Primary Hyperparathyroidism Presumably Caused by Chronic Parathyroiditis Manifesting from Hypocalcemia to Severe Hypercalcemia


Abstract

A 67-year-old woman who presented with hypocalcemia compatible with idiopathic hypoparathyroidism gradually changed into a state of primary hyperparathyroidism. The left upper parathyroid gland, which was larger and harder than other glands, was resected. Despite the operation, hypercalcemia and high levels of intact PTH persisted. Six weeks later total parathyroidectomy was done to induce remission. The resected gland in the first operation had clusters of lymphoid follicles with germinal centers indicating a chronic autoimmune inflammation. This case suggests a transition from hypoparathyroidism to hyperparathyroidism associated with chronic parathyroiditis, possibly by a mechanism analogous to that observed in chronic thyroiditis. (Internal Medicine 44: 60–64, 2005)

Key words: hyperparathyroidism, chronic parathyroiditis, lymphoid follicles with germinal centers, hypercalcemia, hypocalcemia, Hashimoto’s disease

Introduction

Primary hyperparathyroidism is generally caused by parathyroid adenoma, hyperplasia or occasionally carcinoma. The cause of hyperparathyroidism without the above lesions is sometimes difficult to identify. Regarding the pathology of the parathyroid gland, lymphoid follicles with germinal centers are rarely present in the parathyroid tissues. The presence of lymphoid follicles may indicate a chronic inflammatory process in the tissue. Bondeson et al (1) first reported two cases of chronic parathyroiditis associated with hyperparathyroidism. The possibility of hyperparathyroidism caused by autoimmunity in the parathyroid gland in the context of Graves’ disease-like lymphoid infiltrate has been postulated. Since there was no evidence of underlying infections, a developmental anomaly, or drug reactions that could explain the inflammatory component, they suggested that an autoimmune process may have been involved in the pathogenesis (1). Chronic parathyroiditis itself has rarely been reported to date. Furthermore, cases manifesting severe hypocalcemia later changing to severe hypercalcemia associated with chronic parathyroiditis have not been reported to our knowledge. We report here a rare case of primary hyperparathyroidism which was presumably due to chronic parathyroiditis, which manifested from hypocalcemia to severe hypercalcemia.

Case Report

A 67-year-old woman saw a home doctor because of finger numbness in January 2000. She was referred to our hospital because plasma Ca levels were 6.4 mg/dl. When she visited our hospital on February 23, 2000, her plasma Ca and P levels were 7.2 mg/dl and 7.0 mg/dl, respectively. Plasma intact parathyroid hormone (PTH) was less than 9 pg/ml; the threshold of the assay. Her height was 159.2 cm, and her weight was 48.4 kg. Her blood pressure was 143/84 mmHg. In terms of family history her sister died of cerebral bleed-
ing, and she had had lung tuberculosis at 10 years of age. Physical examination on admission showed Chvostek sign and Trousseau sign, although the finger numbness had already disappeared. Laboratory data on admission on March 23, 2000 are summarized in Table 1. The results of Ellsworth-Howard test were compatible with idiopathic hypoparathyroidism. Other basal levels of hormones, with the exception of PTH, were within normal limits. Treatment with 1α, 25-(OH)2 D3, 2 μg/day was initiated.

Plasma Ca and intact PTH gradually increased. The clinical course is shown in Fig. 1. Treatment with 1α, 25-(OH)2 D3 was slowly tapered, then terminated. On November 13, 2000, plasma Ca and also intact PTH levels continued to increase without any treatment. In March 2001, both plasma Ca and intact PTH were above the normal upper limits. According to these state of parathyroid function, the clinical diagnosis was changed to primary hyperparathyroidism. Plasma Ca and intact PTH still increased slowly and consistently over the next several months, and six months after the diagnosis of primary hyperparathyroidism, an acute increase in plasma Ca levels occurred, peaking from 14.7 mg/dl to 16.5 mg/dl in September 2001 (Fig. 1). The patient suffered from severe fatigue, appetite loss and body weight loss of 9 kg, compatible with parathyroid crisis. A series of tests including an ultrasound echogram, 99mTc-MIBI/I-123 subtraction scintigraphy, magnetic resonance imaging (MRI), and computed tomography (CT) of the neck and the chest could not provide any information regarding localization of the causative lesions. Plasma PTH-related protein (PTHrP)

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<th>Table 1. Ca Related Data on First Admission</th>
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<td>1.25-(OH)2 Vitamin D</td>
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( ) : normal range.

