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ORIGINAL PAPER

Normal parathyroid hormone levels in a diabetic patient with parathyroid adenoma

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Abstract *Objective* The incidence of diabetes mellitus in patients with primary hyperparathyroidism and, conversely, primary hyperparathyroidism in diabetic patients are approximately threefold higher than the respective expected prevalence in the general populace. The diagnosis is straightforward when the patient presents hypercalcemia and inappropriately elevated serum parathyroid hormone (PTH) levels. We report a case of parathyroid adenoma in a diabetic patient with persistent hypercalcemia and normal PTH levels. *Patient* A 50-year-old female patient who was referred to our outpatient clinic presented with persistent hypercalcemia (serum Ca levels between 10.5 and 11 mg/dl) with a normal serum intact PTH level of 46.1 pg/ml. Her blood pressure was 120/80 mmHg, and she was being treated with antihypertensive therapy. Her HbA1c was 7.2%, and her triglycerides were in the normal range. A bone densitometry exam revealed osteopenia of radius −1.39, femoral neck −1.39, and the total hip −1.04. A neck ultrasound revealed a mass of 13 mm next to the inferior and posterior of the right thyroid lobe. A dual phase Tc-99m-sestamibi scan revealed an area of increased uptake in the same region, which is indicative of a parathyroid adenoma. The parathyroid adenoma was removed, which resulted in the achievement of normocalcemia. *Conclusion* Diabetic patients should be evaluated for hyperparathyroidism as associated hypertension can complicate the course of the disease. These patients should be evaluated for primary hyperparathyroidism when they exhibit persistent hypercalcemia and when clinical suspicion is aroused even if the serum PTH levels are within the normal range.

Keywords Parathyroid adenoma · Diabetes mellitus · Hypercalcemia

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Introduction

Primary hyperparathyroidism is usually first suggested by the finding of sustained hypercalcemia, and the diagnosis is usually confirmed by finding an inappropriately elevated serum parathyroid hormone (PTH) concentration that is associated with the hypercalcemia. Although the diagnosis is straightforward in most patients, some patients with primary hyperparathyroidism exhibit normal or low serum PTH levels [1].

The incidence of diabetes mellitus in patients with primary hyperparathyroidism is 7.4–8.0%, and the prevalence of primary hyperparathyroidism in diabetic patients is 0.99% [2–5]. Both values are approximately threefold higher than the respective expected incidence in the general populace. The random chance of diabetes mellitus and primary hyperparathyroidism occurring in the same individual has been calculated at 0.011% [2]. Chance, therefore, makes no significant contribution to the much

higher prevalence that has been observed of the two disorders occurring together [6]. Primary hyperparathyroidism is diagnosed first in approximately 20% of patients with both disorders, and diabetes mellitus is presented first in 40% of patients with both disorders; both disorders present together or within 1 year of the diagnosis of the other disorder in 40% of patients with both disorders [6].

Diabetic patients should be evaluated for hypercalcemia because untreated hyperparathyroidism is associated with hypertension, which will complicate the course of the diabetes mellitus. When hypercalcemia is present, the diagnosis is straightforward if the patient has elevated PTH levels. However, we report a case of parathyroid adenoma in a diabetic patient with persistent hypercalcemia and normal PTH levels.

Case report

In January 2008, a 50-year-old female patient was referred to our outpatient clinic for evaluation due to persistent hypercalcemia. Hypercalcemia was first detected in February 2007 (her Ca level was 10.5 mg/dl and the normal range is 8.6–10.2 mg/dl) when she was receiving losartan hydrochlorothiazide therapy for hypertension. Losartan hydrochlorothiazide was replaced with telmisartan 80 mg and nifedipine GIT 30 mg. One month later, her Ca level rose to 11 mg/dl.

