CLINICAL AND OPERATIVE MANAGEMENT OF PERSISTENT HYPERPARATHYROIDISM AFTER RENAL TRANSPLANTATION: A SINGLE-CENTER EXPERIENCE

Hanna Gilat, MD,1 Raphael Feinmesser, MD,1 Yanush Vinkler, MD,2 Sara Morgenstern, MD,3 Jacob Shvero, MD,1 Gideon Bachar, MD,1 Thomas Shpitzer, MD1

1 Department of Otorhinolaryngology, Head and Neck Surgery, Rabin Medical Center, Beilinson Campus, Petah Tiqwa and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. E-mail: thomas-s@zahav.net.il
2 Department of Nephrology, Rabin Medical Center, Beilinson Campus, Petah Tiqwa and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
3 Department of Pathology, Rabin Medical Center, Beilinson Campus, Petah Tiqwa and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Abstract: Background. Persistent (tertiary) hyperparathyroidism (TH) after renal transplantation may cause considerable morbidity and necessitate parathyroidectomy. This study investigated the characteristics of this patient subgroup.

Methods. The medical data and pathology specimens of 20 kidney transplant recipients who underwent parathyroidectomy for TH in 2001 to 2004 were reviewed.

Results. Treatment consisted of subtotal resection of 3.5 glands in 13 patients, resection of 3 to 3.5 glands under intraoperative parathyroid hormone monitoring (iPTH) in 5 patients, and selective resection in 2 patients with markedly asymmetric gland enlargement. Eighteen patients had hyperplasia—diffuse in 10, nodular in 4, or both in 2; 2 patients had 1 large nodule in every gland. Six patients had postoperative complications. Follow-up of 2 years revealed recurrent hypercalcemia in 1 patient and a high level of PTH (>60 pg/mL) in 12.

Conclusion. Subtotal resection for TH may be insufficient. The use of iPTH monitoring is recommended. Renal transplant recipients have distinctive characteristics and require special perioperative attention.

Keywords: renal transplantation; tertiary hyperparathyroidism; PTH monitoring; transplantation; parathyroidectomy

Hyperparathyroidism occurs in as many as 90% of patients with chronic renal failure by the time maintenance hemodialysis is initiated.1 This condition, frequently termed “secondary hyperparathyroidism,” is the result of several factors, the most important being hyperphosphatemia and decreased renal production of active vitamin D (calcitriol), which leads to hypocalcemia and increased parathyroid hormone (PTH) production.2

Successful kidney transplantation usually corrects the abnormalities of mineral metabolism that lead to secondary hyperparathyroidism. The mechanisms that account for this change include the reversal of uremia, abolition of acidosis, abolition of hypocalcemia and hyperphosphatemia, restoration of calcitriol production, and reversal of the skeletal resistance to PTH and vitamin D3,4 Accordingly, the parathyroid glands involute and return to nor-
nal function in the majority of patients.\textsuperscript{5} However, up to 30% may acquire posttransplantation hypercalcemia, which typically resolves within the first year.\textsuperscript{2} Although persistent hyperparathyroidism is the main reason for postoperative hypercalcemia, other contributory factors include resolution of soft tissue calcifications, immobilization, corticosteroid therapy, and hypophosphatemia.\textsuperscript{6}

Persistent renal hyperparathyroidism, attributed to autonomous function of the parathyroid glands, was termed “tertiary hyperparathyroidism” by St. Goar in 1963.\textsuperscript{7} It can lead to several complications, namely, bone disease and pathologic fractures, renal calculi, mental status changes, muscle weakness, pancreatitis, and peptic ulcer disease.\textsuperscript{8,9} It may also endanger the implanted kidney. Some reports describe numerous detrimental effects of hypercalcemia on graft function.\textsuperscript{10} Ultimately, 1.6\% to 3\% of all kidney transplant recipients may require parathyroidectomy, as the definitive treatment for tertiary hyperparathyroidism.\textsuperscript{1}

Few data in the literature refer to patients with posttransplantation hyperparathyroidism as a distinct group. The aim of the present study was to investigate their unique characteristics.

**PATIENTS AND METHODS**

The study group included 20 renal transplant recipients who underwent parathyroidectomy for the treatment of tertiary hyperparathyroidism at our center from March 2001 to July 2004. All had a functioning kidney graft and were receiving immunosuppressive regimens.

The medical files, in addition to outpatient follow-up findings up to December 2004, were reviewed for demographic data and presurgery and postsurgery calcium, phosphate, and PTH levels. The duration of dialysis before transplantation, signs and symptoms of hyperparathyroidism, interval between transplantation and parathyroidectomy, postsurgical complications, and length of hospitalization were recorded as well. The pathology specimens were reviewed for pattern of hyperplasia (nodular/diffuse).

