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Case Report

A Case of Adolescent Girl with Hypercalcemia Resistant to Medical Treatment Due to Giant Breast Fibroadenoma

Çetin K et al. Hypercalcemia due to Giant Fibroadenoma

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What is already known on this topic?
Hypercalcemia may occur due to many reasons in children and adolescents, but malignancy-related hypercalcemia is very rare. Juvenile fibroadenomas are the most common breast masses in adolescent girls and are usually followed without treatment. Giant and symptomatic fibroadenomas can be removed surgically, but these masses have a risk of recurrence. Increased PTHrP in benign tumors such as fibroadenoma is extremely rare and in the literature PTHrP has been associated more with malignancies or endocrine diseases.

What this study adds?
PTHrP can also be elevated in benign tumors as in our case and PTHrP can rapidly normalize when the cause is eliminated and is not always an indicator of poor prognosis. Adolescent girls may not apply to us before their breast masses become apparent because they are embarrassed or have low awareness. Therefore, in cases where the etiology of hypercalcemia is unclear, the clinical history should be detailed and a full systemic examination should be performed. This case shows us that fibroadenoma should also be considered in cases of undetermined hypercalcemia, especially in adolescent girls.

Abstract
Hypercalcemia in children is a rare condition and can result from various etiologies such as genetic, metabolic, iatrogenic and malignancy. In some malignancies, Parathyroid Hormone Related Protein (PTHrP) can mimic the physiological effects of Parathyroid Hormone (PTH) and cause hypercalcemia. In this report , we present a rare case of hypercalcemia secondary to juvenile fibroadenoma, which is a benign breast tumor. A 14-year-old girl presented with a complaint of solid breast mass. Further evaluation with ultrasonography and trucut biopsy, a diagnosis of 14x8 cm juvenile fibroadenoma was made. Laboratory examination revealed hypercalcemia (13.9 mg/dl) and high PTHrP (>24.8 ng/L) although the patient was asymptomatic. Despite pharmacological treatment, the patient continued to experience persistent hypercalcemia and subsequently underwent a successful surgical excision. Serum calcium and PTHrP levels normalized postoperatively. Hypercalcemia secondary to malignancy in children is rare and calcium elevation is usually mild-moderate and asymptomatic. In this case, PTHrP was elevated in breast fibroadenoma, demonstrating that hypercalcemia can also occur in benign tumors. The follow-up data of our patient after surgical treatment supports the notion that PTHrP-related hypercalcemia does not always indicate a poor prognosis. This case emphasizes the importance of considering benign tumors such as juvenile fibroadenoma as a potential cause of hypercalcemia in adolescents.
Keywords: Hypercalcemia, Juvenile Fibroadenoma, Parathyroid hormone-related protein

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Introduction

Hypercalcemia is defined as a serum calcium level of two standard deviations above the normal mean and the reference range varies according to age in childhood. Generally, a serum calcium level above 10.5 mg/dl is considered hypercalcemia and a level above 14 mg/dl is considered severe hypercalcemia (1,2).
Hypercalcemia is rare in childhood, is often mild and asymptomatic. Hypercalcemic disorders in children may include gastrointestinal system findings such as nausea, vomiting, abdominal pain, and constipation, renal system findings such as polyuria, polydipsia, and nephrolithiasis, nervous system findings such as hypotonia, lethargy, inability to feed, and muscle weakness, and cardiovascular system findings such as tachycardia, hypertension, and arrhythmia. In severe cases of hypercalcemia, complications such as bone fractures, renal failure, pancreatitis, and impaired consciousness may develop, and psychiatric manifestations may also be observed, particularly in older children (1,3). Hypercalcemia can be classified as PTH-dependent or PTH-independent. PTH-dependent hypercalcemias can be listed as familial hypocalciuric hypercalcemia, familial isolated hyperparathyroidism, neonatal severe primary hyperparathyroidism, multiple endocrine neoplasias, hyperparathyroid jaw-tumor syndrome, tertiary hyperparathyroidism due to chronic renal failure or treatment for hypophosphatemic rickets and gestational maternal hypocalcemia. PTH-independent hypercalcemias can be caused by hypervitaminosis D and A, malignancies that cause osteolysis or secrete PTHrP or 1,25(OH)2D, certain drugs (e.g., thiazides), milk-alkali syndrome, granulomatous diseases, endocrinopathies (e.g., thyrotoxicosis, congenital hypothyroidism, Addison's disease, pheochromocytoma), distal renal tubular acidosis, immobilization, and nutritional or phosphate depletion in preterm neonates (1-3).
In adults, more than 90% of hypercalcemia is due to primary hyperparathyroidism (PHPT) and malignancy (3), while PTH-related hypercalcemia probably accounts for less than 5% of hypercalcemia in children. Hypercalcemia is associated with malignancy in less than 1% of children and occurs due to osteolysis due to metastasis or leukemias or to tumor-produced hormones such as PTHrP (2). PTHrp is a peptide that mimics PTH functions and plays a role in both normal physiological processes and pathological conditions. PTHrP is the most common cause of hypercalcemia in patients with non-metastatic solid tumors and some non-Hodgkin lymphoma patients and is called humoral hypercalcemia. This protein increases both bone resorption and distal renal tubular calcium reabsorption via parathyroid hormone receptors, causing hypercalcemia (4-6)
The approach to treatment may vary depending on the underlying cause and severity of hypercalcemia. In mild cases, elimination of the cause may be sufficient. In moderate and severe cases, hydration, diuretics, antiresorptive therapy (such as bisphosphonate, calcitonin,