Her history revealed hematuria, recurrent episodes of renal colic, and a diagnosis of urolithiasis. She had no history of bone disease, dyspepsia, constipation, weakness, depression, or loss of vitality. She had been treated for diabetes for 2 years, hypertrigliceridemia for 1 year, and hypertension for 10 years. She was on rapeglinide, metformin, fenofibrat, and telmisartan + nifedipin therapy. She experienced the onset of menopause at the age of 40 and opted to avoid hormone replacement therapy. She had an operation for a lumbar hernia 4 years ago. She denied treatment with thiazide, lithium, calcium supplements, vitamin D, and vitamin A. Her physical examination was normal except that it revealed obesity with a BMI of 33 kg/m^2 and thyromegaly. No evidence of neck masses or lymphadenopathy was observed. Her blood pressure was 120/80 mmHg. Her HbA1c was 7.2%, and her triglycerides were in the normal range. Her Ca level was 10.8 mg/dl, and her ionized Ca was measured as 1.33 mmol/l. The normal range is 1.15–1.29 mmol/l. Her phosphorus level was 2.42 mg/dl (normal range: 2.3–4.7 mg/dl), while her alkaline phosphatase was 63U/L (normal range: 35–129 U/L). Her magnesium level was 2.05 mg/dl (normal range: 1.7–2.55 mg/dl), and her TSH was 2.72 μIU/ml (normal range: 0.27–4.2 μIU/ml). Her 24 h urinary tests revealed that her Ca, P, and creatinine levels were 402 mg/day, 1,143 mg/day, and 1,214 mg/day, respectively. Her PTH level was 46.1 pg/ml and 54 pg/ml (normal range: 9.5–75 pg/ml) based on two different measurements (Immulyte 2000 and Roche Elysees PTH assays, respectively), and her diluted serum PTH level was 48 pg/ml using a Roche Elysees PTH assay. Her serum 25-hydroxivitamin D level was 17.7 μg/l (normal range: 10–60 μg/l). A bone densitometry exam revealed osteopenia with t-scores in the radius at −1.39, the femoral neck at −1.39, and the total hip at −1.04.

Radiological studies included a normal chest X-ray, whereas nephrolithiasis was detected in the abdominal ultrasound. A neck ultrasound revealed a mass of 13 mm next to the inferior and posterior of the right thyroid lobe. A dual phase Tc-99m-sestamibi scan revealed an area of increased uptake in the same region, which is indicative of a parathyroid adenoma (Fig. 1).

On February 2, 2008, a radioguided adenoma resection was performed. The diagnosis of adenoma was histologically confirmed by the pathologist. The histopathological examination of the surgical material revealed chief cells which compose the adenoma without any fat cells and the presence of a thin edematous capsule separating the tumor from the uninvolved parathyroid parenchyma which still contains adipocytes (Fig. 2). Two days postoperatively, the patient's serum Ca level fell to 10.1 mg/dl, and 1 month after the parathyroidectomy, her serum PTH level (Immulyte 2000), serum Ca level, phosphorus level were

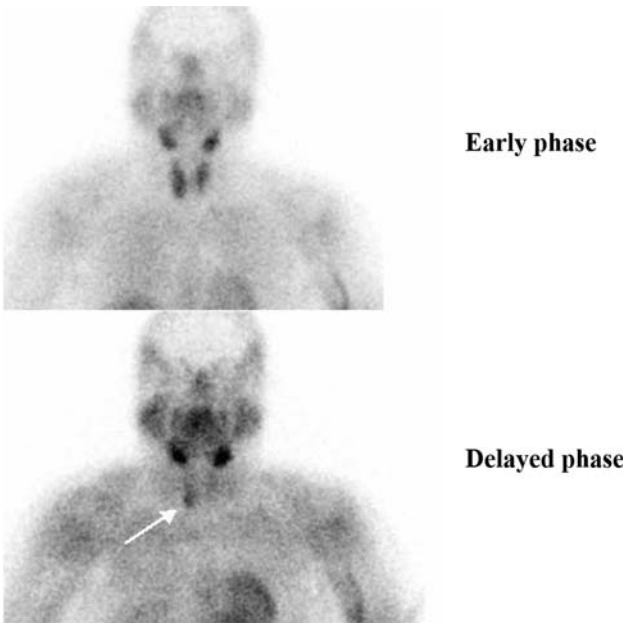

Fig. 1 Dual-phase Tc-99m-MIBI parathyroid scintigraphy shows focal radioactivity retention inferior to the right lobe of the thyroid in the delayed phase anterior image which is consistent with parathyroid adenoma while complete wash-out of the radioactivity is seen throughout the thyroid gland