Postoperative morbidity and hospitalization time were compared with 2 control groups of 77 patients with primary hyperparathyroidism and 6 dialysis patients with secondary hyperparathyroidism who underwent surgery in our institute in the same time period. It was only in 2004 that intraoperative PTH monitoring became routine practice in our department, and it was applied in the last 5 patients in this study. Intraoperative PTH level was measured by the quick PTH assay at induction of anesthesia (baseline) and at 10 and 20 minutes after excision of the last parathyroid gland. A drop of more than 50\% in PTH level indicated a successful resection.

**Statistical Analysis.** Mean values and standard deviations are reported for all data. Statistical significance was determined by Student’s \( t \) test and chi-square test as appropriate. The nonparametric Wilcoxon test was used to compare individual patient data preoperatively and postoperatively. \( p \) values less than or equal to .05 were considered significant.

**RESULTS**

**Background Data.** The study group consisted of 12 men (60\%) and 8 women aged 28 to 70 years (average, 52). Mean duration of dialysis before transplantation was 5.9 ± 4 years (range, 0.5–13 years); 15 patients had hemodialysis, 3 patients had peritoneal dialysis, and 1 patient had both. The remaining patient received a living donor kidney and did not have dialysis at all. The average interval from renal transplantation to parathyroidectomy was 2 years 5 months (range, 1–15 years). The average age of the primary hyperparathyroidism control group was 59 years; of the secondary hyperparathyroidism group, 50 years.

**Preoperative Evaluation.** Mean (±SD) laboratory findings in the study group were as follows: calcium, 11.4 ± 0.7 mg/dL; phosphate, 2.8 ± 0.7 mg/dL; and alkaline phosphatase, 134 ± 94.5 U/L. Mean creatinine level was 1.5 ± 0.4 mg/dL (range, 0.9–2.5; normal, 0.7–1.2).

Mean PTH level was 465 ± 267 pg/mL for the whole group. Mean level for the 9 patients in whom surgery was performed 1 year after transplantation was 530 ± 277 pg/mL, and for the 11 patients in whom surgery was performed 2 years after transplantation, 294 ± 158 pg/mL. There was no statistically significant association between duration of dialysis before transplantation and PTH level.

Seven patients (35\%) reported symptoms consistent with hyperparathyroidism. Four had osteoporosis or osteopenia, 2 had bone pain, and 1 each had nephrolithiasis, abdominal pain, or peptic disease.

**Operative Management.** All patients underwent bilateral neck exploration during surgery to iden-
identify all parathyroid glands. In 13 patients, 4 parathyroid glands were found to be “symmetrically” enlarged, and subtotal resection of 3.5 glands was carried out. Two patients had markedly “asymmetric” enlargement of the glands and were treated with selective resection; 1 had only 2 enlarged glands, and the other, a single markedly enlarged gland and 3 normal-appearing glands. In the last 5 patients in this study, PTH levels were monitored intraoperatively. In 3 of them, PTH levels dropped markedly, reaching normal levels after 3 glands were resected, and in the other 2 patients, PTH levels normalized after 3.5 glands were resected. The results for the patients treated with iPTH monitoring are shown in Table 1.

Pathology Findings. Pathologic study of tissue specimens from the 2 patients treated by selective resection revealed mild hyperplasia in the 2 enlarged glands from 1 of them; the other appeared to have a single enlarged gland with 1 dominant nodule. In the remaining 18 patients, all resected glands were overtly hyperplastic: 10 patients (55%) had a mostly diffuse pattern of hyperplasia, 4 patients (22%) had a mostly nodular pattern, and 2 patients (11%) had both; 2 patients (11%) had 1 big dominant nodule in every gland.

Fibrosis was noted in 44% of the glands, abundant oxyphil cells in 25%, and clear cells in 12.5%.

Postoperative Laboratory Findings. Mean laboratory findings on the first postoperative day were as follows: calcium, $8.77 \pm 0.8 \text{ mg/dL}$; phosphate, $3 \pm 0.8 \text{ mg/dL}$; and PTH, $66 \pm 62.5 \text{ pg/mL}$. Mean postoperative creatinine level was $1.7 \pm 0.6 \text{ mg/dL}$. In 7 patients (35%), the postoperative creatinine level was higher than the preoperative level.

Postoperative Morbidity. Overall, 6 patients (30%) in the study group had postoperative complications: fever above $38^\circ \text{C}$ for more than 24 hours in 3; severe pneumonia combined with increased creatinine level in 1, which warranted transfer to the Department of Internal Medicine for further evaluation and treatment; severe hypophosphatemia in 1; and severe back pain in 1.

