
The Clinical Significance and Anatomic Distribution of Parathyroid Double Adenomas

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- BACKGROUND:** Parathyroid double adenomas are reported to occur in 3% to 12% of cases of primary hyperparathyroidism, but the very existence of double adenomas has been controversial. This study was undertaken to evaluate the clinical significance and anatomic distribution of parathyroid double adenomas.
- STUDY DESIGN:** The medical records of 384 consecutive patients who underwent operation for primary hyperparathyroidism were reviewed.
- RESULTS:** A total of 27 patients (7%) were found to have double parathyroid adenomas. Intraoperative parathyroid hormone (PTH) levels were measured in each case. Two enlarged hypercellular parathyroid glands were identified in 6 possible configurations: 10 both superior, 3 both inferior, 5 both right, 3 both left, 5 right superior and left inferior, and 1 left superior and right inferior. There was preferential distribution to the bilateral superior position ($p = 0.008$). In all patients intraoperative PTH levels dropped by at least 50% from baseline and into the normal range after removal of both abnormal parathyroid glands. All patients remain normocalcemic 1 to 26 months postoperatively. Two patients have persistently elevated PTH values with normal serum calcium levels.
- CONCLUSIONS:** The drop in intraoperative PTH levels and maintenance of normocalcemia postoperatively confirm previous reports that double adenomas do exist and are not simply missed cases of four-gland hyperplasia. Their incidence is more than would be expected by chance alone. The preferential occurrence of bilateral superior double adenomas suggests the possibility that these may represent hyperplasia of parathyroids arising from the fourth branchial pouch rather than isolated neoplastic events. (J Am Coll Surg 2004;198:185–189. © 2004 by the American College of Surgeons)
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Primary hyperparathyroidism is caused by a single adenoma in 87% to 91% of cases.^{1–3} The remaining cases are composed of four-gland hyperplasia, double adenomas, and much less commonly parathyroid carcinoma. The very existence of parathyroid double adenomas is controversial.^{1,4–7} Double adenomas have been reported to occur in 3% to 12% of patients undergoing operation for primary hyperparathyroidism.^{1,2,8} Some investigators have suggested that double adenomas do not exist and instead represent cases of asymmetric primary hyperplasia.^{4,9} This study was undertaken to address the follow-

ing questions: 1) do double adenomas exist, and 2) if so, is there any significant pattern in their anatomic distribution?

METHODS

This study is a retrospective chart review of 384 consecutive patients who underwent operation for primary hyperparathyroidism at Long Island Jewish Medical Center between June 1, 1999, and January 31, 2002. Patients were excluded if they had any of the following: familial hyperparathyroidism, any of the multiple endocrine neoplasia syndromes, renal failure, recurrent or persistent hyperparathyroidism after previous parathyroid operation, or inadequate followup. Of the remaining 376 patients, 27 were identified who had double adenomas. These patients are the subjects of this study. Each operation was performed by one of three attending surgeons. The following data were collected: age at time of operation, gender, preoperative calcium and parathy-

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roid hormone (PTH) levels, intraoperative PTH (IOPTH) levels, type of operation, surgical findings, histopathologic results, and postoperative calcium and PTH levels. Specimens were considered by the pathologists to be abnormal based on gross and histologic criteria including weight, cellularity, fat depletion, and morphology.

The initial operative approach was based on the results of preoperative Sestamibi scanning. Patients whose scans clearly demonstrated a single abnormal parathyroid underwent a minimally invasive procedure identifying and removing only the single abnormal gland. If the IOPTH dropped by at least 50% from the initial baseline and into the normal range, no attempt was made to identify other glands. If the IOPTH did not drop appropriately, the operation was converted to a conventional bilateral exploration. If the Sestamibi scan did not clearly identify a single abnormal parathyroid or suggested the presence of multiple abnormal glands, a conventional bilateral exploration with attempted identification of all four parathyroids was planned. The diagnosis of double adenomas was based on the surgeon's clinical impression that the glands were enlarged, by pathologic confirmation that the glands were enlarged and hypercellular, and by an appropriate decrease in IOPTH after removal of both abnormal glands. Unfortunately, in those patients who had a planned bilateral exploration, the second adenoma was frequently removed so soon after the removal of the first that it could not be determined what the IOPTH decrease would have been after the first abnormal gland was removed.