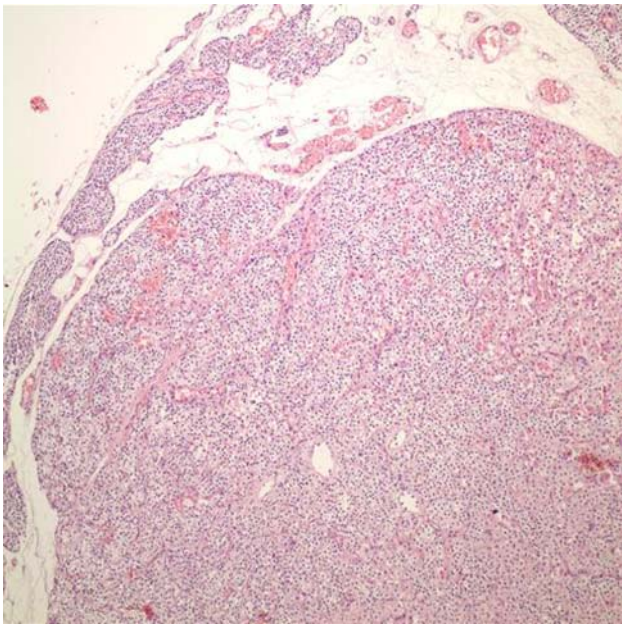

Fig. 2 Chief cells compose this adenoma without any fat cells present. Adenoma shows a rim of atrophic paranchyma at the periphery (HE 100×)

36.5 pg/ml, 9.8 mg/dl, and 3.41 mg/dl, respectively. After 8 months from the surgery the patient's PTH level was 25.9 mg/dl, Ca level was 9.7 mg/dl, and phosphorus level was 4.02 mg/dl.

Discussion

We described the case of a diabetic patient with hypercalcemia and a surgically verified parathyroid adenoma despite normal PTH levels.

Several causes of inappropriately normal serum PTH levels may indeed exist in the occurrence of primary hyperparathyroidism. The sample that is used to test for PTH must be appropriately collected and transported while maintaining the cold chain since PTH degrades rapidly, which may cause a detection of low levels of the hormone if the cold chain is not maintained [7]. PTH levels were measured by two different immunochemical assays. Although it is not common, we diluted the sample and looked for a possible hook effect. The diluted PTH levels were in the normal reference range. We excluded the presence of sarcoidosis, excessive vitamin D levels, and hypomagnesaemia.

As a consequence of poor metabolic control, alterations in calcium homeostasis occur in diabetic patients. Investigations indicate that diabetic patients, whether insulin-dependent or not, are relatively hypoparathyroid. Patients with both high glycosuria and long diabetic duration exhibited especially low values as compared to those with low glycosuria and diabetes of short duration and to normal subjects [8]. The PTH secretion is impaired in poorly controlled diabetes mellitus. The clinical observations indicate that primary hyperparathyroidism may precede diabetes mellitus in approximately 20% of patients or follow diabetes in 40% of patients. Additionally, the two disorders may be presented together or diagnosed within 1 year of one another in 40% of patients [6]. In a hyperparthyroid patient, as the disorder progresses, long-term insulin resistance, and relative insulin insufficiency with overt diabetes mellitus can arise. Such a mechanism might account for those patients whose primary hyperparathyroidism precedes diabetes mellitus or for those patients in whom the two disorders are present together [6]. For patients in whom diabetes occurs first, the experimental studies provide less help. Our patient had good control of her diabetes, and we diagnosed primary hyperparathyroidism within 1 year of the onset of diabetes. She probably had subtle hypercalcemia, which was explained by the hydrochlorothiazide use. In the diagnostic evaluation of the enlargement of her thyroid gland, a mass was reported, which probably suggested that a parathyroid adenoma was detected. Further evaluation with scintigraphy revealed a parathyroid adenoma, which gave rise to radioguided surgery. Hypercalcemia in diabetic patients should be evaluated carefully, and a parathyroid adenoma should be considered even if serum PTH levels are within the normal range.

Intact PTH measurements by second generation PTH assays, which we used in the current study, were shown to measure not only PTH 1–84 but also non-(1–84) PTH [9]. The sensitivity of the intact PTH assay was reported to be 73–86%, whereas bio-intact PTH assays are suggested to exhibit a higher sensitivity (96%) [9, 10]. However, intact and bio-intact assays may not completely detect PTH if a posttranslational alteration has occurred within an adenoma [11]. We could measure neither bio-intact PTH nor PTHrP because of our lack of facilities.

In conclusion, we report the case of a diabetic patient with persistent hypercalcemia, normal PTH levels, and surgically proven primary hyperparathyroidism. Diabetic patients should be evaluated for hyperparathyroidism when they exhibit persistent hypercalcemia and clinical suspicion is aroused even if the serum PTH levels are within the normal range.

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