Surgically Proven Normocalcemic Primary Hyperparathyroidism: Speculation of the Possible Role of Estrogen in the Etiology of this Disease in Premenopausal Women

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Abstract

We herein report a rare case of surgically proven normocalcemic primary hyperparathyroidism (NCHPT). A premenopausal 51-year-old woman was referred to our clinic because parathyroid adenoma was detected on neck ultrasonography (US). The patient’s serum calcium concentration was 9.3 mg/dL and the intact parathyroid hormone (PTH) level was 128.8 pg/mL. The findings of almost all other examinations were also compatible with a diagnosis of NCHPT. Then, parathyroidectomy was performed. The serum calcium and PTH concentrations reduced significantly but remained within the normal ranges. A histological examination demonstrated parathyroid adenoma. A review of this case and the associated literature suggests that estrogen plays a significant role in the etiology of NCHPT in premenopausal women.

Key words: normocalcemic primary hyperparathyroidism, premenopausal women, estrogen, parathyroidectomy, parathyroid adenoma

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Introduction

In general, primary hyperparathyroidism (pHPT) patients present elevated parathyroid hormone (PTH) with hypercalcemia and hypercalciuria, as well as some clinical features such as osteoporosis and urolithiasis. Most pHPT patients are women, with the majority being in their postmenopausal years (1, 2). normocalcemic primary hyperparathyroidism (NCHPT) was first described in the 1960s. In the decades since, NCHPT has been diagnosed by elevated PTH and ionized calcium levels and a persistently normal total serum calcium concentration (3, 4). Recently, NCHPT has been recognized as pHPT with elevated PTH without elevated ionized or total serum calcium concentration (5, 6). In addition, when NCHPT is diagnosed, it is also necessary to rule out vitamin D deficiency and urinary calcium leak. NCHPT is considered as a rare entity, and the management of NCHPT still remains to be established (7). However, a possible relationship between estrogen deficiency and the unmasking of hypercalcemia has been postulated (8). We report a case of NCHPT in which premenopausal state might have contributed to maintain normocalcemia and discuss the pathological etiology of this disease entity.

Case Report

A 51-year-old woman was referred to our clinic because parathyroid adenoma had been detected on neck ultrasonography (US). Despite the suggestion of parathyroid adenoma and a high titer of intact PTH, the patient’s serum calcium concentration was normal. Therefore, she was suspected of having NCHPT. From the measurements obtained at the first visit, the patient was 155.3 cm tall and weighed 63.5 kg with a body mass index of 26.3. Her blood pressure was 130/98 mmHg and her pulse rate was 80 beats/min and regular. Her palpebral conjunctivae were not anemic, and her bulbar conjunctivae were not icteric. Her thyroid gland

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was not palpable. Her heart and breath sounds were clear. Her abdomen was flat and soft, and her liver and spleen were not palpable. There was no pretilial edema. The patient had a history of hypertension without medication use, and her family history showed paternal hypertension. There was no family history of pHPT. She had no history of smoking and was not a drinker.

The laboratory data obtained in our clinic are shown in Table. The serum calcium concentration corrected by serum albumin was 9.3 mg/dL, the ionized calcium concentration (eCa\(^{2+}\)) was 1.20 mmol/L, and the whole PTH level was 59.7 pg/mL. A urinary examination did not indicate any urinary calcium leaks, and the concentrations of 1\(\alpha\), 25-dihydroxy-vitamin D and 25-hydroxy-vitamin D were 66.6 pg/mL and 18 ng/mL, respectively. Neck US revealed an enlarged right lower parathyroid gland (Fig. 1a) and multiple thyroid nodules in the bilateral lobes. One of the thyroid nodules in the right lobe was suggestive of papillary thyroid carcinoma. A fine needle aspiration biopsy (FNAB) of the nodule showed benignity. Fig. 1b demonstrates significant accumulation of \(^{99m}\)Tc MIBI in the enlarged right lower parathyroid gland. Neck enhanced CT showed a contrasted nodule behind the right lobe of the thyroid that was compatible with parathyroid adenoma (Fig. 1c). The bone mineral densities (BMD) of the lumbar spine (L2-4) and radius were 1.039 g/cm\(^2\) and 0.577 g/cm\(^2\), respectively, and the percentages of the patient’s BMD divided by the BMD of the young adult mean (YAM) (% of YAM) of the lumbar spine and radius were 103% and 120%, respectively (Hologic QDR-4500, USA).

