

# Tertiary Hyperparathyroidism

## *Histologic Patterns of Disease and Results of Parathyroidectomy*

Electron Kebebew, MD; Quan-Yang Duh, MD; Orlo H. Clark, MD

**Hypothesis:** Patients with tertiary hyperparathyroidism (THPT) commonly have parathyroid hyperplasia and should have a bilateral neck exploration with subtotal or total parathyroidectomy with autotransplantation to obtain long-term cure.

**Design:** A retrospective cohort study.

**Setting:** Tertiary referral medical center.

**Patients:** Thirty-four consecutive patients (21 women and 13 men; mean age, 48 years) who underwent neck exploration for THPT.

**Main Outcome Measures:** Sites and histologic pattern of parathyroid disease, and postoperative normalization of serum calcium and parathyroid hormone levels.

**Results:** Twenty-seven patients underwent initial bilateral neck exploration and 7 patients underwent repeat neck exploration for persistent or recurrent THPT. The mean serum total calcium level was 11.2 mg/dL (2.8 mmol/L) (range, 10.3-13.5 mg/dL [2.6-3.4 mmol/L]) and the mean intact parathyroid hormone level was 355 ng/L

(range, 95-1236 ng/L). The THPT was due to 4-gland hyperplasia in 33 patients and a single adenoma in only 1 patient. The parathyroid glands were in the normal position in 23 patients and in ectopic locations in 11 patients (8 intrathyroidic, 1 carotid sheath, 1 tracheoesophageal groove, and 1 intramuscular). Preoperative localizing studies did not identify ectopic or supernumerary glands in any of the patients (ultrasonography, 14 patients; technetium Tc 99m sestamibi, 15; and magnetic resonance imaging, 7). Persistent (n=5) and recurrent (n=2) THPT was more common in patients who had an initial 1- or 2-gland excision instead of subtotal or total parathyroidectomy with autotransplantation ( $P<.001$ ). Four patients had transient hypocalcemia ( $<8.0$  mg/dL [ $<2.0$  mmol/L]), and no other permanent complications or deaths occurred. Biochemical cure was achieved in 94% of patients with a mean follow-up of 4.8 years.

**Conclusions:** Tertiary hyperparathyroidism is usually due to multiple hyperplastic parathyroid glands, and patients who have initial limited parathyroidectomy have a higher risk of persistent or recurrent THPT.

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**T**ERTIARY HYPERPARATHYROIDISM (THPT) is uncommon and occurs in less than 8% of patients with secondary hyperparathyroidism after a successful kidney transplantation.<sup>1-3</sup> In patients with secondary hyperparathyroidism due to chronic renal failure, THPT results from autonomous proliferation of the parathyroid glands and hypersecretion of parathyroid hormone (PTH) after a successful kidney transplantation.<sup>4,5</sup> The THPT results in significant metabolic complications and symptoms, especially in patients who have had kidney transplants and are taking immunosuppressive therapy, which can be treated only by successful parathyroidectomy.<sup>6-8</sup>

Tertiary hyperparathyroidism is commonly due to parathyroid hyperplasia in-

volving 4 or more glands. Some investigators have reported that 2.6% to 32% of THPT may be due to a single adenoma or double adenomas.<sup>1,2,5,6,9-15</sup> These variable findings of single- or double-gland disease have important implications for the surgical approach used to treat patients with THPT. There is a consensus that patients with secondary or tertiary hyperparathyroidism should have a bilateral neck exploration with subtotal or total parathyroidectomy and autotransplantation. Many surgeons are now using a focused surgical approach (eg, minimally invasive parathyroidectomy, videoendoscopic parathyroidectomy, unilateral neck exploration) in patients with sporadic primary hyperparathyroidism, who usually (85%) have single adenomas, based on preoperative localizing studies and intraoperative PTH (IOPTH) measurement.<sup>16</sup> Some

*From the Department of Surgery, University of California, San Francisco.*

may, therefore, consider that up to one third of patients with THPT may also be candidates for a focused parathyroidectomy approach.<sup>9,14,15,17</sup>

The main objectives of this retrospective study were to determine the frequency of "true" single or double adenomas as a cause of THPT and to determine the accuracy of localizing studies in patients with THPT. Furthermore, long-term follow-up results of parathyroidectomy in patients with THPT were used to determine risk factors associated with recurrent or persistent THPT.