The QuiCK-IntraOperative Intact PTH Assay (Nichols Institute Diagnostics) was used during all procedures. Blood samples were drawn either from an indwelling intravenous or a radial arterial catheter. Samples were obtained at the following times: baseline-1 (before skin incision or induction of anesthesia), baseline-2 (after identification but before removal of an abnormal gland), at 5 and 10 minutes after each gland was excised, and at various times thereafter when appropriate.

RESULTS

A total of 27 patients (7%) were found to have double parathyroid adenomas. Of the patients, 22 were women (81%) and 5 were men (19%). Their ages ranged from 30 to 85 years (median 61 years). The median age of the remaining 349 patients was 58 years. The median pre-

operative total calcium and PTH levels were 11.3 and 93 for the double-adenoma patients and were 11.1 and 104 for the remaining patients. These differences between the two groups are not significant.

Preoperative Sestamibi scans identified a single abnormal gland in 16 patients, 2 abnormal glands in 8 patients, and more than 2 abnormal glands in 3 patients. Of the 27 patients with double adenoma, 24 (89%) underwent bilateral exploration either as the planned initial surgical procedure or after the IOPTH failed to drop appropriately after removal of a single adenoma. Three patients (11%) underwent unilateral exploration. In two of the unilateral explorations a single adenoma was removed and the IOPTH failed to fall appropriately. Further exploration on the same side revealed a second adenoma that was removed with an adequate drop in the IOPTH. In the third unilateral exploration the patient had a single adenoma excised and an ipsilateral hemithyroidectomy performed for a separate indication. Pathologic examination revealed an unexpected intrathyroidal parathyroid adenoma.

An average of 3.5 parathyroids were identified in each patient undergoing bilateral exploration. Two enlarged hypercellular parathyroid glands were identified in 6 possible configurations: 10 both superior, 3 both inferior, 5 both right, 3 both left, 5 right superior and left inferior, and 1 left superior and right inferior. The preferential distribution to the bilateral superior position is statistically significant (two-sided binomial Z test, $p = 0.008$). In all patients the IOPTH levels dropped by at least 50% from baseline and met the requirement for adequate parathyroidectomy. All patients remain normocalcemic 1 to 26 months (median 7 months) postoperatively. Two patients have persistent, mildly elevated PTH values with normal serum calcium levels.

DISCUSSION

In 1977 Wang and Reider⁴ wrote of the experience at the Massachusetts General Hospital, "The so-called 'double adenomas' if they indeed exist, are extremely rare, and we have not encountered a single case since 1958." Cope¹⁰ expressed similar doubt in 1978: "It is such a biological feat to make one hyperfunctioning adenoma that a coincidental second hypersecreting neoplasm is highly unlikely." In contrast, in many recent series, double adenomas have been reported to occur in 3% to 12% of patients with primary hyperparathyroidism.^{1,2,8}

Accurate identification of double adenomas depends

on the ability of the surgeon and pathologist to distinguish adenomatous from hyperplastic glands. Castleman and Mallory¹¹ first described the normal and abnormal pathologic conditions of the parathyroid glands in 1935. These investigators described the adenoma as a neoplastic lesion that was solitary and surrounded by a rim of normal appearing parathyroid tissue. In contrast, hyperplasia was defined as "a diffuse enlargement of all glands" with a "rather monotonous uniformity."

