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Primary Hyperparathyroidism in Patients with Multiple Endocrine Neoplasia Type 1: Experience by a Single Surgical Team in Japan

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Primary Hyperparathyroidism in Patients with Multiple Endocrine Neoplasia Type 1: Experience by a Single Surgical Team in Japan

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Nineteen patients were surgically treated for hyperparathyroidism associated with multiple endocrine neoplasia type 1 syndrome. Fourteen patients (74%) had removal of three or more parathyroid glands at the first operation, and five (26%) by removal of 2 1/2 or fewer glands. Two patients had recurrent hypercalcemia during the mean follow-up period of 65 months. One had a recurrence 10 years after subtotal parathyroidectomy. Reexploration in this patient revealed enlargement of the remaining tissue in the neck and an enlarged supernumerary gland in the aorticopulmonary window. The other patient had persistent hypercalcemia after removal of two hyperplastic parathyroid glands until after another 1 1/2 more glands were removed. After reoperation the patient was normocalcemic for 10 years before hypercalcemia was again noticed. The patient subsequently died from renal carcinoma metastases, which might have been the cause of the hypercalcemia before death. (Henry Ford Hosp Med J 1992;40:191-4)

In the hyperparathyroidism (HPT) associated with multiple endocrine neoplasia type I (MEN 1) syndrome, chief cell hyperplasia is found in all of the parathyroid glands. Recurrent or persistent HPT occurs at a high rate after parathyroidectomy in patients with MEN 1 (1). Removal of fewer than three parathyroid glands at the initial operation has resulted in a high incidence of recurrence (1-6). The most effective treatment is either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation with the identification of all four glands at the initial operation, although supernumerary hyperplastic parathyroid glands occasionally cause recurrent or persistent hyperparathyroidism (7). On rare occasions, some type of malignant tumor may be a source of hypercalcemia in patients with MEN 1 (8). We report the outcome of parathyroid surgery in our series of MEN 1 patients with special reference to uncommon causes of recurrent hypercalcemia.

Patients and Methods

From 1968 through 1990, 363 patients with verified primary HPT had their first parathyroid surgery performed by us. Twenty patients (5.5%) had HPT as part of the MEN 1 syndrome. Nineteen were from 10 families with verified MEN 1 and the other had no known relatives with the syndrome. Patients included 10 males and 10 females, with an age range of 22 to 73 years (mean 46 years).

The patients have been followed for 8 to 171 months (mean 65 months) after the initial operation. The information collected included operative procedures for parathyroid disease and data from pathological reports and clinical records including associated disorders and the current serum calcium (Ca) levels. The clinical and autopsy records of a patient who died during the follow-up period were evaluated. Eleven patients were followed by us and eight by physicians at other institutions. In patients followed by others, hypercalcemia or hypocalcemia refers to levels of serum Ca outside the normal range established in each laboratory. One patient who underwent subtotal parathyroidectomy in 1976 was excluded from the study because clinical information or the current serum Ca level data were not available, although he was stated to be "healthy."

Surgical procedures were classified as 2 1/2 glands or fewer removed or three glands or more removed. Removal of three or more glands included either subtotal (3 1/2 glands) parathyroidectomy or total parathyroidectomy with autograft of a portion of the gland into a muscle or subcutaneous tissue. Excision of three glands and autotransplantation along with partial thyroidectomy, total thymectomy through median sternotomy, or cervical thymectomy for a missing fourth gland were included in the latter group.