Figure 1. Clinical course of the patient.
was within normal ranges. Antibodies against parathyroid gland and calcium-sensing receptor were not measured in the present study.

A parathyroidectomy was done on October 29, 2001. The left upper parathyroid gland, which was larger and harder than the other glands, was resected. Intraoperative frozen section showed that it was compatible with the tumorous change. However, final detailed histological examination revealed that the resected gland was histologically almost normal and had infiltration of scattered lymphocytes and clusters of lymphoid follicles with germinal centers, indicating a chronic autoimmune inflammation (Fig. 2). Unfortunately, remission was not obtained after the operation. Venous sampling of the neck and the chest for intact PTH was performed. The levels of intact PTH were higher near the superior vena cava than the other regions. From this result, re-operation was elected.

After obtaining the informed consent, on December 7, 2001, total thyroidectomy and paratracheal neck-upper thoracic dissection (Fig. 3) were performed. After the operation, plasma Ca decreased and intact PTH was not detected: below the assay threshold. At present this state continues up, and 1α, 25-(OH)D3, and thyroxine are given for replacement. With regard to the histology of the parathyroid glands, examinations of 4 mm slices identified the two additional parathyroid glands, that is, 1.8×0.7 mm in the tissue around the thyroid gland and 5 mm diameter in the paratracheal region. The former was atrophic (Fig. 4), and the latter was normal without any tumorous change and histologically there was focal infiltration of lymphocytes. Immunohistochemical staining for PTH was weakly positive in approximately 5% of the cells within the parathyroid gland resected at the first operation but the intensity of staining was weaker than that generally observed for normal parathyroid glands. Other glands resected at the second operation had been completely sliced thin, and thus no block was available for staining.

**Discussion**

The patient had clinical manifestations featuring a drastic change from hypocalcemia to hypercalcemia with pathological findings of lymphoid follicles with germinal centers in
the parathyroid gland but no evidence of commonly observed parathyroid adenoma, hyperplasia or carcinoma. Spontaneous remission due to sudden hemorrhage or infarction of parathyroid adenomas was reported in several cases of primary hyperparathyroidism (2, 3). This can be confirmed by findings of degenerative or necrotic tissues with hemosiderin deposits. Such rare cases are considered to be different from our case since there was neither hemorrhagic nor infarctive trace in the present study.

The pathological findings observed seem to simply lead us to the conclusion that the complicated clinical course could be explained by a mechanism associated with chronic parathyroiditis similar to that of Hashimoto’s disease. Hashimoto reported patients with diffuse goiter and clarified the four histological characteristics: diffuse lymphocytic infiltration, formation of lymphoid follicles, destruction of epithelial cells, and proliferation of fibrous tissue (4). The term “Hashimoto’s disease” or “Hashimom thyroiditis” is used to refer not only to goitrous thyroiditis but also chronic thyroiditis or autoimmune thyroiditis including atrophic and nongoitrous thyroiditis. Thyroid function of this disease is variable, from hypothyroidism or euthyroidism to hyperthyroidism. There are some case reports in which the clinical manifestations change as a result of transition between chronic thyroiditis and Graves’ disease (5–16). Graves’ disease is also classified among autoimmune organ-specific diseases characterized by lymphocytic infiltration of the thyroid and circulating antibodies directed to thyroid-stimulating hormone (TSH) receptors including thyroid-stimulating antibodies. Some patients with primary hypothyroidism subsequently develop hyperthyroidism (5–13). Several factors are considered to explain the changes of thyroid function: disappearance or decrease in titer of a blocking type of TSH receptor antibodies (7–9, 11–13) and emergence or increase in titer of a stimulating-type of TSH receptor antibodies (6–10, 12, 13). Although antibodies against the parathyroid gland were not studied in this case, there was the possibility that such parathyroid-stimulating and/or -blocking antibodies might be involved. Immunohistochemical staining for PTH was weakly positive in lymphoid follicles in the parathyroid gland of this case. However the results of immunohistochemical staining for PTH do not reveal the state of function of the parathyroid glands, whether they are hypofunctional or hyperfunctional. Negative or weak staining is caused by hormone deficiency or by hypersecretion. For example, the vasopressin content in the posterior lobe can be evaluated using magnetic resonance (MR) imaging. On MR T1-weighted images, the posterior lobe is demonstrated as a characteristic hyperintense signal under normal conditions (17), and the signal intensity of the posterior lobe is thought to reflect the content of neurosecretory granules containing vasopressin. The hyperintense signal of the posterior lobe of the pituitary gland is absent in diabetes insipidus on MR T1-weighted imaging, in which vasopressin-deficient hypersecretion occurs. In contrast, the vasopressin content in the posterior lobe is also decreased in patients with uncontrolled diabetes mellitus, which was thought to be caused by persistent vasopressin hypersecretion (18).