Histopathologic differentiation of adenoma from hyperplasia is difficult at best. Ghandur-Mnaimneh and Kimura⁹ state that endocrine gland hyperplasia does not necessarily occur diffusely, but instead can be asymmetric and focal "resulting in an adenoma-like enlargement." They describe the hyperplastic thyroid nodule, which can be histologically distinguished from thyroid adenomas, as an analogous process. These investigators argue that most single enlarged parathyroid glands are labeled as adenomas because pathologists lack appreciation of the concept of focal hyperplasia. The result is a gross overdiagnosis of parathyroid adenomas and underdiagnosis of hyperplasia. These investigators suggest a revised set of histologic criteria for parathyroid adenoma and hyperplasia. A hyperplastic mass exhibits one of the following: the presence of fat cells within the mass, a lobular pattern, or merging of the tissue within the mass with the normal surrounding parathyroid tissue. By comparison an adenoma should fulfill all of the following criteria: absence of fat within the mass, absence of a lobular pattern, and a well-defined demarcation between the mass and the surrounding parathyroid tissue. Using the above criteria the investigators reviewed pathologic specimens from 172 patients who underwent operation for primary hyperparathyroidism at Jackson Memorial Hospital. Their diagnosis was hyperplasia in 83.8% of cases, normal parathyroid tissue in 8.1%, adenoma in 5.8%, and "not able to be classified" in 2.3%. These conclusions represent a marked departure from traditional thinking.

A study by Saxe and colleagues¹² further highlights the ambiguity of parathyroid histopathology. A total of 50 slides containing parathyroid sections were given to 3 pathologists for review. The sections came from adenomas and hyperplastic glands defined clinically. An adenoma was defined as a single enlarged gland excised with positive identification of another normal gland at operation in a patient with at least 1 year of postoperative normocalcemia. Parathyroid tissue taken from patients

with four enlarged glands or from patients with familial hyperparathyroidism was considered to be hyperplastic. The interpretations of each of the three pathologists were then compared with the impression of the surgeon. The interpretation of the pathologists matched the surgeon's clinical definition of adenoma in 35%, 55%, and 83% of cases, and hyperplasia in 0%, 38%, and 60% of cases. The pathologists agreed with the surgeon's definition of normal parathyroid tissue in 71%, 78%, and 78% of cases. There was also a great deal of interpathologist variability on many sections.

Clearly the histologic differentiation of adenomatous from hyperplastic parathyroid glands is confusing and unreliable. Efforts to make this distinction more objectively have been attempted based on the clonality of the abnormal parathyroid glands and other molecular biologic methods. One technique of clonal analysis involves the use of X-linked Glucose-6-phosphate dehydrogenase deactivation. Using this method Jackson and colleagues¹³ analyzed normal and abnormal parathyroid tissue from 10 patients with primary hyperparathyroidism caused by single adenomas. They found that both the normal and abnormal tissue were polyclonal in origin. Arnold and associates¹⁴ addressed the same issue using restriction fragment length polymorphism directed at hypoxanthine phosphoribosyltransferase. Tissue specimens from eight patients with single adenomas and five patients with four-gland hyperplasia were analyzed using the restriction fragment length polymorphism. These researchers found evidence of monoclonal origin in six of eight adenoma specimens, and evidence of polyclonal origin in five of five hyperplasia specimens.

Larian and coworkers⁵ studied six patients with primary hyperparathyroidism; three with single adenomas, and three with double adenomas. In all six patients the abnormal glands were removed and a normal gland was identified and biopsied. All six patients maintain postoperative normocalcemia. Clonal analysis of all of the excised parathyroid tissue was performed using restriction fragment length polymorphism in the phosphoglycerolkinase gene. In addition, proliferative activity was measured in each specimen using immunohistochemical markers PCNA and Ki-67. All adenomatous tissue from both the single- and double-adenoma patients was monoclonal in origin. The biopsy specimens from the normal glands were all found to be polyclonal in origin. High levels of proliferative activity were found in all adenomas. Normal proliferative activity was found

in the normal glands from the single-adenoma patients, but higher than normal proliferative activity was found in two of the three normal glands from the double-adenoma patients. The investigators conclude that parathyroid adenomas are monoclonal neoplastic lesions. They suggest that double adenomas may occur in the background of hyperstimulation and hyperproliferation and that this may account for an increased incidence of spontaneous mutation.

