Case Report

PARATHYROID CARCINOMA OCCURRING IN MULTIPLE ENDOCRINE NEOPLASIA TYPE I

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ABSTRACT

Objective: To describe a patient with multiple endocrine neoplasia type I (MEN-I) in whom parathyroid carcinoma developed.

Methods: A case report is presented, including detailed history, laboratory findings, and pathologic features.

Results: A 49-year-old man with a known history of MEN-I syndrome had hypercalcemia and profoundly increased parathyroid hormone levels. Seven years earlier, he had been diagnosed with a gastrinoma, prolactinoma, and primary hyperparathyroidism. A neck exploration at that time consisted of resection of a right inferior parathyroid gland and parathyroid tissue in the thyroid gland as well as biopsies of two left-sided glands, after which microscopic examination revealed parathyroid hyperplasia and his serum calcium levels normalized. On reexploration of the neck, resection revealed pathologic findings consistent with parathyroid carcinoma.

Conclusion: Parathyroid carcinoma has rarely been reported in the setting of MEN-I. This case illustrates the need for near-complete resection of parathyroid tissue in the patient with MEN-I. Subtotal or total parathyroidectomy in conjunction with forearm autotransplantation should be performed, not simply to prevent recurrence of benign disease but also to prevent the potential development of carcinoma over time. (Endocr Pract. 1999; 5:347-349)

INTRODUCTION

The multiple endocrine neoplasia type I (MEN-I) syndrome is characterized by neoplasms of the parathyroid, anterior pituitary, and pancreatic islet cells (1,2) as well as tumors in several other tissues, such as bronchial, thymic, and gastric carcinoids, adrenocortical tumors, lipomas, and, possibly, thyroid tumors (3). Hyperparathyroidism is the most common feature to manifest in patients with this disorder, reaching a prevalence of almost 100% by age 40 years; it is usually due to chief cell hyperplasia or adenoma (1). The recommended initial treatment for this cause of primary hyperparathyroidism is surgical intervention—a subtotal parathyroidectomy or total parathyroidectomy in conjunction with autotransplantation, primarily because of the high rate of recurrences with lesser procedures (4,5). Recurrences usually result from continued growth of residual hyperplastic tissue in patients who undergo less than total parathyroidectomy (4,5).

Herein we describe a patient with MEN-I who had documented gastrinoma, prolactinoma, and hyperparathyroidism, in whom hypercalcemia recurred because of a parathyroid carcinoma. The carcinoma was discovered in the neck of the patient, who had previously been operated on for benign parathyroid hyperplasia.

CASE REPORT

A 49-year-old man came to the Wilmington Veterans Affairs Medical Center because of nephrolithiasis. His serum calcium concentration was 12.8 mg/dL.

The patient had been well until he was 34 years old, when he had passed a kidney stone. At age 43 years, he had a recurrence of kidney stones and was found to have a serum calcium concentration of 13.3 mg/dL and an increased intact parathyroid hormone (PTH) level (310 pg/mL). During further evaluation, he was found to have a fasting serum gastrin of 1,196 pg/mL (normal, <100) and a serum gastrin after secretin stimulation of 2,005 pg/mL. Magnetic resonance imaging of his pituitary gland revealed an 8-mm sellar mass. A serum prolactin at that time was 76 ng/mL (normal, <15).

Surgical exploration of the patient’s neck revealed an enlarged right inferior parathyroid gland (1.0 by 0.5 cm). The right superior parathyroid gland was not found despite a thorough search. A palpated nodule in the right upper

Abbreviations:
MEN-I = multiple endocrine neoplasia type I; PTH = parathyroid hormone

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lobe of the thyroid gland was excised (and later determined to be parathyroid tissue by histologic examination). Exploration of the left side of the neck revealed normal-sized superior and inferior parathyroid glands. Biopsy specimens of these glands were obtained, and the exploration was terminated.

