Chapter 20
Tertiary Hyperparathyroidism

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Case Presentation

A 47-year-old female initially presented at age 13 with intermittent paresthesias and tetany associated with hypocalcemia (5.5 mg/dL, normal, 9.5–10.4), hyperphosphatemia (8.4 mg/dL, normal, 4.0–5.2), increased parathyroid hormone (PTH) (8.5 pmol/L, normal, 1.0–5.2), and mild osteitis fibrosa on bone biopsy. She had no features of Albright's hereditary osteodystrophy or family history of hypocalcemia. She was treated with calcium and vitamin D supplementation and her symptoms resolved. Repeat bone biopsy showed healed osteitis fibrosa. Subsequently, her urine cyclic AMP (cAMP) was found unresponsive to exogenous PTH, and she was diagnosed with pseudohypoparathyroidism (PHP) type Ib. During the ensuing years, she reported intermittent paresthesias associated with mild

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hypocalcemia on supplemental elemental calcium of 1800 mg, 1,25-dihydroxyvitamin D (calcitriol) 0.25 mcg, and hydrochlorothiazide 25 mg each day.

In the year prior to her current presentation, her serum PTH concentrations increased dramatically above her baseline level, and her serum calcium became mildly elevated despite lack of changes in her medications and diet or due to other medical conditions. At her initial evaluation, she was asymptomatic and had in fact not experienced paresthesias for quite some time. Her overall health was excellent, with no history of fractures or kidney stones. Other than relatively short stature (155 cm), her physical examination was unremarkable, including a normal thyroid examination. Her initial laboratory assessment included serum calcium 10.2 mg/dL (normal, 8.9–10.1), phosphorus 3.2 mg/dL (normal, 2.5–4.5), creatinine 0.9 g/dL (normal, 0.6–0.9), and PTH 21 pmol/L (normal, 1.0–5.2).

Assessment and Diagnosis

The primary function of the parathyroid glands is to secrete PTH in response to a fall in the blood ionized calcium (iCa) concentration as "measured" by the calcium-sensing receptor (CaSR) on the plasma membrane [1, 2]. Short-term and modest decreases in iCa result in the release of stored PTH from secretory vesicles, decreased intracellular degradation of PTH stores, and increased PTH mRNA expression and lifespan. This physiologic or secondary hyperparathyroidism (SHP) may normalize iCa by increasing renal reabsorption of iCa, by increasing intestinal absorption of iCa by increasing renal production of 1,25 dihydroxyvitamin D, and by increasing osteoclastic activity and mobilization of calcium from the skeleton. However, should dietary calcium intake or absorption be limited, 25 hydroxyvitamin D be deficient, and bone mineral be depleted, overt and

chronically low iCa may occur, stimulating an increase in the number of PTH-secreting parathyroid cells (i.e., hyperplasia) and the potential for even higher serum PTH concentrations [3].

Parathyroid gland function and growth is also regulated by plasma phosphate and 1,25 dihydroxyvitamin D concentrations. In chronic kidney disease (CKD), increased binding of plasma phosphate to ionized calcium in the setting of hyperphosphatemia and reduced intestinal calcium absorption due to inadequate production of 1,25 dihydroxyvitamin D can both contribute to a decline in iCa. Increases in FGF-23 that suppress 1,25-dihydroxyvitamin D production and decrease vitamin D receptors in parathyroid tissue in advanced CKD both reduce suppression of PTH secretion [4]. Simultaneously, increasing serum phosphate concentrations have a direct effect on parathyroid glands resulting in increased PTH synthesis and by promoting the stability of PTH mRNA [5]. Ultimately, any disorder that persistently disturbs multiple targets of or modifiers of PTH action leading to hypocalcemia and/or hyperphosphatemia can greatly stimulate parathyroid gland function and growth through multiple clinically modifiable mechanisms.