steroids, denosumab), calcimimetics and parathyroid surgery and dialysis are treatment options for treatment-resistant-severe hypercalcemia (2).

Breast fibroadenoma is the most common benign breast tumor in children and adolescents. It is seen in 70% to 95% of breast biopsies in this age group (7). Fibroadenoma is felt as a round, firm, smooth-surfaced, painless mass in the breast. It may change size due to hormonal changes in the menstrual cycle (8). Fibroadenomas that are larger than 5 cm in diameter, weigh more than 500 g, or occupy more than four-fifths of the breast are defined as giant. In addition, fibroadenomas of childhood or adolescence are defined as juvenile (9).

In this article, a case of giant juvenile fibroadenoma and associated hypercalcemia, a rare condition in adolescence, is presented, and the details of the diagnosis and treatment process are discussed with the aim of contributing to the literature.

Case Presentation

Initial presentation and clinical findings

A 14-year-old girl was admitted to an outpatient pediatric clinic with complaints of gradual swelling in the left breast for the past four months. The patient had no breast pain and no other local inflammation findings. There was no local trauma history, weight loss, additional clinical history, or any other feature in her past medical history. She was the first child of a non-consanguineous couple and there was no family history of breast cancer.

The patient's vital signs were stable, height was 157.2 cm [standard deviation score (SDS):-0.58], weight was 38 kg (SDS:-2.67) and body mass index (BMI) was 15.5 kg/m2 (SDS:-2.7, underweight). On physical examination, there was approximately 14x10 cm hard-soft immobile mass in the left breast and there was no accompanying axillary lymphadenopathy or additional physical examination finding (Figure 1). The patient, who was Tanner stage 5 of pubertal development, had an irregular menstrual cycle.

Laboratory work-up and ultrasonography on admission

On detailed examination; calcium: 13.9 mg/dl (8.5-10.5), ionized calcium: 1.4 mmol/L (1.0-1.3), phosphorus: 1.8 mg/dl (2.8-4.5), alkalen phosphatase (ALP): 147 U/L (57-254), magnesium: 1.5 mg/dl (1.7-2.2), albumin: 41 g/L (32-45), 25-hydroxy vitamin D [25(OH)D]: 3.3 mcg/L (20-100), PTH: 8 ng/L (15-65), 1,25-dihydroxy vitamin D [25(OH)D]: 8.1 mcg/L (15-60), Urinary Calcium/Creatinine: 0.43 (<0.2). The patient's PTHrP value was >24.8 ng/L (normal range: 0-13.9) (Table 1). All cell lines in the complete blood count were normal and the peripheral blood smear was normocellular. Tumor markers (alpha feto protein, carcinoembryonic antigen and beta human chorionic gonadotropin) were negative. By performing breast ultrasonography (USG) to the related(lesion, it was 14x8 cm in diameter, regular-circumscribed, heterogeneous and solid lesion with vascular signal which classified as BI-RADS category 4.