Results

Associated features of the MEN 1 syndrome

A growth hormone-producing pituitary tumor preceded HPT in one patient and prolactin-producing pituitary adenomas and HPT were simultaneously diagnosed in two patients. Two other patients were found to have prolactinomas 10 and 11 years after the initial parathyroidectomy. In another patient, autopsy revealed clinically asymptomatic microadenomas of the pituitary gland. On immunohistologic examination, the microadenomas

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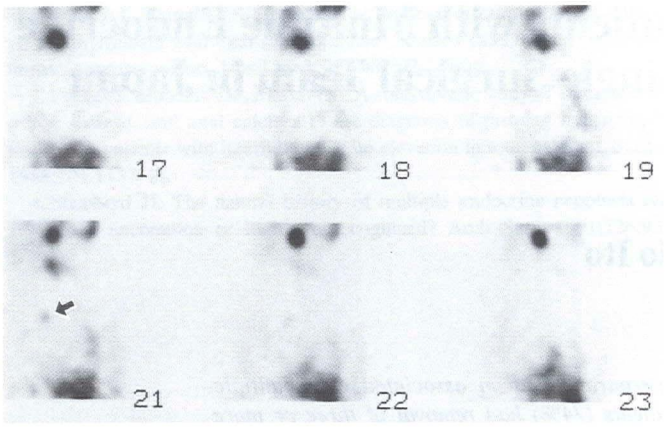

Fig 1—SPECT scan with thallium of case 1 (sagittal view) demonstrating increased activity (arrow) in the middle mediastinum.

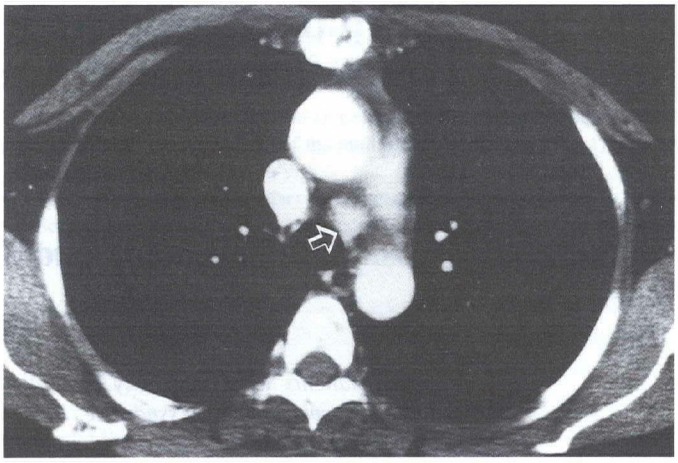

Fig 2—Computed tomography scan of case 1 disclosing the abnormal tumor (arrow) in the aorticopulmonary window.

stained for adrenocorticotrophic hormone (ACTH) and prolactin. In total, six of the 19 patients (32%) had pituitary tumors associated with HPT.

Endocrine pancreatic tumors were histologically verified in two patients and suspected from hormone levels and the clinical course in three others. Clinically, two of the patients had verified and one had suspicious Zollinger-Ellison (ZE) syndrome. Another patient had the ZE syndrome combined with hypoglycemia. In one patient, asymptomatic islet cell tumors were found at autopsy.

Other associated features found in one patient each included renal carcinoma, bronchial carcinoid tumors and pelvic sarcoma, thymic carcinoid tumor, papillary thyroid carcinoma, gastric carcinoid tumor and thymoma, and nonfunctioning cortical adenoma of the adrenal. Five of the 19 patients (26%) had malignant lesions outside of the pancreas with the diagnosis established concomitantly with the HPT in two patients and subsequently to the HPT in three patients. Bronchial carcinoid, renal carcinoma, or gastric carcinoid developed in each of the latter three patients. The intervals between the initial parathyroidectomy and the diagnosis of these tumors were 11, 9, and 5 years, respectively.

Outcome of parathyroidectomy

Fourteen patients (74%) were treated by removal of three or more parathyroid glands as the initial surgical procedure, and five (26%) by removal of 2 1/2 or fewer glands. In the latter five patients, the surgeons thought that the procedure was appropriate because the other two parathyroid glands were of normal size or were not identified despite meticulous search. After resection of 2 to 2 1/2 glands, four patients were normocalcemic at follow-up of 1 to 6 years (mean 3.8 years). None of the patients required vitamin D or Ca substitution postoperatively. One of these five patients had persistent HPT requiring reoperation (resection of the remaining 1 1/2 glands).

