Humoral Hypercalcemia of Twin Pregnancy: Not a Laughing Matter

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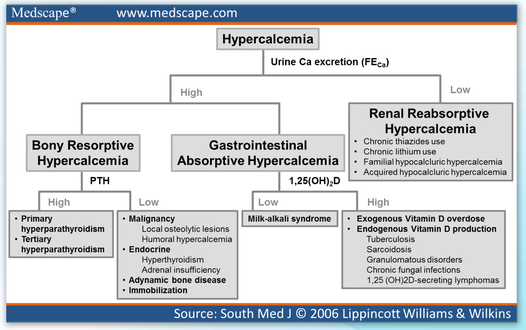
Introduction

Hypercalcemia is a relatively common clinical condition that can occur secondary to one of several etiologies. Among all causes, the most common are primary hyperparathyroidism and malignancy. Even though these two causes account for greater than 90% of cases, the differential diagnosis when encountering hypercalcemia should remain broad to in order to accurately diagnose and treat this potentially lethal condition. One of the less common hormonal abnormalities causing hypercalcaemia is an elevation in PTHrP, parathyroid hormone related protein. The presence of PTHrP was first identified as the cause of hypercalcemia in the setting of malignancy. It is most associated with lung and breast cancer. The protein, which mimics the effects of native parathyroid hormone, is usually undetectable in healthy individuals. However, recent studies and case reports have shown that PTHrp levels have been measurable during pregnancy and lactation in females and have disappeared or decreased after delivery. This phenomenon is described as humoral hypercalcemia of pregnancy, which is a peripartum increase in release of PTHrp by mammary and placental tissue. Here, we present a case of a healthy 26-year-old female who developed severe hypercalcemia after delivery and during breast feeding secondary to elevated PTHrP.

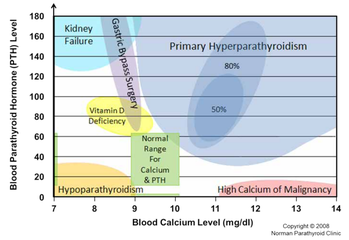


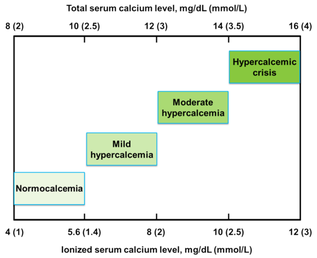
Abstract

Clinical Case: A 25 year old female presented to the emergency department six days post-partum of spontaneous vaginal delivery of twins at 28 and 4/7 weeks. Her chief complaints included bilateral leg pain, weakness, and difficulty ambulating for the previous two days. The patient reported complaints of recent fatigue, polyuria, and polydipsia. She was breastfeeding as well as pumping her breast milk and reported only taking pre-natal vitamins and occasional acetaminophen for headaches. Given her leg pain, venous Doppler studies of the lower extremities were ordered which revealed bilateral deep vein thromboses (DVT). A CT of the chest was also performed that revealed bilateral lower lobe pulmonary emboli (PE). Her calcium level prior to delivery was noted to be normal, however, on presentation, she had an elevated hypoalbuminemia-corrected calcium of 17.14mg/dL and an elevated ionized calcium of 8.70 mg/dl. Her alkaline phosphatase was slightly elevated at 184 U/L. Her remaining electrolytes were all within normal limits. Her CT Chest did not reveal any signs of mediastinal masses. Due to her bilateral DVT and PE, she was started on a Heparin drip and admitted to the hospital. The patient was started on normal saline at 300mL/hr and 200 units of Calcitonin two times per day for her severe hypercalcemia.

Upon admission, her PTH was found to be extremely low. Levels of Vitamin D 1,25, angiotensin converting enzyme, vitamin A and serum urine protein electrophoresis were obtained in the workup for non-PTH mediated causes of hypercalcemia and all were within normal ranges. Her PTHrP was found to be elevated to 27.0 pmol/L endorsing a diagnosis of rare and benign Humoral Hypercalcemia of Pregnancy.

The patient was treated with intravenous fluids, six days of calcitonin, and one dose of pamidronate. Her calcium normalized and she was clinically improved for discharge after 6 days. During her hospital course, she was bridged to Coumadin for anticoagulation secondary to her DVT and PE. To date, the patient has been lost to outpatient follow up.





Laboratory Data

	Normal Ranges	Patient Lab Values on 2/17/15	Patient Lab Values During Admission 4/4/15	Patient Lab Values During Admission	Patient Values on Day of Discharge 4/19/15	Patient Lab Values on Follow up 6/17/15
Serum Calcium	8.5-10.1 mg/dl	8.7 mg/dl	16.5 mg/dl		10.1 mg/dL	9.4 mg/dL
Albumin	3.5-4/6 g/dl		3.2 g/dl		3.3 g/dL	3.9 g/dL
Corrected Calcium	8.5-10.1 mg/dl		17.14 mg/dl		10.6 mg/dL	n/a
Ionized Calcium	4.6-5.40 mg/dl		8.70 mg/dl			
Phosphorus	2.3-4.6 mg/dl		2.5 mg/dl		3.1 mg/dL	
Alkaline Phosphatase	25-120 U/L		184 U/L			89 U/L
PTH	14.0-72.0 pg/ml			1.7 pg/ml		
PTHrP	0.0-3.4 pmol/L			27 pmol/L		
Vitamin D, 25-OH	30-100 ng/mL			11 ng/mL		
ACE level	9-67 U/L			38 U/L		
Vitamin A, Retinol Free	0.30-1.20 mg/L			0.39 mg/L		
IFG-1	87-368 ng			101 ng/ml		
SPEP	Ranges			Negative		
UPEP	Ranges			Negative		

Summary of Conclusions

- Calcium is actively transported through the placenta from the mother to the fetus during pregnancy.
- Most pregnant woman experience total hypocalcemia due to over 20g of calcium being provided to the developing fetus. During delivery, the calcium transport mechanism through the placenta is abruptly halted, which does not affect the majority of women who are total calcium depleted.
- Common pathologies associated with hypercalcemia are Sarcoidosis, Vitamin A overdose, Acromegaly, adrenal insufficiency, multiple myeloma, humoral hypercalcemia of malignancy, milk alkali syndrome, primary hyperparathyroidism, and less commonly humoral hypercalcemia of pregnancy.
- Sarcoidosis, Vitamin A overdose, milk alkali syndrome, primary hyperparathyroidism and multiple myeloma were definitively ruled out. Acromegaly and adrenal insufficiency were low on the differential diagnosis list and would have been ruled out with tests at an outpatient office visit. However, of note, the patient did not have any physical exam findings of Acromegaly. Adrenal insufficiency was low on the differential diagnosis as the patient was not hypotensive and did not have any sodium or potassium irregularities.
- Humoral hypercalcemia of pregnancy is a benign and rare entity of excessive production of PTHrP resulting in hypercalcemic crisis during pregnancy, puerperium, and lactation.
- PTHrP is produced physiologically by placental tissues and mammary glands, during pregnancy and lactation respectively.
- Suckling is a stimulant for prolactin secretion which stimulates PTHrP production in the mammary gland. When a large amount of PTHrP from the breast enters the blood stream it stimulates calcium to shift from maternal bone into breast milk to supply the developing newborn. If there is an excessive amount of PTHrP produced, this can lead to a hypercalcemic crisis during lactation.
- Humoral hypercalcemia of pregnancy is a rare entity with no reported cases involving twin gestation.