## METHODS

Between September 1, 1982, and April 30, 2002, 34 patients underwent parathyroidectomy for THPT at the University of California, San Francisco, hospitals. Tertiary hyperparathyroidism was defined as the presence of hypercalcemia and elevated PTH level in a patient with successful kidney transplant who previously had secondary hyperparathyroidism due to chronic renal failure.

Pathology reports, operative notes, clinical medical records, laboratory data, and clinic follow-up notes were reviewed. In patients undergoing initial parathyroidectomy, a bilateral neck exploration was used with a subtotal parathyroidectomy leaving a 40- to 80-mg remnant and cryopreservation of the most normal parathyroid gland. In patients with persistent or recurrent THPT, a unilateral or focused approach based on preoperative localizing studies was used. As part of routine care, before and after parathyroidectomy, serum calcium and PTH levels were collected prospectively. Intraoperative PTH measurement was used in some patients with THPT. Baseline IOPTH levels were checked twice before resection of any enlarged glands (once before dissection and once right before parathyroid gland excision), and postoperative PTH levels were measured, 10 minutes or longer after resection of an enlarged parathyroid gland. A decrease of more than 50% in the PTH level was used to define a successful neck exploration and parathyroidectomy.<sup>16</sup> Tertiary hyperparathyroidism due to parathyroid hyperplasia was defined as hypercellular parathyroid tissue present on permanent histologic examination of all resected glands, operative findings of enlarged glands, and normalization of postoperative calcium and PTH levels after subtotal parathyroidectomy. Tertiary hyperparathyroidism due to parathyroid adenoma was defined as hypercellular parathyroid tissue present on permanent histologic examination of a resected gland, operative findings of 1 enlarged gland in conjunction with at least 1 normal-appearing gland, and normalization of postoperative calcium and PTH levels after gland excision.

The accuracy of preoperative localizing studies was determined by comparing the results of the imaging studies with the operative finding, pathology report, and normalization of the postoperative serum calcium and PTH levels. Persistent THPT was defined as elevated calcium and PTH levels within 6 months after parathyroidectomy. Recurrent THPT was defined as elevated calcium and PTH levels more than 6 months after initial parathyroidectomy. A true-positive result of the localizing studies was based on the imaging study correctly identifying all abnormal parathyroid glands. The  $\chi^2$  test and unpaired, 2-tailed *t* test were used for comparison of categorical data and continuous data, respectively. A difference was defined as statistically significant if the *P* value was less than .05. Unless stated, numerical values in the text and table represent mean  $\pm$  SD.

## RESULTS

Thirty-four patients had THPT, and their clinical, biochemical, and pathological characteristics are summa-

### Clinical, Biochemical, and Pathological Characteristics of Patients With THPT

Characteristic	Finding
Sex, No. F/M	21/13
Age, y	
Mean	47.8 $\pm$ 14.1
Range	13-71
Calcium level, mg/dL	
Mean	11.2 $\pm$ 1.2
Range	10.3-13.5
PTH level (intact), ng/L	
Mean	355 $\pm$ 590
Range	95-1236
Creatinine, mg/dL	1.6 $\pm$ 0.6
Alkaline phosphatase, U/L	208.7 $\pm$ 233.8
Phosphorus, mg/dL	2.6 $\pm$ 0.5
THPT	
Initial	27
Persistent	5
Recurrent	2
Histopathologic finding	
Hyperplasia	33
Single adenoma	1
Parathyroid gland size, cm	
Mean	1.66 $\pm$ 0.63
Median (range)	1.6 (0.5-3.6)
Parathyroid gland location (per patient), No.	
Normal anatomic distribution	23
Ectopic	11*
Sensitivity of localizing studies, No. (%)	
Initial THPT	
Ultrasonography (n = 9)	6 (67)
Sestamibi scan (n = 9)	5 (9)
MR imaging (n = 1)	1 (100)
Persistent/recurrent THPT	
Ultrasonography (n = 5)	5 (100)
Technetium Tc99m sestamibi scan (n = 6)	6 (100)
MR imaging (n = 6)	6 (100)
Concurrent procedures during parathyroidectomy, No.	2†
Complications (transient hypocalcemia), No.	4

Abbreviations: MR, magnetic resonance; PTH, parathyroid hormone; THPT, tertiary hyperparathyroidism.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; creatinine to micromoles per liter, multiply by 88.4; and phosphorus to millimoles per liter, multiply by 0.323.