Attempts have been made to distinguish double-adenoma patients on clinical grounds. Tezelman and colleagues⁸ reviewed 416 patients with primary hyperparathyroidism: 309 with single adenomas, 58 with hyperplasia, and 49 with double adenomas. These researchers compared the following: clinical manifestations; pre- and postoperative calcium, PTH, and phosphorous; and the surgical success rate. They found that double-adenoma patients were older than those with single adenomas. Fatigue, muscle weakness, and bone pain were more common and preoperative PTH was higher in patients with double adenomas than in those with single adenomas or hyperplasia. In a similar study Szabo and associates¹⁵ reviewed 866 cases of patients who underwent operation for primary hyperparathyroidism, including 77 with double adenomas. These investigators were unable to confirm the findings of Tezelman and colleagues. Our findings agree with those of Szabo and associates.¹⁵ We found no difference between patients with double adenomas and other patients with primary hyperparathyroidism with regard to age, preoperative calcium, or preoperative PTH.

The inability to distinguish adenoma from hyperplasia on histologic grounds has resulted in different recommendations about the appropriate surgical management of primary hyperparathyroidism. In 1970 Haff and Ballinger¹⁶ argued that because of this, subtotal parathyroidectomy should be performed in all cases. They feared that undetected hyperplasia remaining in the patient would predispose to failure. This concern was not substantiated in the 1981 report by Harrison and coworkers¹⁷ of 39 patients undergoing operation for primary hyperparathyroidism. There were 17 patients with hyperplasia, 6 with solitary adenomas, and 16 with solitary adenomas and evidence of microscopic hyperplasia in the biopsied grossly normal remaining glands. In those patients with evidence of microscopic residual hyperplasia, there were no cases of recurrent hyperparathyroidism after 4 to 8 years of followup. These researchers con-

cluded that residual microscopic hyperplasia is of no clinical significance. Attie and colleagues,^{1,18} in studies from 1978 and 1990, also argued against routine subtotal parathyroidectomy. They suggested removal of only those glands that appeared grossly enlarged, and reported a 2.2% failure rate using this method.

In 1998 Nussbaum and associates¹⁹ introduced the use of IOPTH measurement in parathyroid operation. Irvin and coworkers²⁰ established parameters for its use as an indicator of adequate parathyroidectomy. An appropriate decrease in the IOPTH suggests that all hyperfunctioning parathyroid tissue has been removed, and predicts postoperative normocalcemia. In our series of 27 patients with double adenomas, all patients demonstrated an appropriate decrease in IOPTH after excision of 2 abnormal glands and all of these patients have maintained postoperative normocalcemia. Two patients have mildly elevated PTH levels, with normal serum calcium. Postoperative elevation of parathyroid hormone levels with normocalcemia has been described.^{21,22} It is thought to occur in about 28% of cases after successful parathyroidectomy. The significance of this observation has not yet been determined.

The existence of double adenomas has caused confusion and debate in the literature, because it would seem extraordinarily unlikely that two separate neoplastic events could occur randomly in the parathyroid glands of a single patient. Pathologists have been unable to clarify the issue. They cannot reliably distinguish between parathyroid adenomas, hyperplasia, and even normal functioning parathyroid tissue. Ultimately it is the judgment of the surgeon that determines which glands will be removed from the patient. The advent of IOPTH monitoring has provided an additional means of ensuring adequate parathyroidectomy. More research is needed to determine the exact nature of double parathyroid adenomas, but our data provide further evidence that double adenomas do exist.

There is scarce mention in the literature about the anatomic distribution of double adenomas. In their 1958 description of chief cell hyperplasia Cope and associates²³ wrote, "As with primary water-clear cell hyperplasia, the upper glands are generally much larger than the lower ones." Tezelman and colleagues⁸ reported that 55% of their series of 49 double adenomas were bilateral. Similarly, Attie and colleagues¹ reported that 25 of 29 double adenomas in their series were bilateral. Our data indicate that there is a significant preferential dis-

tribution of double adenomas to the bilateral superior position. The superior parathyroids arise from the fourth branchial pouch.²⁴ This suggests the intriguing possibility that some double adenomas may be a manifestation of hyperplasia of parathyroids arising from the fourth branchial pouch rather than isolated neoplastic events.

Author Contributions

Study conception and design: Heller

Acquisition of data: Bergson

Analysis and interpretation of data: Bergson

Drafting of manuscript: Bergson

Critical revision: Heller

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