Among the 14 patients in whom three or more glands were removed at the initial operation and one patient who had a subsequent reoperation, subtotal parathyroidectomy was performed in nine and total parathyroidectomy with autotransplantation in six patients. Only one of the nine patients undergoing subtotal parathyroidectomy required substitution of vitamin D and/or oral Ca for eight months, while all the patients receiving total parathyroidectomy and transplantation required medication postoperatively. Eight of the patients became normocalcemic later without medication 3 to 16 months after the operation, although one patient required permanent supplemental medication.

Twelve patients have had normal serum Ca levels for 0.8 to 10.8 years (mean 5.0 years), while in two patients hypercalcemia recurred 9.4 and 10.8 years after the exploration. Both presented unusual features of recurrence.

Case Reports

Case 1

A 33-year-old woman with primary HPT and recurrent renal stones underwent subtotal parathyroidectomy for primary parathyroid hyperplasia and had remained normocalcemic for 10 years. Nevertheless, hypercalcemia recurred accompanied by the amenorrhea-galactorrhea syndrome, peptic ulcer diathesis, and hypoglycemic symptoms. Hyperprolactinemia and detection of a pituitary tumor by computed tomography and magnetic resonance imaging led to a definite diagnosis of prolactinoma. Both a gastrinoma and an insulinoma of the pancreas, which had been confirmed by hormone measurements and preoperative localization studies, were removed. The neck was reexplored and an enlarged hyperplastic parathyroid gland removed; a portion of the gland was autografted in the forearm muscle. However, the patient remained persistently hypercalcemic (the serum Ca level was 11 to 12 mg/dL). Localization studies including thallium scanning and computed tomography suggested the presence of a parathyroid gland in the anterior mediastinum. Mediastinal exploration failed to locate an abnormal parathyroid gland in the thymus or anterior mediastinal fat tissue. Further investigations were made to locate a missing supernumerary parathyroid gland. Eventually, single photon emission computed tomography (SPECT) using thallium demonstrated increased activity in the mid mediastinum (Fig 1), and computed tomography revealed the presence of a tumor in the aorticopulmonary window (Fig 2). At exploration of the mid mediastinum through a right thoracotomy, a hyper-

plastic parathyroid gland was successfully excised. Postoperatively the patient has remained normocalcemic without supplementation. The concentration of parathyroid hormone (PTH) in the antecubital vein of the grafted arm was 17 times that in the nongrafted arm.

Case 2

A 56-year-old man, father of the patient in case 1, underwent initial cervical exploration for primary HPT in which two hyperplastic parathyroid glands weighing 1.2 g and 0.5 g were removed. The serum Ca level remained normal for two months but hypercalcemia recurred. At a second cervical exploration the two remaining hyperplastic parathyroid glands were removed leaving approximately 60 mg in one gland. This procedure rendered the patient normocalcemic for a nine-year follow-up period when he complained of right epigastric pain, and ultrasonography and computed tomography disclosed a large right abdominal tumor. The tumor was a renal carcinoma, stage IV. Simultaneously, recurrent hypercalcemia (11.2 to 12.0 mg/dL) was noted. The serum C-PTH level was less than 0.1 ng/mL (normal level less than 0.3 ng/mL), and chemotherapy along with administration of prednisolone reduced the serum Ca level. The patient later died of the metastatic renal carcinoma; at autopsy tumorous lesions mimicking hyperplastic parathyroid glands were found around the thyroid gland which were metastases of renal carcinoma, with the remaining parathyroid gland totally involved with metastatic tumor cells. However, a tiny supernumerary hyperplastic parathyroid gland was found in the neck. The pituitary gland contained microadenomas which stained immunohistologically for ACTH and prolactin. The pancreas contained small islet cell tumors associated with islet hyperplasia.

