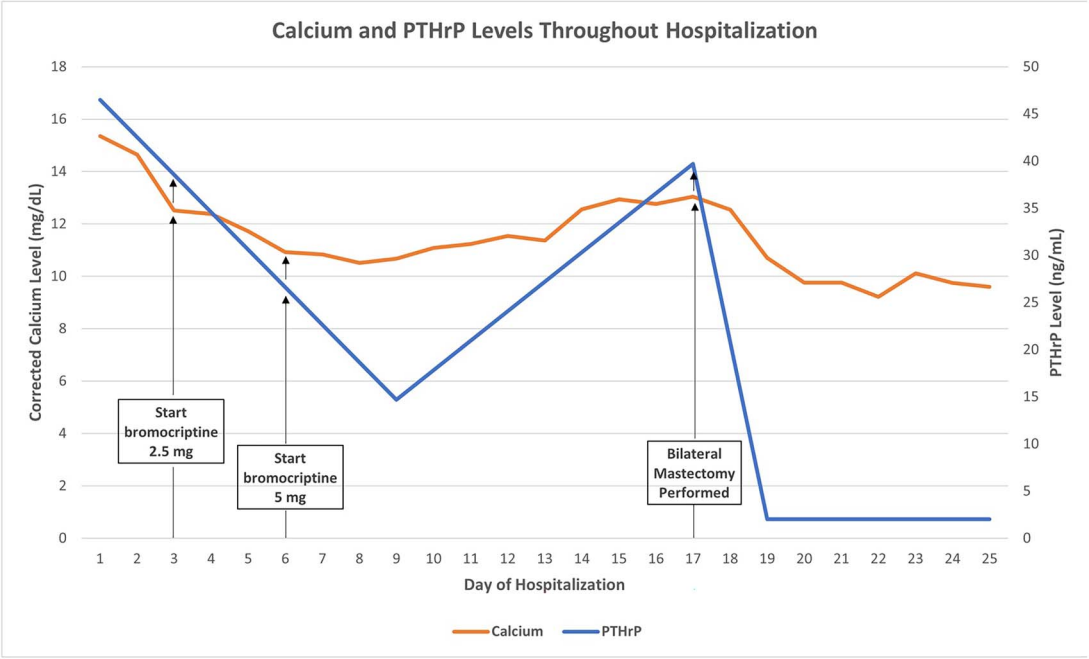


Figure 2. Trend of calcium (orange, left axis) and PTHrP levels (blue, right axis) throughout hospitalization and in response to treatment.

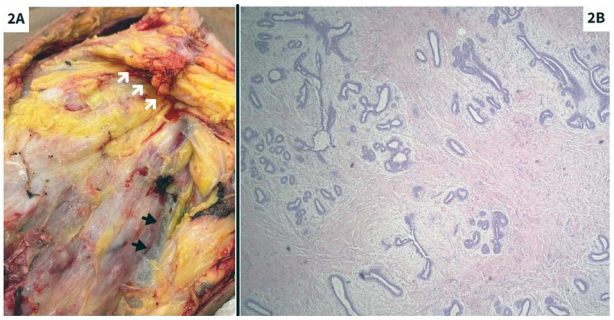


Figure 3. (A) In situ anatomic picture of the right breast pathology. The bluish hue is indicative of parenchymal hypervascularity and vascular derangement (black arrows). Dissection along the loose areolar plane allowed for minimal blood loss (white arrows). (B) Benign breast tissue with pseudoangiomatous stromal hyperplasia and fibroadenomatoid change (hematoxylin and eosin 40×).

patient's presentation is the resultant massive enlargement of breast tissue (PASH is rarely seen in lesions >5 cm).[15]

Mammary hyperplasia, mammary hypersensitivity to prolactin, and placental overproduction of PTHrP have all been implicated as possible etiologies of PTHrP-mediated hypercalcemia of pregnancy.[8-11] Excessive PTHrP production can occur during pregnancy when mammary tissue is hypersensitive to the physiologic rise of prolactin. This is accompanied by breast hyperproliferation; so-called "gigantomastia of pregnancy."[16] Winter et al. reported a 32-yr-old female with gigantomastia at the 15th wk of pregnancy. PTHrP was high at 5.5 pmol/L and prolactin was 57 mcg/mL (normal for pregnancy). Bromocriptine (2.5 mg three times daily) suppressed prolactin activity, leading to complete remission of hypercalcemia within 3 wk; PTHrP became undetectable and breast growth stopped.[8] In contrast, despite 2 wk of bromocriptine treatment in our case, neither gigantomastia nor hypercalcemia improved.

