Chapter 16
Primary Hyperparathyroidism: Association with Coexistent Secondary Causes of Hypercalcemia

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Case Presentation

A 30-year-old female was referred for evaluation and management of hypercalcemia, first discovered during a routine clinical evaluation by her primary care physician. She was not taking any medications, but took vitamin D3 1000 international units once daily as a supplement. She did not take calcium supplementation. Her serum calcium was within the normal range 2 years ago. Her only symptom was fatigue. Her family history was unremarkable for hypercalcemia.

Her laboratory studies showed:

- Calcium 11.8 mg/dL (normal, 8.9–10.1 mg/dL)
- Phosphorus 3.0 mg/dL (normal, 2.5–4.5 mg/dL)
- Creatinine 0.8 mg/dL (normal, 0.6–1.1)

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- Parathyroid hormone (PTH) 60 pg/mL (normal, 15–65 pg/mL)
- Albumin 4.0 g/dL (normal, 3.5–5.0)
- 25-hydroxyvitamin D 18 ng/mL (optimal, 25–50)
- 24-h urine calcium 317 mg/dL (normal, 20–275)

X-rays of her kidneys, ureters, and bladder showed nephrocalcinosis.

Her parathyroid sestamibi scan showed discordant uptake localizing to her right inferior parathyroid gland, without uptake elsewhere in her neck or chest.

Her age less than 50 years, serum calcium level greater than 11.0 mg/dL, evidence of kidney stones, and positive sestamibi scan were felt to represent indications for parathyroid surgery. She underwent elective right inferior parathyroidectomy. After removal of her right inferior parathyroid adenoma, her PTH value decreased by more than 50 % within 15 min of resection of her adenoma. During the first several days after surgery, her PTH unexpectedly continued to decrease to a nadir of 12 pg/mL, while her phosphorus level increased to 4.4 mg/dL, and her calcium level remained persistently increased at 10.7 mg/dL. Her pathology review confirmed that a right inferior parathyroid adenoma weighing 320 mg had been removed.

Her serum 1,25-dihydroxyvitamin D level was found to be increased after surgery. Her chest x ray was normal except for a few hilar lymph nodes. She felt better after surgery in spite of her persistently increased serum calcium level.

Assessment and Diagnosis

Persistent serum calcium elevation after successful parathyroidectomy, with a decreased PTH level, should raise the suspicion that a second cause of hypercalcemia is present. In this patient, her serum 1,25-dihydroxyvitamin D was increased despite the fact that her PTH level was decreased. Patients with primary

hyperparathyroidism (PHPT) may have vitamin D deficiency, with decreased levels of serum 25-hydroxyvitamin D, and as a consequence, compensatory increase in serum 1,25-dihydroxyvitamin D due to PTH stimulation of renal 1-alpha-hydroxylase production of this form of vitamin D. Surgical cure of PHPT should result in a normal serum 1,25-dihydroxyvitamin D because PTH levels are normal.

The differential diagnosis of hypercalcemia is determined by the patient context. Outpatient hypercalcemia is most commonly caused by PHPT, whereas inpatient hypercalcemia is most commonly caused by malignancy. During hospitalization, supplementation with calcium, diets containing calcium, medications such as thiazide-type diuretics or lithium, immobilization, or dehydration can increase serum calcium levels.

Sporadic parathyroid adenomas causing PHPT are not usually diagnosed at her young age. The incidence of PHPT increases with age, with an increased incidence in women occurring between the ages of 50 and 60 years [1]. PHPT at her age may be due to familial genetic causes, which are more commonly associated with multi-gland hyperplasia.

The fact that she is less than 50 years old should raise the possibility of familial forms of PHPT, which are more common in younger patients, especially those less than 30 years of age. Familial forms of PHPT could also explain the persistence of hypercalcemia, since these forms may be associated with multigland parathyroid hyperplasia that may be missed at initial surgery. The fact that she had no family history of hyperparathyroidism, and had no other apparent endocrine disease, and that her PTH decreased significantly after surgery all argue against multigland disease. These findings suggest that her persistent hypercalcemia was not mediated by PTH after surgery and therefore less likely to be caused by a genetic mutation such as occurs in multiple endocrine neoplasia (MEN) type 1 or 2A, familial-isolated hyperparathyroidism, or hyperparathyroidism-jaw tumor syndromes. Nevertheless, genetic causes of hyperparathyroidism

should always be considered in younger patients.

In the differential diagnosis of PHPT, familial hypocalciuric hypercalcemia (FHH) [2] is also a consideration. FHH is a rare autosomal dominant disease caused by inactivating mutations in the calcium-sensing receptor gene (*CASR*), leading to reduced parathyroid and renal tubular cell sensitivity to extracellular calcium, compensatory hyperparathyroidism, hypercalcemia, and hypocalciuria. Given that the patient's urine calcium was increased before surgery and that she had normal serum calcium documented several years earlier, it is highly unlikely that she has FHH, since this is a life-long benign condition that leads to hypercalcemia without complications, unlike what was described in the case presented.