Discussion

Involvement of more than one and perhaps invariably of all (four or more) parathyroid glands is the characteristic feature of HPT in MEN 1. Rizzoli et al (1) substantiated this observation with an unusually high failure rate for parathyroidectomy for primary HPT in patients with MEN 1. The ideal surgical strategy for primary HPT in patients with MEN 1 remains controversial. Some authors have continued to recommend subtotal parathyroidectomy (2,3,9), while others advocate total parathyroidectomy (4,10,11). In the present series, only two of the 19 patients have had documented recurrence of hypercalcemia. Persistent HPT was avoidable in one of the five patients who underwent removal of only two enlarged glands at the initial operation. Despite removal of only two glands, four patients have remained normocalcemic to date. Since the mean time of follow-up is only four years, additional recurrence may be observed later and further follow-up is warranted.

None of the six patients who underwent total parathyroidectomy with autotransplantation has had a recurrence to date, but one (17%) became permanently hypocalcemic. Graft-dependent hypercalcemia was not seen. Among the eight patients who underwent subtotal parathyroidectomy at the initial exploration, none developed permanent hypoparathyroidism, but one patient (12.5%) had recurrent HPT. In the patient presented as case 1, however, the removal of four glands and parathyroid autotransplantation at the initial operation would not have been curative since an aberrant fifth gland was the cause of persistent hypercalcemia after the second exploration. Therefore, our view is that the treatment of choice in patients with the MEN 1 syndrome and HPT rests between subtotal and total (with autograft) parathyroidectomy.

A functioning supernumerary parathyroid gland is rare. Most are located in the anterior mediastinum closely related to the thymus (7). Nevertheless, several authors reported cases of supernumerary hyperfunctioning parathyroid glands (12-15). To the best of our knowledge, only two patients with MEN 1 syndrome and supernumerary hyperplastic parathyroid gland at this site have been reported, including our case 1 (12). Preoperative localization of the ectopic lesion is difficult. In our experience, SPECT using thallium chloride is useful for detecting a lesion in the mid mediastinum (15).

In the patient (case 2) who underwent subtotal parathyroidectomy at reexploration, recurrent hypercalcemia occurred in conjunction with metastatic renal carcinoma. Although an association of MEN 1 syndrome with renal carcinoma has been reported previously (2), this is probably coincidental. However, it should be noted that renal carcinoma is often associated with hypercalcemia with a reported incidence as high as 16.8% (16). Most of the patients with hypercalcemia caused by renal cell carcinoma presented with advanced disease. We believe the patient in case 2 had humoral hypercalcemia of malignancy caused by renal carcinoma with metastases. It is unlikely that the remnant of parathyroid tissue left at the second exploration was hyperfunctioning because the supernumerary parathyroid gland found at autopsy was small and presumably the gland partially resected at the second exploration was totally involved by the carcinoma.

Parathyroid hormone-related protein (PTHrP) has been invoked as a cause of humoral hypercalcemia of malignancy (17). PTHrP messenger RNA has been identified by in situ hybridization in tumors associated with hypercalcemia, such as bronchial carcinoid, malignant pheochromocytoma, squamous cell lung cancer, hepatocellular carcinoma, malignant islet cell tumor, renal carcinoma, and breast cancer (18,19).

Of note is that carcinoid tumors and islet cell tumors are components of MEN 1. Various other endocrine or nonendocrine malignancies are occasionally associated with primary HPT (20). In the present series, three patients (16%) had carcinoid tumors and three had various carcinomas. The diagnosis of MEN 1 requires a close follow-up of the identified patient and close relatives.

In conclusion, surgeons should be aware that recurrence of hypercalcemia in MEN 1 may require a search for an ectopically located fifth parathyroid gland or for an associated malignancy, particularly in MEN 1 patients who have had subtotal or total parathyroidectomies.

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