\*Eleven patients had 1 parathyroid gland each located in the thymus (n = 8), tracheoesophageal groove (n = 1), carotid sheath (n = 1), and strap muscle (n = 1).

†Total thyroidectomy for papillary thyroid cancer and near-total thyroidectomy for Graves disease.

rized in the **Table**. The mean age was 47.8  $\pm$  14.1 years. The mean duration of THPT after successful kidney transplantation was 3.6 years, ranging from 4 months to 15 years. The mean total calcium level was 11.2  $\pm$  1.2 mg/dL (2.8  $\pm$  0.3 mmol/L), and the mean intact PTH level was 355  $\pm$  590 ng/L.

Twenty-seven patients underwent initial bilateral neck exploration, and 7 patients underwent repeat neck exploration for persistent (n = 5; 3 patients after 1-gland excision, 2 patients after 2-gland excision) or recurrent (n = 2; after 3½-gland excision in the remnant gland) THPT. Only 2 of the 7 patients with persistent or recurrent THPT were initially treated at our institution. In these 2 patients, recurrent disease was from a remnant parathyroid gland after subtotal parathyroidectomy in one

patient, and in the other patient, persistent disease occurred after an initial unilateral neck exploration and 2-gland resection. This patient had his initial operation performed by another surgical service and was thought to have only 2-gland disease on the basis of preoperative neck ultrasonographic findings.

Tertiary hyperparathyroidism was due to 4-gland hyperplasia in 33 patients and a single adenoma in only 1 patient. Twenty-eight of the patients had a bilateral neck exploration with subtotal parathyroidectomy and 6 had a unilateral neck exploration (5 patients who had persistent or recurrent THPT and 1 patient with initial THPT who had a single adenoma). In 23 patients with THPT, the parathyroid glands were located in the normal anatomic distribution. Eleven patients had 1 ectopically located parathyroid gland: 8 intrathyroid, 1 carotid sheath, 1 tracheoesophageal groove, and 1 intramuscular (strap muscle).

Four patients, all with 4-gland hyperplasia, had IOPTH measurements during their neck explorations. In 2 patients, the IOPTH level fell appropriately after 3½-gland resection by 74.5% and 68.6%. The IOPTH level was a false-negative finding in 1 patient; it decreased by only 27% after a 3½-gland resection. One patient had a false-positive PTH result with a decrease of 76.4% after excision of only 1 gland and a total decrease of 83.5% after a 3½-gland resection. All 4 patients had postoperative calcium and PTH levels within the reference ranges at follow-up.

Preoperative localizing studies in patients with persistent or recurrent THPT were true positive in 5 of 5 neck ultrasonography scans, 6 of 6 technetium Tc 99m (<sup>99m</sup>Tc) sestamibi scans, and 6 of 6 neck and mediastinal magnetic resonance images. In patients with initial THPT, localizing studies suggested multiple-gland disease in 6 of 9 neck ultrasonography scans, 5 of 9 <sup>99m</sup>Tc sestamibi scans, and 1 of 1 neck and mediastinal magnetic resonance images. None of the localizing studies identified ectopically located glands, and there were no patients with supernumerary parathyroid glands.

The total complication rate was 11.8% and consisted of transient hypocalcemia (calcium level, <8.0 mg/dL [ $<2.0$  mmol/L]) in 4 patients who had subtotal parathyroidectomy. There were no transient or permanent recurrent laryngeal nerve injuries, no permanent hypoparathyroidism, and no deaths. The mean duration of hospitalization was 1.1 days (range, 1-6 days). The 1 patient who was hospitalized for 6 days developed severe hypocalcemia due to bone hunger and required intravenous calcium replacement. The mean follow-up time was 4.8 years (range, 1-13.25 years); 94% of patients were cured on the basis of total serum calcium levels within the reference range, and 70.6% were cured on the basis of PTH levels within the reference range. Of the 10 patients with elevated PTH levels after parathyroidectomy, 5 had developed chronic renal failure due to kidney graft function failure. Patient age, race, sex, PTH level, and kidney transplant graft failure were not associated with persistent or recurrent THPT as defined by hypercalcemia during normal renal function. Persistent or recurrent THPT, however, was more common in patients who had 1- or 2-gland excision instead of subtotal parathyroidectomy ( $P<.001$ ).