Although most commonly associated with CKD, malabsorption, and vitamin D deficiency, SHP also occurs due to failure of target tissues to respond to the actions of PTH. PTH resistance occurs in the proximal renal tubule as evidenced by lack of phosphaturic response and increased cAMP excretion with exogenous PTH administration as was seen in the case above [6]. In other target tissues, PTH action remains intact including in the thick ascending tubule which likely explains relative hypocalciuria compared to patients with hypoparathyroidism [7]. That PTH action remains in bone [8] has been demonstrated clinically [9, 10] and histologically in the case above at first presentation with osteitis fibrosa. Similar to other causes of SHP, treatment of PHP includes calcium supplementation, phosphate restriction, and calcitriol treatment intended to normalize serum calcium and phosphorus which in turn will reduce multiple stimuli of PTH production and parathyroid gland growth.

Tertiary hyperparathyroidism (THP) is characterized by excessive secretion of PTH after long-standing SHP, and which may now include hypercalcemia [11]. THP can be the end result of long-standing SHP in which the parathyroid glands now exhibit autonomous function even after correction of underlying disease (e.g., post renal transplantation) [12]. The cellular etiology of THP is unknown but is postulated to be a result of a monoclonal expansion of parathyroid cells [13]. It is believed that these cells have an altered set point of their calcium-sensing receptor (CaSR) so that PTH is secreted despite elevated iCa concentrations [14].

Patients with long-standing chronic stimulation of their parathyroid glands often develop autonomy, such that they do not respond to calcium and calcitriol supplementation or phosphate restriction in their diet. In this situation, little can be done to stop overproduction of PTH short of parathyroidectomy, although certain interventions may be successful in temporarily reducing excess secretion of parathyroid hormone. Phosphate binders such as calcium acetate, sevelamer, or lanthanum are usually used to control hyperphosphatemia in patients where dietary restriction of phosphorus to 800–1000 mg each day is not sufficient. Lowering serum phosphorus may help lower FGF-23 and PTH secretion also as described above.

Certain synthetic active vitamin D analogues such as paricalcitol, doxercalciferol, and others have been shown to reduce PTH secretion by moderate amounts without simultaneously stimulating absorption of calcium and phosphate by the intestine. These have a modulating effect on the amount of PTH release by autonomous glands by direct transcriptional inhibition of PTH synthesis in the parathyroid glands and tend to reduce circulating PTH concentrations [15, 16]. Higher doses of these agents may lead to an increase in serum calcium or phosphate by stimulating intestinal absorption and tend to increase FGF-23 levels.

Cinacalcet is a calcimimetic compound that effectively lowers PTH secretion by autonomous or semiautonomous parathyroid glands. This allosteric sensitizer of the calcium-sensing receptor

causes parathyroid chief cells to sense higher levels of extracellular calcium than are actually present, leading to decreased production of PTH, which leads to decreased serum calcium [17–19]. Cinacalcet is typically started at 30 mg once daily, with follow-up serum calcium measurement within 1 week. The most common side effect is nausea with vomiting, but taking cinacalcet with meals minimizes these side effects. Hypocalcemia may also occur, and cinacalcet should not be given if serum calcium is less than 8.4 mg/dL. Cinacalcet may be titrated upward to a maximum of 90 mg four times daily in the setting of parathyroid cancer, but is titrated to a maximum of 60 mg three times daily for THP. Patients with THP are usually at least moderately responsive to cinacalcet.

Hemodialysis or peritoneal dialysis will help control calcium and phosphorus abnormalities in end-stage chronic kidney disease, but usually do not help reduce PTH secretion in most patients. Renal transplantation corrects many abnormalities as long as the transplanted kidney continues to function well, and usually helps improve PTH secretion overall, but not in all cases.

For patients who have persistent THP despite optimal medical management, or after beginning dialysis treatment, or undergoing renal transplantation, surgery is usually recommended as a last resort. Because patients with THP typically have all four parathyroid glands oversecreting PTH, surgery usually removes three and one-half glands or all four glands with autotransplantation of a part of one gland into the neck, chest, or forearm muscle. Surgery to remove three and one-half glands leaves the remaining half-gland in place with intact blood supply. Autotransplantation of one-half gland usually leads to revascularization of the parathyroid tissue from surrounding muscle blood supply. In both cases, success of control of PTH oversecretion is high, and risk of hypoparathyroidism is low. In some cases four-gland hyperplasia is associated with four mildly to moderately enlarged glands of the about same size, but in other cases, asymmetry is noted, with some glands larger than the others. In

patients who develop recurrent THP later due to continued autonomy of the half-gland left in situ or autotransplanted, medical therapy may be tried again, and if this fails, surgery may be recommended again. Repeat surgery for THP is associated with a higher risk of hypoparathyroidism [20].