Right hemithyroidectomy and parathyroidectomy were performed. During the operation, the right upper parathyroid was not found to be swollen, which suggested a normal parathyroid gland. The data of calcium metabolism during surgery and on the first postoperative day are shown in Fig. 2. The patient did not complain of postsurgical hypocalcemia, and there was no need to administer vitamin D or calcium after surgery. After surgery, the serum levels of bone metabolic markers were as follows: the bone alkaline phosphatase (BAP) level was 15.3 IU/L and the serum type I collagen cross-linked N-telopeptide (NTx) level was 12.4 nMBCE/L. The results of a histological examination of the resected parathyroid and thyroid were compatible with a diagnosis of parathyroid adenoma (Fig. 3a) and adenomatous goiter (Fig. 3b).

### Discussion

We herein report a typical case of surgically proven NCHPT. To diagnose NCHPT, vitamin D insufficiency and urinary calcium leakage should be ruled out (7). In this case, the level of 25-hydroxy-vitamin D was 18 ng/mL and the level of 1\(\alpha\), 25-dihydroxy-vitamin D was slightly increased due to the effects of PTH. It has been reported that, when the level of 25-hydroxy-vitamin D is below 30 ng/mL, the secretion of PTH increases (6). From this perspective, this patient was diagnosed as having vitamin D insufficiency. However, it has also been reported that the level of 25-hydroxy-vitamin D in Asian populations is lower than that of Caucasians, and the mean level of 25-hydroxy-vitamin D was found to be 15.9 ng/mL (9). We could not explain the normal serum calcium concentration using only vitamin D insufficiency at this level. The results of an elevated level of 1\(\alpha\), 25-dihydroxy-vitamin D indicated that secreted PTH exhibited biological activity. The results of urinary calcium/creatinine and FE\(\text{Ca}\) suggested that there were no urinary calcium leaks. However, we therefore considered these results to be compatible with a diagnosis of NCHPT. Although this was also suspected on US.

By measuring the levels of both intact and whole PTH during surgery, we were able to exclude the possibility that our patient had a non-functioning parathyroid adenoma. PTH shows a high degree of immunoheterogeneity due to the occurrence of various fragments of PTH. It is known that intact PTH assays cross-react with 7-84PTH, which is biologically inactive, and the whole PTH assay was shown...
specifically to measure 1-84 PTH, which is biologically active. Strictly speaking, if patients have parathyroid adenomas that can produce 7-84 PTH exclusively, they should be diagnosed as having non-functioning parathyroid adenoma, not NCHPT, despite their high serum intact PTH levels with normocalcemia. In other words, we might make a misdiagnosis of NCHPT by using the ratio of 7-84 PTH production by parathyroid adenomas. Our results of sequential changes in the PTH concentration during surgery demonstrated that the patient had a functioning parathyroid adenoma.

Silverberg et al. hypothesized that NCHPT is a precursor of hypercalcemic pHPT and that early recognition of this condition might be beneficial for treating and preventing bone loss (5). From this perspective, it is important to recognize the natural history of pHPT. Silverberg et al. followed pHPT patients who did or did not undergo parathyroid surgery for 10 years (10). In their study, 52 asymptomatic pHPT patients were followed without surgery, and 14 of these 52 patients (27%) exhibited disease progression. Rubin et al. also followed pHPT patients who did or did not undergo parathyroid surgery for 15 years and reported that 37% of the asymptomatic pHPT patients who did not undergo surgery exhibited disease progression (11). These reports included patients with hypercalcemic pHPT; however, they suggested that the progression of pHPT requires various periods of time. Considering the factor of disease progression, we need to pay attention to the results reported by Silverberg et al. in which 14 patients who exhibited disease progression were younger at baseline than those who did not exhibit progression. Six of these 14 patients became menopausal during follow-up (10).

