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Behind the Storm: A Case of Severe Hypercalcemia Due to an Atypical Parathyroid Tumor During Late Pregnancy

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Abstract

A 37-year-old pregnant woman who developed life-threatening hypercalcemia and acute pancreatitis at 33 weeks of gestation. The patient was presented with premature contractions, altered mental status, and fetal distress, requiring emergency delivery. Initial laboratory findings revealed elevated calcium levels at 17.1 mg/dL and parathyroid hormone at 1194 pg/mL. Despite intense medical management including intravenous hydration, zoledronic acid, and dialysis, hypercalcemia persisted. Imaging studies identified multiple parathyroid nodules and osteolytic bone lesions. The patient underwent a successful parathyroidectomy with removal of a 3 cm adenoma. Histopathological analysis revealed an atypical parathyroid tumor with trabecular architecture, preserved parafibromin expression, and low Ki-67 index, indicating low malignancy risk. Postoperatively, parathyroid hormone levels dropped dramatically from 1194 pg/mL to less than 4 pg/mL within 24 hours, though subsequently rose to 189 pg/mL during follow-up. At three months of postpartum, calcium levels remained normal with supplementation. This case highlights the diagnostic challenges of hyperparathyroidism during pregnancy and emphasizes the importance of early recognition, multidisciplinary management, and long-term surveillance for atypical parathyroid lesions.

Introduction:

Calcium (Ca) is an essential mineral for bone mineralization, neuromuscular function, and intercellular signaling. Its disorders have a significant morbimortality (1). For this reason, adequate management of dyscalcemia is crucial. Hypercalcemia is defined by a high level of adjusted total Ca –practically used- above 10.5 mg/dL (mild 10.5-12 mg/dL, moderate 12.1-14 mg/dL, and severe >14 mg/dL) (2, 3, 4). The main cause of hypercalcemia is primary hyperparathyroidism (mild and moderate) and cancers (severe or malignant) (5, 6). Most commonly hyperparathyroidism is due to parathyroid adenoma (PA) or hyperplasia, but rarely a parathyroid carcinoma (PC). Atypical PA is an uncommon histological feature, rarely discussed i the literature. Here, we report a rare case of life-threatening hypercalcemia due to an atypical parathyroid adenoma during the peripartum period (PPP).

Case presentation:

A 37-year-old woman with no significant medical history, gravida 3 para 2, presented to our department

during the PPP for a severe hypercalcemia. At 33 weeks of gestation, she developed premature uterine contractions complicated by acute confusion and fetal distress. Perioperative workup revealed severe hypercalcemia (serum calcium 17.1 mg/dl) associated with acute pancreatitis (lipase 1086 U/L). Abdominal CT imaging demonstrated severe pancreatitis (Balthazar grade E, severity score 8) with significant intraperitoneal fluid collection. Initial management included aggressive intravenous hydration, zoledronic acid 4mg, furosemide, and urgent dialysis for stabilization and ultimately fetal extraction, prior to transfer to our department for comprehensive evaluation and ongoing management
On admission, the patient was asthenic, GCS 15, with tachycardia at 116 bpm, mild dehydration, and normal blood pressure. Physical examination found a mild conjunctival pallor, bilateral basal rhonchi, and significant ascites with diffuse abdominal tenderness. The electrocardiogram was normal with cQT at 387 ms.

Laboratory tests confirmed a hyperparathyroid hypercalcemia with parathyroid hormone (PTH) at 1194 pg/mL (4-64), serum phosphate low at 12 mg/L (25-45), and 25-hydroxyvitamin D at 8.4 ng/mL (30-60). Assessment of hypercalcemia complications revealed elevated alkaline phosphatase (360 U/L), preserved renal function with no lithiasis on ultrasound, and normal cardiac function.Cervical ultrasound showed a solid-cystic parathyroid nodule on the right side and parathyroid scintigraphy with 99mTc-MIBI –on PPP- revealed a left-sided parathyroid lesion. CT imaging confirmed a large hypodense lesion displacing the thyroid and revealed osteolytic lesions in the scapula and vertebrae. Genetic screening for multiple endocrine neoplasia (MEN) syndromes was negative. Comprehensive malignancy workup was unremarkable.