In the case presented, it is presumed that suboptimal calcium or calcitriol replacement led to chronic mild hypocalcemia, which led to chronic stimulation of her parathyroid glands. At some point one or more of her parathyroid glands became autonomously secreting, and she developed THP with hypercalcemia. Cessation of her paresthesias was a harbinger of development of THP.

Management

Bone mineral density for the case discussed was above average for age and gender (*T*-score = 1.2, *Z*-score = 3.1). Parathyroid sestamibi scan and neck ultrasound each suggested two enlarged inferior parathyroid glands. At surgery, both the right and left inferior parathyroid glands were visibly enlarged, whereas the superior glands were of normal size and appearance. Baseline intraoperative PTH was 43.7 pmol/L. After the right inferior 720-mg gland was removed, PTH decreased to 31 pmol/L. After the left inferior 130-mg gland was removed, PTH decreased further to 6.9 pmol/L (Fig. 20.1). Histopathology indicated parathyroid hyperplasia in both glands. Tissue tumor markers Ki-67 and p27 were normal, thus not suggestive of malignant transformation. Postoperative serum calcium decreased to 8.6 mg/dL, with a PTH nadir of 3.3 pmol/L. Remaining asymptomatic, she began oral calcium supplementation of 2400 mg and 1,25-dihydroxyvitamin D 0.50 mcg daily. By postoperative day three serum calcium was normal at 9.2 mg/dL. Two weeks later, serum calcium remained normal and PTH had increased to

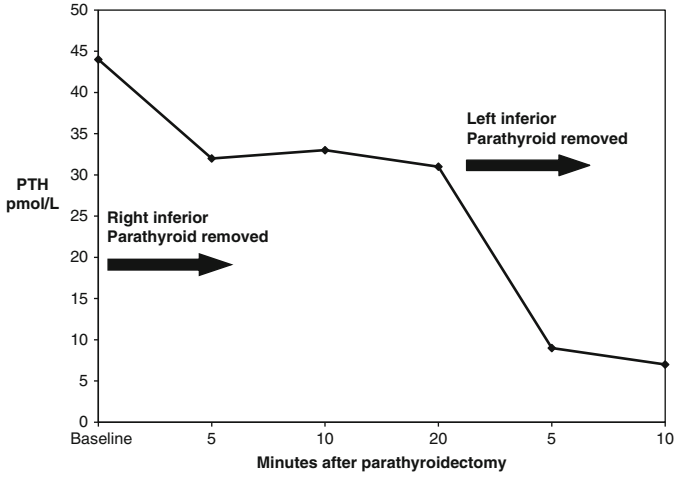

Fig. 20.1 Intraoperative parathyroid hormone levels after sequential resection of hyperplastic right inferior and left inferior parathyroid glands to treat tertiary hyperparathyroidism in a patient with pseudohypoparathyroidism type Ib

16.3 pmol/L (1.3–7.6), indicating return of function of remaining parathyroid tissue and suggesting mild residual hyperparathyroidism in her remaining glands.

Outcome

At 10-year follow-up, she felt well. Her serum calcium remained in the normal range with consistent use of 1000 mg elemental calcium daily, 1,25-dihydroxyvitamin D 0.25 mcg daily, and hydrochlorothiazide 25 mg every other day over 10 years of follow-up. PTH remained elevated but stable at 7.8 pmol/L. BMD remained normal and above average for age.

Clinical Pearls/Pitfalls

- Chronic stimulation by mild ionized hypocalcemia due to chronic PTH resistance and related disorders may result in parathyroid gland hyperplasia and even greater extent of PTH elevation sufficient to cause mild hypercalcemia.
- Tissue-specific decreases in Gsα expression in the proximal renal tubules with preserved expression in bone and other tissues may be clinically evident in disorders such as pseudohypoparathyroidism type Ib and may influence determination of optimal PTH concentrations in such patients.
- In patients with underlying conditions for whom elevated serum concentrations of PTH may be necessary to optimize physiologic functions related to calcium and phosphorus, need for and extent of parathyroidectomy should be carefully discussed with an endocrine surgeon.