Patients with THPT commonly have significant symptoms and metabolic complications that improve after parathyroidectomy.<sup>5-8</sup> In THPT, the autonomous growth and hypersecretion of PTH from the parathyroid glands is thought to subside after successful kidney transplantation. Indeed, less than 8% of patients who have secondary hyperparathyroidism due to chronic renal failure have parathyroidectomy for THPT.<sup>1,3,4</sup> Generally, operative intervention is recommended in patients with THPT who have asymptomatic disease with total calcium level greater than 12.0 mg/dL (3.0 mmol/L) for more than 1 year, acute hypercalcemia, and symptomatic hypercalcemia.<sup>12</sup> No clinical factors such as duration of dialysis requirement, cause of chronic renal failure, or immunosuppressive regimens have been found to predict which patients will require a parathyroidectomy.<sup>18</sup> Biochemical factors such as PTH, creatinine, phosphorus, and alkaline phosphatase levels do not reliably distinguish which patients will require a parathyroidectomy.<sup>18</sup> Only the posttransplant serum total calcium level predicts the need for parathyroidectomy, but this is used as an indication for operative intervention. In our cohort, all patients with THPT had symptoms associated with THPT (79.4%), metabolic complications (32.3%), or serum total calcium level greater than 12.0 mg/dL (3.0 mmol/L) (20.6%) for 1 or more years.

Although up to one third of patients with THPT have been reported to have single or double adenomas, we found only 1 patient (3%) who had a single adenoma, which is consistent with most studies.<sup>1,2,4,6,9-15</sup> Many of these patients, however, have marked variation in the size of their abnormal parathyroid glands. It is unclear why most patients with THPT have parathyroid hyperplasia of 4 or more glands, especially a long time after successful kidney transplantation, as the stimuli for compensatory parathyroid hyperplasia from hypocalcemia, hyperphosphatemia, and decreased level of  $1\alpha,25$ -dihydroxyvitamin D are reversed after successful kidney transplantation. Although one would expect autonomous growth of the parathyroid glands to be monoclonal, this has not always been observed in the parathyroid glands of patients with THPT.<sup>11,19,20</sup> Nodular hyperplasia is associated with autonomous growth of the parathyroid glands, but both diffuse and nodular patterns of parathyroid hyperplasia have been reported in THPT.<sup>11</sup> It is, therefore, unclear whether single or double adenomas in THPT represent (1) an autonomous monoclonal parathyroid gland growth, (2) a primary hyperparathyroidism that was present before a patient developed secondary and then tertiary hyperparathyroidism, or (3) an asymmetric regression of hyperplastic parathyroid glands after successful kidney transplantation.

In addition to the rarity of single or double adenomas, localizing studies were not accurate in identifying all abnormal parathyroid glands in the patients who had initial bilateral neck exploration. The combined sensitivity of all the imaging studies (ultrasonography, <sup>99m</sup>Tc sestamibi scans, and magnetic resonance imaging) in this group was 63.2%. Although some experts recommend localizing studies to identify ectopic and supernumerary parathyroid glands in patients with

secondary and tertiary hyperparathyroidism, none of these imaging studies identified ectopically located parathyroid glands and no patient in our cohort had a supernumerary parathyroid gland. The localizing studies were, however, accurate in the patients with persistent or recurrent THPT and allowed a unilateral neck exploration to be performed in these patients. The main factor associated with persistent and recurrent THPT was an incomplete parathyroidectomy due to an initial unilateral neck exploration or an enlarged parathyroid gland not correctly identified at the time of an initial bilateral neck exploration.

Intraoperative PTH measurement was used in 4 patients in the latter part of the series. Although our finding is drawn from a small number of patients, it documents that IOPTH measurement cannot be used reliably in patients with multiglandular disease, as we have similarly reported in patients with primary hyperparathyroidism caused by double adenomas.<sup>21</sup>

Our study documents that most patients with THPT have multiple hyperplastic parathyroid glands, so that a bilateral neck exploration should be done. Furthermore, localizing studies and IOPTH measurement do not appear to be accurate enough to select patients who would be candidates for a focused neck exploration without the confirmation of other normal parathyroid gland(s) being present on bilateral neck exploration. The main cause of persistent or recurrent THPT was an incomplete exploration at the initial operation.

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Correspondence: Electron Kebebew, MD, Department of Surgery, University of California, San Francisco/Mount Zion Medical Center, San Francisco, CA 94143-1674 (kebebewe@surgery.ucsf.edu).

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