Despite initial medical therapy, hypercalcemia persisted with progressive elevation to 147 mg/L, hence the resort to zoledronic acid, cinacalcet, and supportive care for pancreatitis. The patient underwent successful parathyroidectomy with removal of multiple parathyroid nodules, seen directly, including a 3 cm right-sided adenoma.

Histopathological examination revealed an atypical parathyroid tumor. It was positive for GATA3 and chromogranin A, negative for TTF1 and thyroglobulin, having a low mitotic index (1/10), cellular protrusions within the capsule without capsular breach or vascular emboli. The proliferation showed atypical trabecular architecture without significant cytonuclear atypia. Immunohistochemical analysis demonstrated Ki-67 index of 2% and preserved parafibromin expression. Final diagnosis was an atypical parathyroid tumor with trabecular architecture, without malignant features, carrying low recurrence risk.

In the immediate postoperative period, PTH levels showed an excellent biochemical response, falling from 1194 pg/mL to <4 pg/mL within 24 hours of surgery, representing a greater than 99% reduction. However, PTH levels raised to 8 pg/mL by postoperative day 8 and further increased to 189 pg/mL during follow-up (2.9-fold above the upper limit of normal). and serum calcium levels stabilized at 95 mg/L. At the three-month of PPP follow-up, calcium levels remained normal (84 mg/L) with adequate vitamin D supplementation. The patient is currently under close observation while waiting for ultimate genetic counseling.

Discussion:

Our patient was presented with an exceptionally severe form of hyperparathyroidism during pregnancy. This degree of biochemical derangement is rarely encountered in obstetric practice and poses significant management challenges for both maternal and fetal wellbeing (1). The simultaneous occurrence of acute

pancreatitis further complicated the clinical picture, as this represents a serious but uncommon consequence of severe hypercalcemia that requires careful multidisciplinary coordination.
Despite achieving excellent initial biochemical control, the pathological examination revealed atypical architectural features that deviated from the typical adenomatous pattern seen in most cases of primary hyperparathyroidism (7). While primary hyperparathyroidism commonly affects women of reproductive age, with benign adenomas accounting for approximately 80% of cases, the unusual histological findings and clinical behavior in our patient underscore the importance of genetic testing and long-term monitoring (5).
Clinically, most patients are asymptomatic, but rarely do they present severe symptoms involving neurological, muscular, gastrointestinal, renal, and cardiovascular systems as did our patient (1,7).
In pregnancy, maternal PTH does not cross placenta, and is usually decreased to the lower normal range, 1,25(OH)2D increases up to three times, and calcium marks major metabolic changes driven by PTH-related peptide (PTHrP) to ensure mineralization of the skeleton in the fetus and newborns. PTHrP is physiologically produced by the placenta leading to calcium transfer and mammary tissue contributing to calcium transport into breast milk during lactation. After delivery, 1,25(OH)2D return to normal, while insufficient data have been reported on PTH levels, (8,9). PHPT in pregnancy is uncommon (1% of all patients with PHP), its symptoms may be unspecific, resembling to normal pregnancy complaints such as tiredness, nausea, vomiting, muscle weakness, polyuria –which were present in our patient-, and can be associated to polyhydramnios related to fetus osmotic polyuria. The association between calcium levels and adverse pregnancy outcomes remains controversial (10).
Parathyroid cancer is the underlying etiology in less than 1% of cases, with a similar sex prevalence, and an age range between 40 and 50 years old (11). For parathyroid carcinoma (PC), the diagnosis is based on a histopathological examination to differentiate it from benign parathyroid adenoma. The World Health Organization has established clear diagnostic criteria, emphasizing that evidence of infiltrative growth or vascular invasion is the cornerstone for confirming malignancy (16). Among the various histological features, capsular invasion is the crucial diagnostic marker. Conversely, vascular invasion carries profound clinical implications, because it increases the risk of recurrence and mortality (12). The diagnostic arsenal has been strengthened by immunohistochemical markers, especially parafibromin loss, which occurs in approximately half of all cases and provides valuable confirmatory evidence when combined with clinical features (13,14). In our patient, the lesion showed atypical trabecular architecture without significant markers of malignancy, which makes it an atypical case to diagnose (table 1 may summarize the difference between the three cases).
Following successful surgical resection of a PC, long-term surveillance is of most need, as recurrence can occur even decades after initial treatment. Contemporary follow-up regimens recommend regular biochemical monitoring every six months during the first five years, followed by annual assessments thereafter, with particular attention to PTH and calcium levels as harbingers of disease recurrence (15), as we recommended to our patient, since the histological examination is atypical and still needs short and long term follow-up. The surgical approach has an important role in outcomes, with achieving adequate resection margins being paramount for long-term survival, while the inevitable postoperative complications, including hypocalcemia in over half of patients, underscore the need for comprehensive perioperative care and lifelong endocrine support (16,17).