Another possibility is that she could have hypercalcemia of malignancy, although the patient had no clinical evidence of cancer. The major causes of hypercalcemia due to malignancy [3] are humoral hypercalcemia of malignancy (HHM) in 80 % and osteolytic lesions due to metastatic bone disease in 20 %. Humoral hypercalcemia of malignancy involves secretion of an endocrine factor, most commonly parathyroid hormone-related peptide (PTHrP) overproduction by cancer cells. 1,25-dihydroxyvitamin D overproduction occurs in <1 %, while overproduction of PTH by cancer cells has only been described in case reports [4–11].

The most common cause of PTHrP-mediated hypercalcemia is solid organ malignancy, as confirmed by a recently published large case series. The diagnosis of PTHrP-mediated hypercalcemia portended a poor prognosis in this study, with the median survival less than 2 months [12].

PTHrP was initially purified from human cancer cells in 1987 [13, 14]. The PTHrP gene encodes a 141-amino acid protein that shares 60–70 % sequence homology with PTH over the first 13 amino acids at the N-terminus [15]. Both PTH and PTHrP bind to a common PTH/PTHrP1 receptor (PTH/PTHrP1R) despite having structural differences [16, 17]. Hypercalcemia ensues only when PTHrP reaches a

threshold concentration that surpasses the analogous actions of PTH [3]. PTHrP has equivalent actions to PTH in regulating bone resorption and renal calcium/phosphorus handling, via activation of osteoclastic bone resorption through increased osteoblast RANKL expression and via increased renal tubular calcium reabsorption and inhibition of phosphate reabsorption. However, PTHrP does not stimulate renal 1α-hydroxylase activity as much as PTH or increase serum 1,25-dihydroxyvitmain D levels as much [3, 18]. The discordant effects of PTH and PTHrP on 1,25-dihydroxyvitamin D production were confirmed in human-controlled clinical trials evaluating the effects of PTH (1-34) and PTHrP (1-36) infusions in healthy adults [19].

The clinical case described demonstrated increased levels of serum 1,25-dihydroxyvitamin D after surgery, which would not be expected in HHM caused by PTHrP, making HHM very unlikely. Asymptomatic skeletal metastasis would also be unusual in this setting. The rare hypercalcemia of malignancy caused by overproduction of 1,25-dihydroxyvitamin D occurs in less than 1 % of cases [3, 20] and is usually associated with hematologic malignancies such as Hodgkin or non-Hodgkin lymphoma, since immune cells of the lymphocyte and macrophage lineage normally produce a small amount of 1,25-dihydroxyvitamin D that acts as a local cytokine [21, 22].

In a patient with known malignancy who has increased or inappropriately normal PTH levels, it should be assumed that the patient has coexisting PHPT. Ectopic overproduction of PTH by tumor cells is highly unlikely, and patients with HHM caused by PTHrP overproduction have high calcium with low phosphorus levels as seen in PHPT, with PTH typically physiologically suppressed due to increased serum calcium.

In a prospective study [23] of consecutive patients with a first episode of hypercalcemia during an 18-month period, plasma PTHrP levels were increased in 82 % of patients with hypercalcemia due to malignancy. Hypercalcemia was attribut-

able to parathyroid disease in 10 % of patients with malignancy. Median survival for patients with PHPT and coexisting malignancy was 13 months, compared to 3 months for those with hypercalcemia due to malignancy alone.

It should not be assumed that every patient with cancer and hypercalcemia must have a malignant etiology of their hypercalcemia. On the contrary, in a large series of cancer patients [24], nonmalignant causes of hypercalcemia in cancer patients were a frequent and neglected finding. Hypercalcemia was not due to cancer in 97 % (84/87) of the patients who were in complete remission from their cancer. Even in patients with active neoplastic disease, the number of patients whose hypercalcemia was not due to cancer was clinically relevant (115/555 = 20.5 %). In the 158 patients with PHPT, 92 patients were in complete remission, and 66 patients had active neoplastic disease. PHPT was the leading cause of non-cancer-related etiologies.

The most likely etiology of persistent hypercalcemia in the clinical case is granulomatous disease (Table 16.1), causing overproduction of 1,25-dihydroxyvitamin D by extra-renal 1α-hyroxylase activity. Of the various granulomatous diseases that can cause hypercalcemia, sarcoidosis, fungal disease, and tuberculosis are the most common in the USA. Therefore the next best step is to measure the angiotensin-converting enzyme (ACE) level and appropriate fungal serologies and to perform purified protein derivative (PPD) skin testing or Quantiferon measurement.