Macroscopic examination of the surgical specimens revealed an aggregate weight of 900 mg for the parathyroid tissue removed (right inferior = 750 mg, right upper pole of thyroid = 94 mg, left superior = 38 mg, and left inferior = 18 mg). Histologic examination demonstrated an increased cellularity of the parenchymal cells in conjunction with a decrease in the amount of adipose tissue. The cells were arranged in vague nodules and cords. The dominant cell type was chief cell, although several small oncocytic nodules were noted. The oncocytic cells contained abundant eosinophilic cytoplasm surrounding hyperchromatic nuclei without nucleoli. The ratio of nucleus to cytoplasm was decreased because of an increase in the amount of cytoplasm. No residual uninvolved or atrophic parathyroid tissue was identified, nor were mitotic figures, necrosis, hemorrhage, and fibrosis seen. Moreover, no adherence to the thyroid gland was noted. Collectively, these features were diagnostic of parathyroid hyperplasia.

Postoperatively, the serum calcium level was 9.7 mg/dL, and there was no record of postoperative hypocalcemia. The patient was dismissed from the hospital. With the exception of subsequent treatment with a proton pump inhibitor for gastrinoma, he was lost to endocrine follow-up.

During the 7 years before the current consultation, the patient had had intermittent diarrhea and weight gain (36.3 kg). He denied having headache, erectile dysfunction, change in shoe size, hypertension, or hoarseness. He had no family history of MEN-I or of hyperparathyroidism, and he had never had irradiation to his neck. His only medication was omeprazole, 30 mg daily. On examination, he was in mild distress attributable to flank pain. His blood pressure was high (160/110 mm Hg), but the rest of his vital signs were within normal limits. He was obese but did not have the characteristic appearance of a patient with Cushings syndrome or acromegaly. Visual fields were intact to confrontation. The thyroid gland was difficult to palpate because of obesity. No neck masses were felt. The abdomen was soft; no abdominal masses and no hepatomegaly were detected. The testicles were 5 cm in length bilaterally and of normal consistency. Gynecomastia, striae, peripheral edema, and rashes were not present.

Laboratory studies revealed the following: serum calcium 12.3 mg/dL (normal, 8.4 to 10.2), phosphorus 2.8 mg/dL (normal, 2.5 to 4.5), intact PTH (immunoradiometric assay) 243 pg/mL (normal, 12 to 72); plasma glucose 115 mg/dL (normal, 75 to 110), creatinine 0.8 mg/dL (normal, 0.8 to 1.5), serum sodium 143 mEq/L (normal, 137 to 145), prolactin 539 ng/mL (normal, <15), growth hormone <0.1 ng/mL (normal, 0.1 to 5), testosterone 311 ng/dL (normal, 241 to 827), luteinizing hormone 3.9 mIU/mL (normal, 1.5 to 9.3), follicle-stimulating hormone 4.7 mIU/mL (normal, 1.4 to 18.1), vasoactive intestinal peptide <10 pg/mL (normal, 23 to 63), and 24-hour urinary free cortisol 34 μg/24 h (normal, <105).

Radiographic studies of the neck and sella turcica were performed. Magnetic resonance imaging disclosed a pituitary mass in the sella turcica that indented the inferior aspect of the optic chiasm. A sestamibi parathyroid scan revealed avid uptake in the right side of the neck. Treatment with bromocriptine was begun, and a proton pump inhibitor was used.

On admission to the hospital for the planned neck exploration, the patient complained of profound fatigue. The serum calcium level was 15.5 mg/dL. He was hydrated with saline and given an intravenous infusion of 45 mg of pamidronate. One week later, and 7 years after the initial operation, reexamination of the neck was performed. A thorough search of the right side of the neck initially revealed no parathyroid tissue; however, within the excised right lobe of the thyroid gland, a mass (3.5 by 3.0 cm) was found that proved to be parathyroid tissue on frozen section.