Table 1. Histological and Immunohistochemical Features of Parathyroid lesions

Feature	Typical Parathyroid Adenoma	Atypical Parathyroid Adenoma	Parathyroid Carcinoma
Capsule	Thin and intact capsule	Thick fibrous capsule	Thick fibrous capsule with breach/invasion
Growth Pattern	Solid, follicular, or mixed	Trabecular architecture	Trabecular/lobular pattern with dense trabeculae
Fibrous Bands	Minimal or absent	thick fibrous bands	Prominent thick fibrous bands
Mitotic Activity	Rare (<1/10 HPF)	Low (1-2/10 HPF)	Increased (>2/10 HPF)
Cellular Atypia	Minimal	Moderate cellular atypia	Clear cellular atypia
Necrosis	Absent	Absent or minimal	May be present
Vascular Invasion	Absent	Absent	Present
Capsular Invasion	Absent	Cellular protrusions without breach	Definitive capsular breach
Perineural Invasion	Absent	Absent	May be present
Lymphovascular Invasion	Absent	Absent	Present
Adjacent Tissue Invasion	Absent	Absent	Present
Ki-67 Index	<2%	2-5%	>5%
Parafibromin Expression	Preserved (nuclear staining)	Preserved	Lost (absence of nuclear staining)
GATA3	Positive	Positive	Positive
Chromogranin A	Positive	Positive	Positive
TTF1	Negative	Negative	Negative
Thyroglobulin	Negative	Negative	Negative
Prognosis	Excellent, no recurrence	Low risk of recurrence	High risk of recurrence and metastasis
Metastatic Potential	None	None	Present

HPF: high power field; TTF1: thyroid transcription factor 1

For genetic basis, many studies have discussed the complex molecular alterations behind the pathogenesis of PC. CDC73 gene mutations are the predominant, in nearly half to two-thirds of all PC (18, 19). This

important gene, coding parafibromin, a key regulatory protein that controls both gene expression and cellular growth, is the main tumor suppressor (20).
Most commonly PHPT and PC are sporadic, and in 5-10% of cases is linked to hereditary syndromes like MEN, familial isolated hyperparathyroidism, hyperparathyroidism jaw tumor syndrome, neonatal severe primary hyperparathyroidism...etc (5,11). For this reason, hereditary patterns are to be checked. Recent genetic counseling recommendations emphasize comprehensive screening strategies, with an initial gene screening that includes MEN1, CDC73, RET, and CASR, followed by second line panels incorporating emerging genetic markers (21).

Conclusion:

Pregnancy knows many calcium changes. When PHPT occurs, its diagnosis can be triggered, with potential adverse outcomes. Many recent studies and societies recommend a genetic screening for potential underlying syndrome. This case highlighted the importance of considering hyperparathyroidism as a differential diagnosis in pregnant women presenting with non-specific symptoms and severe complications. Atypical histological features require careful interpretation and close follow-up.

Conflict of Interest

The authors declare that they have no conflict of interest in this work.

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