An alternative source of PTHrP during pregnancy is the placenta. Eller-Vainicher et al. reported a 35-yr-old pregnant woman with PTHrP-related hypercalcemia (PTHrP 26 pmol/L), presumed to be placental in origin, as delivery resulted in prompt reduction in calcium levels.[9]

Modarressi et al. reported a 33-yr-old female who developed gigantomastia by 8-wk gestation, hypercalcemia at 13 wk, with PTHrP level of 32 mg/dL (normal 14-27). Pregnancy was terminated at 20-wk gestation and both PTHrP and calcium levels normalized within 48 h. Since PTHrP and calcium normalized while gigantomastia persisted, this was interpreted as evidence for a placental source of PTHrP.[10]

Jackson et al. also reported a 24-yr-old female who had developed gigantomastia in pregnancy.[11] She was treated with bromocriptine 30 mg twice daily, with no significant change in breast size. Calcium levels peaked at 14.3 mg/dL, with undetectable prolactin. Bilateral mastectomy normalized calcium within 5 d. Pathology showed benign mammary hyperplasia with microscopic features of "virginal hypertrophy" (benign breast enlargement independent of hormonal stimulation). Serum PTHrP was not measured, but immunohistochemistry of the breast specimen demonstrated PTHrP antigenic activity in the myoepithelial cells of the breast. The postulated etiology of hypercalcemia was PTHrP production by hypertrophied breast tissue. A limitation in our report is the lack of available PTHrP immunostaining of the breast sample, which would have further corroborated the etiology of hypercalcemia but could not be performed by the institution.

Our case highlights the importance of a systematic evaluation for hypercalcemia in pregnancy to identify etiology. Herein, we demonstrate the resolution of PTHrP-induced hypercalcemia in a patient with gigantomastia following surgical removal of both breasts and axillary mass, all demonstrating stromal hyperplasia. Additionally, mastectomy using modern surgical techniques to minimize blood loss is a potential option in the second trimester for pregnant patients with

PTHrP-induced severe hypercalcemia due to gigantomastia refractory to treatment with dopamine agonist therapy. Breast reduction should be cautioned against, given the hypervascularity of the breast parenchyma itself.

Author contributions

All authors participated in the preparation of this manuscript. All authors have reviewed and approved the final draft of this manuscript. Wade Jodeh (Conceptualization, Investigation, Writing—original draft, Writing—review & editing), Payton J. Sparks (Investigation, Writing—review & editing), Jasmine M. Higgins (Investigation, Writing—review & editing), Alan Tom (Investigation, Writing—review & editing), Natanie Anilovich (Investigation, Writing—original draft, Writing—review & editing), Harley Moit (Investigation, Writing—review & editing), Lisa Korff (Investigation, Writing—review & editing), Ivan Hadad (Investigation, Writing—review & editing), Xiaoyan Wang (Investigation, Writing—review & editing), Erik A. Imel (Investigation, Writing—review & editing), and Diane M. Donegan (Conceptualization, Investigation, Supervision, Writing—original draft, Writing—review & editing)

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Conflicts of interest

All authors confirm that there are no conflicts of interest pertaining to the content of the manuscript entitled: "Parathyroid Hormone-Related Peptide Induced Hypercalcemia of Pregnancy due to Mammary Hyperplasia." All authors have no disclosures to declare.

Patient consent

Patient has provided written informed consent regarding the use of health information for the purpose of publication. The signed consent form covers publication of any data collected. Patient information is anonymized to the extent possible.

Data availability

The data underlying this article are available in the article itself and its figures.

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