Emergent Management of the hypercalcemia

The patient was consulted to our pediatric endocrinology clinic due to hypercalcemia. The patient did not have symptoms associated with hypercalcemia. High volume (3000 ml/m^2/day) intravenous (IV) isotonic fluid hydration, oral neutral phosphorus solution (30 mg/kg/day) and vitamin D supplementation 1200 IU/day were started. Diuretic (furosemide, 1mg/kg/day) and methylprednisolone (1 mg/kg/day) were administered IV. The patient's control tests showed serum calcium: 9.3 mg/dl and phosphorus: 4.0 mg/dl.

Management of solid breast mass

Tumor Fluorodeoxyglucose Positron Emission Tomography (FDG PET) was performed and no metastatic focus or lymph node involvement was seen (Figure 2). The patient underwent a Tru-cut biopsy and the pathology report resulted as juvenile fibroadenoma. The patient was evaluated in a multidisciplinary council and a decision was made for segmental mastectomy (NSM) and intraoperative prosthesis.

Long-term follow-up of the case

The patient was admitted to the ward two weeks later for preoperative preparation; however, the operation was postponed due to hypercalcemia (calcium: 15.4 mg/dl). The patient was started high-volume IV isotonic fluid hydration and IV bisphosphonate (1 mg/kg/day, 2 days). On the fifth day of the patient's hospitalization, the serum calcium level was 9.6 mg/dl. The patient underwent NSM and intraoperative prosthesis. The pathology result was reported as giant juvenile fibroadenoma (16x14 cm)(Figure 3). No problems were experienced in postoperative wound healing (Figure 4). The patient's postoperative control serum calcium and phosphorus levels were within the normal range and the PTHrP level decreased to the normal range (7.4 ng/L. One year has passed surgery, and the patient's control calcium levels have always remained within the normal range.

Discussion

In this article, we present a case of PTHrP related hypercalcemia secondary to a breast fibroadenoma. To the best of our knowledge, this is the first reported case of PTHrP-related hypercalcemia due to a fibroadenoma in the adolescent population. Despite being resistant to medical treatment, the rapid normalization of serum calcium levels following surgical excision, along with the favorable prognosis, makes the case remarkable and instructive. Hypercalcemia may occur due to many reasons in children and adolescents, but malignancy-related hypercalcemia is very rare. Juvenile fibroadenomas are the most common breast masses in adolescent girls and are usually followed without treatment. Giant and symptomatic fibroadenomas can be removed surgically, but these masses have a risk of recurrence (8).

The aim of hypercalcemia treatment is to eliminate the underlying causes, increase urinary calcium excretion, prevent intestinal calcium absorption, prevent bone calcium resorption, and prevent complications secondary to hypercalcemia (2). In our patient, high volume IV isotonic fluid hydration, oral neutral phosphorus solution, diuretic, methylprednisolone and bisphosphonate treatments were applied in stages and temporary normocalcemia was achieved; However, definitive treatment is provided by eliminating the underlying cause, that is, removing the fibroadenoma.

Although short-term normocalcemia was achieved with pharmacological treatments for hypercalcemia in our patient, this was temporary and resistant hypercalcemia was observed. Fibroadenoma is a benign breast mass and its prognosis is very good and as a natural result of this, the pathologically high PTHrP level rapidly returned to the normal range after surgical excision of the fibroadenoma and the patient's serum calcium levels have always been within the normal range during follow-ups.

Increased PTHrP in benign tumors such as fibroadenoma is extremely rare and in the literature PTHrP has been associated more with malignancies or endocrine diseases. PTHrP, secreted by tumor tissue, induces bone resorption primarily through the activation of osteoclasts, a process modulated by humoral factors such as tumor necrosis factor (TNF) and transforming growth factor-alpha (TGF-α). It also enhances calcium reabsorption in the distal renal tubules, thereby contributing to elevated serum calcium concentrations. In addition, by decreasing phosphate excretion and stimulating 1α-hydroxylase activity, PTHrP further aggravates hypercalcemia (10,11). In this picture, also called humoral hypercalcemia, hyperkalemia, hypophosphatemia, increased urinary calcium excretion, normal/low PTH and high PTHrP are expected (12,13) and are consistent with the laboratory data of our case.