Histologically, tumor cells were identified in immediate association with the thyroid parenchyma, surrounded and intersected by dense bands of acellular, fibrous connective tissue. The tumor cells were seen in the surrounding adipose connective tissue. At the edge of the main mass, vascular invasion of small to medium-sized vessels could be identified just beyond the thickened capsule. Although capsular transgression may have been present, distortion at the periphery and areas of dense fibrous connective tissue scarring made this determination impossible. The tumor cells were arranged in trabeculae, with areas of spindling. An overall monotonous pattern of the cells showed an increased ratio of nucleus to cytoplasm, condensed nuclear chromatin, and prominent nucleoli. Mitotic figures were noted along with areas of individual cell necrosis (apoptosis). The pathologic features were consistent with a diagnosis of parathyroid carcinoma (6,7) (Fig. 1 and 2).

Two days postoperatively, the intact PTH level was 47 pg/mL. Two weeks postoperatively, the serum calcium level declined to 9.7 mg/dL in association with a serum albumin concentration of 3.5 g/dL and an intact PTH level of 60.7 pg/mL. At 12 weeks postoperatively, the PTH level was 61.2 pg/mL, the serum calcium concentration was 10.1 mg/dL, and the serum albumin was 3.7 g/dL. At 20 weeks, the intact PTH was 68.4 pg/mL, and the serum calcium was 10.5 mg/dL.

**DISCUSSION**

Parathyroid carcinoma in the setting of MEN-I is extremely rare. Our review of the literature (MEDLINE, 1966 through 1997) revealed only three cases with this possible association. One case in 1974 was in a 43-year-old man with a family history of familial hyperparathyroidism, but the index case did not have evidence of pancreatic or pituitary tumors (8). In 1985, parathyroid
carcinoma was reported to exist in a large kindred in Tasmania affected with MEN-I (9). One additional case reported in 1992 documented the presence of a nonfunctioning pituitary adenoma in a 42-year-old man, in whom a parathyroid carcinoma subsequently developed (although it was not established that the man had the MEN-I syndrome) (10). Our patient, because of preexisting gastrinoma, prolactinoma, and parathyroid hyperplasia, clearly had the MEN-I syndrome.

Exactly how hyperplastic parathyroid tissue becomes malignant is not entirely clear. Parathyroid carcinoma has been reported coexisting in the same gland as parathyroid hyperplasia (11), as well as in a kindred in which affected family members had pathologic features ranging from parathyroid hyperplasia to carcinoma (12).

No histologic features are pathognomonic for the diagnosis of parathyroid carcinoma (6,7,13). Instead, an aggregate of features are used to determine the diagnosis, including adherence to surrounding soft tissue or thyroid gland, vascular invasion, capsular invasion, dense, acellular fibrous connective tissue bands, increased mitotic figures, trabecular growth pattern, cellular spindling, necrosis and apoptosis, increased nuclear to cytoplasmic ratio, nuclear pleomorphism and atypia, and prominent eosinophilic irregular nucleoli (6,7,13). The histopathologic findings in the current case fulfilled most of these criteria and are consistent with parathyroid carcinoma. Whereas recurrence of hypercalcemia is common after parathyroidectomy, especially in patients with the MEN-I syndrome, the cause is usually growth of residual hyperplastic tissue after the initial operation (5) and not a parathyroid carcinoma.

CONCLUSION

In this report, we describe a man with MEN-I who underwent a neck exploration that revealed parathyroid hyperplasia. On subsequent recurrence of hypercalcemia, repeated neck exploration disclosed parathyroid carcinoma. This case is important because it clearly documents the existence of parathyroid carcinoma in the setting of MEN-I. Furthermore, it underscores the need for near-complete resection of parathyroid tissue in the patient with MEN-I by subtotal or total parathyroidectomy in conjunction with forearm autotransplantation—not just to prevent recurrence of benign disease but also to prevent the development of carcinoma over time.

REFERENCES