The patient was found to have a mildly increased ACE level of 60.9 units/L (normal, 8–53), negative fungal serologies, and negative PPD skin test. These findings were interpreted as suggesting the patient had coexisting sarcoidosis with her PHPT. ACE levels, although nonspecific, are useful in conjunction with other diagnostic procedures such as bronchoscopic needle biopsy, or biopsy of other accessible tissue such as bone marrow, with pathology showing noncaseating granulomas. The patient underwent bronchoscopic needle biopsy of one

Table 16.1 Causes of hypercalcemia

Differential diagnosis					
PTH excess	Malignancy	Non-PTH endocrine causes	Granulomatous disease	Medications	Miscellaneous
PHPT Parathyroid adenoma Parathyroid carcinoma Multiglandular hyperplasia as part of MEN syndromes (MEN1 and 2A) FIH HPT-JT	HHM PTHrP (80 %) $1,25\text{-}(OH)_2D$ (<1 %) PTH (<1 %) Bone mets/ local osteolysis (20 %): cytokines, local PTHrP	Thyrotoxicosis Adrenal insufficiency Pheochromocytoma VIPoma Acromegaly	Sarcoidosis Tuberculosis Coccidioidomycosis Histoplasmosis Blastomycosis Berylliosis Leprosy Crohn's disease	Lithium Thiazides Vitamin D intoxication Excessive vitamin A Teriparatide Theophylline toxicity Milk-alkali syndrome	Immobilization Parenteral nutrition
FHH (UCCR <0.01)					
Tertiary HPT (renal failure)					

PHPT primary hyperparathyroidism, *MEN* multiple endocrine neoplasia, *FIH* familial-isolated hyperparathyroidism, *HPT-JT* hyperparathyroidism-jaw tumor syndrome, *FHH* familial hypocalciuric hypercalcemia, *UCCR* urinary calcium-creatinine clearance ratio, *HHM* humoral hypercalcemia of malignancy, *Mets* metastasis

of her mediastinal lymph nodes, with her pathology report noting noncaseating granulomas, consistent with sarcoidosis.

A large health maintenance organization-based study estimated the annual incidence of sarcoidosis in Caucasians at 9.6 per 100,000 person-years and in African Americans at 35.5 per 100,000 person-years [25]. A Rochester Epidemiology Project population-based study in Rochester, Minnesota, estimated the annual incidence of sarcoidosis at 6.1 per 100,000 person-years [26]. Another Rochester Epidemiology Project population-based study indicated that the annual incidence of PHPT ranged between 15.8 and 129 per 100,000 person-years over 30 years, depending on the year incidence was assessed [1].

Patients may be suspected of having two coexisting causes of hypercalcemia, with PHPT often being the easier of the two to recognize. The first cases of coexisting PHPT and sarcoidosis were reported in 1958 [27]. Since then there have been mostly case reports or small case series of these coexisting disorders [28–30]. Evaluation of a recent large cohort of 50 patients with coexisting PHPT and sarcoidosis reported from the Mayo Clinic in Rochester, Minnesota [31], showed that patients with PHPT who had active sarcoidosis had higher serum ACE levels (60.9 ± 38.1 vs. 20.2 ± 14.0 units/L, *P*-value <0.0001), lower PTH levels (60 ± 24 vs. 96 ± 41 pg/mL, *P*-value 0.01), and lower phosphorus levels (2.7 ± 0.6 vs. 3.2 ± 0.5 mg/dL, *P*-value 0.02) than patients with PHPT alone. Reports of coexisting PHPT and secondary causes of hypercalcemia other than malignancy are less common.

Management

Recognition of the additional diagnosis of coexisting sarcoidosis, which was made evident after parathyroidectomy, led to treatment of the patient with prednisone 20 mg each day for 1 month, with rapid normalization of her serum calcium and a trend toward normalization of her serum phosphorus during her first

week of treatment. Her prednisone was gradually tapered over the next 4 months, with persistently normal serum calcium.

Outcome

The patient was followed every 6 months for the next 5 years without recurrence of either her PHPT or sarcoidosis. Other patients may develop recurrence of either or both disorders in time.

Clinical Pearls/Pitfalls

- Age, gender, and magnitude of hypercalcemia should be considered, as well as variation in serum PTH, calcium, phosphorus, and 1,25-dihydroxyvitamin D levels and patient context, when assessing possible etiologies of hypercalcemia.
- When coexisting causes of hypercalcemia are suspected or known to be present, classical findings of PHPT should not be expected.
- When faced with the possibility of coexisting causes of hypercalcemia, the clinical approach should be tailored to the patient after analyzing all available laboratory and imaging data.
- Patients presenting with hypercalcemia may have several causes contributing to their hypercalcemia. Dehydration, renal insufficiency, or vitamin D or A excess, in addition to increased PTH or granulomatous overproduction of 1,25-dihydroxyvitamin D, may all contribute to hypercalcemia in the same patient. The challenge for the clinician is to tease out the major cause or causes of hypercalcemia.
- Consideration of the complete differential diagnosis of hypercalcemia in each case is important since different causes of increased serum calcium levels are treated in distinctive ways.

Conflict of Interest All authors state that they have no conflicts of interest.

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