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

References

1. Brown EM, Gamba G, Riccardi D, Lombardi M, Butters R, Kifor O, et al. Cloning and characterization of an extracellular Ca2+-sensing receptor from bovine parathyroid. Nature. 1993;366(6455):575–80.
2. Grant F, Conlin P, Brown E. Rate and concentration dependence of parathyroid hormone dynamics during stepwise changes in serum ionized calcium in normal humans. J Clin Endocrinol Metab. 1990; 71:370–8.
3. Jüppner H, Gardella T, Brown E. Parathyroid hormone and parathyroid hormone-related peptide in the regulation of calcium homeostasis and bone development. In: DeGroot L, Jameson J, editors. Endocrinology: adult and pediatric. 7th ed. Philadelphia: Elsevier; 2015.

4. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. Kidney Int. 2007;74:276–88.
5. Moallem E, Kilav R, Silver J, Naveh-Many T. RNA-protein binding and post-transcriptional regulation of parathyroid hormone gene expression by calcium and phosphate. J Biol Chem. 1998;273:5253–9.
6. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. Ann Intern Med. 1988;109:800–4.
7. Stone MD, Hosking DJ, Garcia-Himmelstine C, White DA, Rosenblum D, Worth HG. The renal response to exogenous parathyroid hormone in treated pseudohypoparathyroidism. Bone. 1993;14:727–35.
8. Ish-Shalom S, Rao LG, Levine MA, Fraser D, Kooh SW, Josse RG, et al. Normal parathyroid hormone responsiveness of bone-derived cells from a patient with pseudohypoparathyroidism. J Bone Miner Res. 1996;11:8–14.
9. Zvi F. Pseudohypohyperparathyroidism-pseudohypoparathyroidism type Ib. J Bone Miner Res. 1999;14:1016.
10. Tollin SR, Perlmutter S, Aloia JF. Serial changes in bone mineral density and bone turnover after correction of secondary hyperparathyroidism in a patient with pseudohypoparathyroidism type Ib. J Bone Miner Res. 2000;15:1412–6.
11. Park-Sigal J, Don BR, Porzig A, Recker R, Griswold V, Sebastian A, et al. Severe hypercalcemic hyperparathyroidism developing in a patient with hyperaldosteronism and renal resistance to parathyroid hormone. J Bone Miner Res. 2013;28:700–8.
12. Bleskestad IH, Bergrem H, Leivestad T, Gøransson LG. Intact parathyroid hormone levels in renal transplant patients with normal transplant function. Clin Transplant. 2011;25:E566–70.
13. Krause MW, Hedinger CE. Pathologic study of parathyroid glands in tertiary hyperparathyroidism. Hum Pathol. 1985;16:772–84.
14. Grzela T, Chudzinski W, Lasiecka Z, Niderla J, Wilczynski G, Gornicka B, et al. The calcium-sensing receptor and vitamin D receptor expression in tertiary hyperparathyroidism. Int J Mol Med. 2006;17:779–83.
15. Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder GJ, Strippoli GFM. Meta-analysis: vitamin D compounds in chronic kidney disease. Ann Intern Med. 2007;147:840–53.
16. Zisman AL, Ghantous W, Schinleber P, Roberts L, Sprague SM. Inhibition of parathyroid hormone: a dose equivalency study of paricalcitol and doxercalciferol. Am J Nephrol. 2005;25:591–5.
17. Indridason OS, Quarles LD. Comparison of treatments for mild secondary hyperparathyroidism in hemodialysis patients. Kidney Int. 2000;57:282–92.

18. Lindberg JS, Moe SM, Goodman WG, Coburn JW, Sprague SM, Liu W, et al. The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism. Kidney Int. 2003;63:248–54.
19. Koizumi M, Komaba H, Nakanishi S, Fujimori A, Fukagawa M. Cinacalcet treatment and serum FGF23 levels in haemodialysis patients with secondary hyperparathyroidism. Nephrol Dial Transplant. 2012;27:784–90.
20. Pitt SC, Sippel RS, Chen H. Secondary and tertiary hyperparathyroidism, state of the art surgical management. Surg Clin North Am. 2009;89:1227–39.