Humoral hypercalcemia constitutes 80% of patients with malignancy-related hypercalcemia and is usually an indicator of advanced disease and poor prognosis (14,15). However, PTHrP can also be elevated in benign tumors as in our case and PTHrP can rapidly normalize when the cause is eliminated and is not always an indicator of poor prognosis. Edwards et al. (16) in the study, PTHrP was quantified in the breast tissue of 132 breast cancer patients, four fibroadenoma patients and 27 healthy adults using immunoassay, and PTHrP was detected in 68% of the breast cancer patients, 33% of the healthy group and all of the breast fibroadenoma patients (100%). The highest tissue PTHrP median value was also seen in patients with breast fibroadenoma. It is thought that the high estrogen levels in young women may affect PTHrP expression. In the study, the high PTHrP levels in patients with breast fibroadenoma were explained by the higher cellularity of the tissue and the younger age of the patients. We consider that our case is valuable because it will be the first in the literature for the childhood period in terms of showing PTHrP elevation associated with breast giant fibroadenoma and secondary hypercalcemia. The study of Edwards et al. (16) and our case also show that we should be careful about hypercalcemia in patients with fibroadenoma.

Adolescent girls may refrain from seeking medical attention for breast masses until they become apparent, often due to embarrassment or limited awareness. . Therefore, in cases where the etiology of hypercalcemia is unclear, the clinical history should be detailed and a full systemic examination should be performed. In conclusion, determining the etiology of hypercalcemia and eliminating the underlying cause are the main principles of successful treatment. This case shows us that fibroadenoma should also be considered in cases of undetermined hypercalcemia, especially in adolescent girls.

Ethics

Written informed consent was obtained from the parents of the patient for the publication of this case report

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Figure 1. Giant juvenile fibroadenoma of left breast

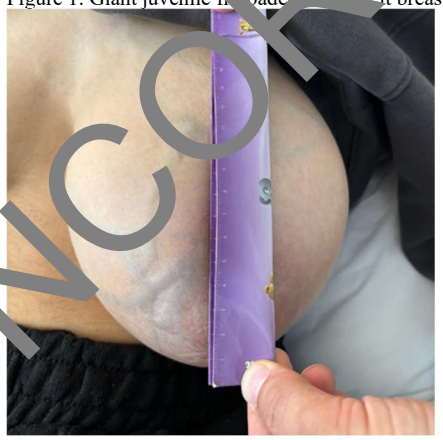

Figure 2. Tumor imaging with FDG uptake PET

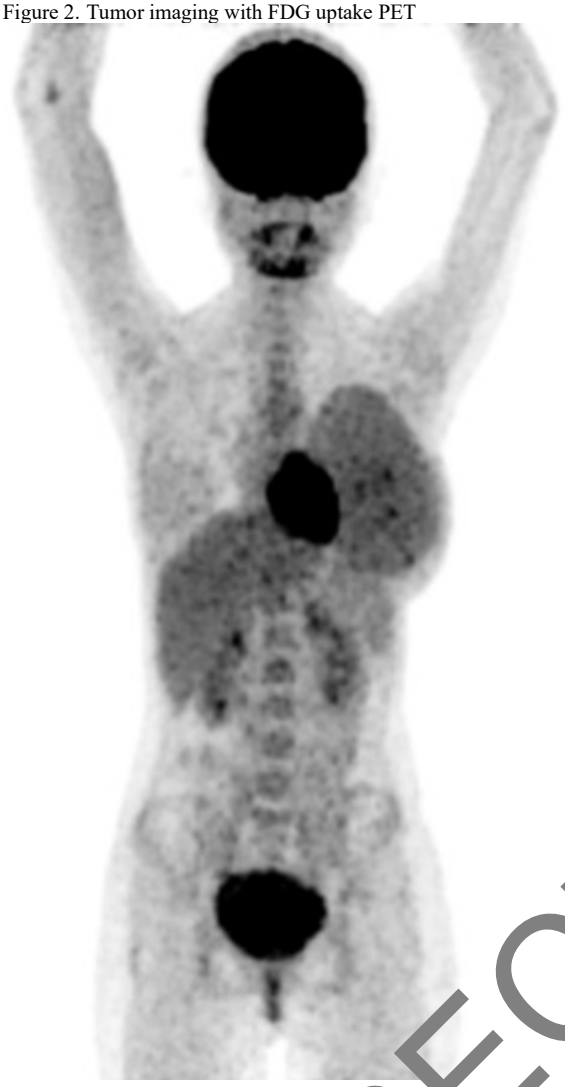

Figure 3. Histopathological image of the breast fibroadenoma specimen from the patient