Homeostasis of the serum calcium concentration is maintained by absorption from the intestines, supply from bone and excretion from the kidneys. In this case, the calcium supply from the intestines was normal because the vitamin D level was within the normal limit and urinary calcium leakage was ruled out. Estrogen may play an important role in the disease progression of pHPT and also the etiology of NCHPT by modulating the calcium supply from bone. It is well known that estrogen suppresses the rate of bone remodeling and thus protects against bone loss (12). In addition, Muneyyirci-Delale et al. reported that the ionized calcium concentration of postmenopausal women is significantly increased compared with that of younger women in both the follicular and luteal phases (13). This report also suggests that the premenopausal estrogen level affects the serum cal-

Figure 1. a. An enlarged right lower parathyroid gland was detected on neck US. b. 99m-Tc MIBI scintigraphy also indicated a right lower parathyroid adenoma. Significant accumulation of 99m-Tc MIBI was observed in the early and delayed phases. c. A contrasted nodule behind the right lobe of the thyroid was detected on neck enhanced CT. This contrasted nodule was compatible with a parathyroid adenoma.
the patient menstruated regularly. It is difficult to prove the estrogen were compatible with a premenopausal state, and in our case, the serum concentrations of gonadotropin and the serum phosphorus level (IP) slightly increased. Both the intact and whole PTH concentrations were also decreased but remained within the normal ranges. The concentration of 1α, 25-dihydroxy-vitamin D (1,25-(OH)2VD) was slightly increased after surgery.

calcium supply from bone. On the other hand, excess PTH tilts the balance between bone resorption and formation in favor of the former. Cosman et al. reported that the estrogenized postmenopausal skeleton is less sensitive to the bone-resorbing effects of acutely administered PTH than is the postmenopausal skeleton (14). There have been no reports directly demonstrating an association between estrogen deficiency and disease progression of pHPT. However, there have been many reports about pHPT and estrogen replacement therapy (ERT) (15-18). These reports have shown modest (-0.5 mg/dL) reductions in the serum calcium levels without changes in serum PTH in postmenopausal women with pHPT who receive ERT (15, 16, 18, 19). Markers of bone turnover, which is generally elevated in pHT patients, appear to decline during ERT (16, 18, 19). These results suggest that estrogen prevents the bone resorption induced by excess PTH in pHPT patients to some extent. Therefore, some premenopausal pHPT patients have normal serum calcium levels. These findings also explain why the prevalence of pHPT suddenly becomes high after menopause, in spite of the fact that the doubling time of parathyroid adenoma cells is long at this stage. Theoretically, there may be more cases of NCHPT in premenopausal women who are not diagnosed with pHPT because their calcium levels are normal. In our case, the serum concentrations of gonadotropin and estrogen were compatible with a premenopausal state, and the patient menstruated regularly. It is difficult to prove the effects of endogenous estrogen on pHPT directly in this case; however, almost all clinical and laboratory data were compatible with the findings of the above-mentioned pHPT patient treated with estrogen replacement therapy. Adequate estrogen might prevent the effects of excess PTH on bone and may play an important role in maintaining a normal calcium concentration in NCHPT patients.

We herein reported a rare case of surgically proven NCHPT that suggests the significant role of estrogen in the etiology of this disease in premenopausal women. As cervical US has recently become widespread for the evaluation of arteriosclerotic disease and the screening of thyroid diseases, more cases of suspected parathyroid tumors may be encountered. Therefore, the likelihood of NCHPT must be considered, especially in premenopausal women.

The authors state that they have no Conflict of Interest (COI).

References

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