Chronic parathyroiditis is rarely studied. In two extensive studies of parathyroid glands from 800 autopsies, only a single case of chronic parathyroiditis was found (19, 20). Hyperplastic parathyroiditis was also reported in a necropsy case, the function of which was unknown (21). Chronic parathyroiditis was also observed in a few cases of hyperparathyroidism (22, 23).

Thus far five cases of isolated hyperplastic parathyroiditis presenting with hyperparathyroidism have been reported. Two cases of chronic parathyroiditis associated with parathyroid hyperplasia and hyperparathyroidism are described by Bondeson et al (1). One case was a 62-year-old male whose serum calcium continually increased to 11.2 mg/dl (normal range 8.8–10.4 mg/dl). The patient became normocalcemic the day after parathyroidectomy, and serum calcium remained normal at follow-up after 4 years. The removed parathyroid glands contained lymphoid follicles with germinal centers. At the operation four enlarged parathyroid glands were identified. The three larger parathyroid glands were removed while the smallest one was left intact. The other case was a 53-year-old male whose serum calcium was increased to 10.8 mg/dl. Three enlarged parathyroid glands were removed while the smallest one, considered to be normalized, was left intact. This patient also became normocalcemic the day after the operation, and serum calcium remained normal at follow-up after 3 years. A third case of hyperparathyroidism associated with parathyroiditis coexisting with brachial-cleft cysts was reported (24). A 57-year-old man, whose calcium levels ranged from 13.52 to 13.60 mg/dl (normal range, 8.4–9.6 mg/dl) and whose PTH was 79.0 pg/ml (normal range, 0–55 pg/ml), had both enlarged inferior parathyroid glands removed. Both glands had similar features, including lymphoid tissue organized into follicles (some of which were replete with germinal centers), and numerous plasma cells (24). The fourth case of hyperparathyroidism associated with chronic parathyroiditis occurred in a multiple endocrine neoplasia type 1 (MEN-1) patient (25), and the fifth case remained hypercalcemic after removal of one parathyroid gland with lymphoid infiltration with germinal centers and one gland normal in microscopic appearance; the other glands were not investigated. In this case PTH was elevated to 164 pg/ml (normal range 10 to 55). Six months postoperatively serum calcium was 11.76 mg/dl and PTH was 90 pg/ml (26). All five cases presented clinically as primary hyperparathyroidism. The clinical course of our case is considered to have initially started as hypofunction, as in Hashimoto’s disease, then to gradually have changed to hyperfunction as in Graves’ disease, similar to autoimmune abnormalities often observed in the thyroid gland (5–13). Further similar case reports are required to analyze the details of the pathogenic mechanism of the parathyroid dysfunction associated chronic parathyroiditis.

In conclusion, we reported a case of hyperparathyroidism which initially presented with hypocalcemia associated with
lymphoid follicles with germinal centers in one parathyroid gland and later one atrophic and one normal parathyroid gland pathologically.

References