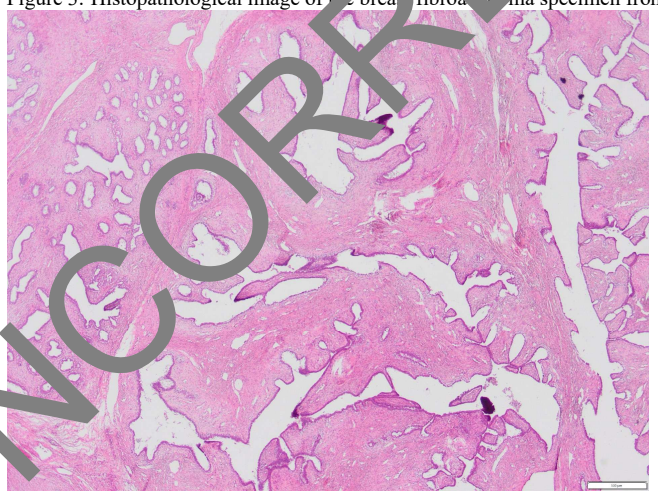

Figure 4. Postoperative left breast image

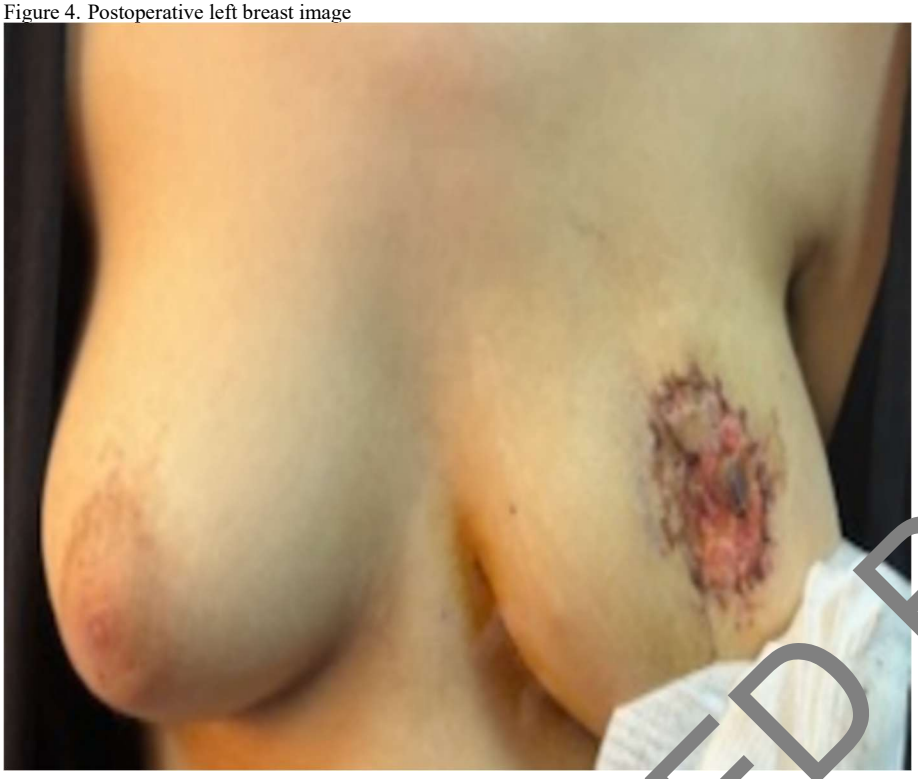

Table 1. Laboratory Findings at Initial Presentation and After Surgery

Laboratory findings	İnitial findings	Postoperative findings	Normal range
Calcium	13.9	9.4	8.5-10.5 mg/dl
İonized calcium	1.4	0.9	1.0-1.3 mmol/L
Phosphorus	1.8	4.5	2.8-4.8 mg/dl
Magnesium	1.5	1.9	1.7-2.2 mg/dl
Albumin	41	38	32-45 g/L
Alkaline phosphatase (ALP)	147	100	57-254 U/L
25-hydroxy vitamin D [25(OH)D]	3.3	18.8	20-100 mcg/L
1,25-dihydroxy vitamin D [1,25(OH)D]	8.1	13.4	15-60 mcg/L
Parathyroid hormone (PTH)	8 ng	43	15-65 ng/L
Parathyroid hormone related protein (PTHrP)	>24.8	7.4	0-13.9 ng/L
Urinary Calcium/Creatinin	0.43	0.1	<0.2