Seven patients had symptoms related to hypocalcemia (finger tingling, muscle twitching). Four of them had true hypocalcemia ($<8 \text{ mg/dL}$) and were treated with intravenous calcium and vitamin $\alpha$D3 until levels normalized, followed by oral supplement for a few weeks. The decision to stop this treatment was made by the attending physician and was based on the calcium level at outpatient follow-up. In the other 3 patients with hypocalcemic symptoms, laboratory values were normal and the symptoms were attributed to a transient drop in postoperative calcium (“relative hypocalcemia”).

| Table 1. Patients-resection with iPTH monitoring. |
|---|---|---|---|---|---|---|---|
| Patient No. | No. of glands resected | Pre-op Ca, mg/dL | PTH 1, pg/mL | PTH 2, pg/mL | Hysterological findings (type of hyperplasia) | PTH f/u, pg/mL | Ca f/u, mg/dL |
| 1 | 3.5 | 11.7 | 830 | 5.4 | Diffuse | 133 | 10.7 |
| 2 | 3 | 10.3 | 700 | 40 | Diffuse | 134 | 8.5 |
| 3 | 3 | 11.4 | 268 | 57 | Diffuse | 40 | 8.9 |
| 4 | 3 | 10.7 | 400 | 37 | Nodular | 66 | 8.7 |
| 5 | 3.5 | 8.6 | 228 | 27 | Diffuse | 41 | 8.7 |

Abbreviations: Pre-op Ca, preoperative calcium level; PTH 1, at induction of anesthesia; PTH 2, 10 minutes after resection of last parathyroid gland; PTH, Ca f/u, on follow-up of 2 years.

| Table 2. Postoperative complications and hypocalcemia after parathyroidectomy. |
|---|---|---|---|
| Complications/Hypocalcemia | Primary ($n = 77$) | Secondary ($n = 6$) | Tertiary ($n = 20$) |
| Relative hypocalcemia | 2 (2.5) | 4 (66) | 3 (15) |
| True hypocalcemia | 2 (2.5) | 4 (66) | 4 (20) |
| Total complications | 12 (15) | 4 (66) | 6 (30) |
| Type of complications | | | |
| Local | 5 (6.5) | 1 (17) | |
| Systemic | 3 (4) | | 6 (30) |
By comparison, postoperative complications occurred in 8 patients (10.5%) in the primary hyperparathyroidism group, and in 1 patient (16%) in the dialysis group (local complication) (Table 2).

The average length of hospitalization of the tertiary hyperparathyroidism group was 6 ± 3 days, which was significantly longer than that of the primary hyperparathyroidism group (mean, 4.2 ± 1 days) (p < .05).

**Follow-Up.** Patients were followed for 2 years. At the last follow-up, 12 patients (60%) had a high level of PTH (>60 pg/mL), and 1 of them also had hypercalcemia (>10.5 mg/dL). Overall, mean calcium level was 9.4 ± 0.9 mg/dL, and mean PTH level was 98 ± 54 pg/mL. There was a significant reduction in PTH (p < .001) and calcium level (p < .001) compared with the preoperative levels. No significant difference was noted in PTH and calcium levels on follow-up between patients treated with subtotal resection without intraoperative PTH monitoring and patients treated with selective resection or under PTH monitoring.

In patients with persistently high levels of calcium after parathyroidectomy, it is common practice to perform repeated imaging studies (ultrasound and MRI) and to re-explore the neck or mediastinum for ectopic and supernumerary glands.

**DISCUSSION**

In their study of posttransplantation hyperparathyroidism, D’Alessandro et al5 reported that the hypercalcemia resolved at 6 months to 7 years following renal transplantation in 69% of patients. Nevertheless, only 2% showed resolution of the hypercalcemia after more than 2 years. In our study, PTH levels 2 years after transplantation were noticeably lower than levels after 1 year.

Traditionally, a conservative approach to hyperparathyroidism is used in kidney transplant recipients. There are reports that the novel calcimimetic drug cinacalcet may offer an alternative to surgery, though its efficacy in renal transplant recipients requires further study. Moreover, the economic burden of lifelong treatment with calcimimetics needs to be considered.11 At present, surgery is reserved for symptomatic or acute posttransplant hypercalcemia (calcium >12.5 mg/dL), and it remains the only definitive treatment for asymptomatic patients with persistent hypercalcemia above 12.5 mg/dL at more than 1 year after transplantation.1,5 The standard modes of surgery are subtotal parathyroidectomy or total parathyroidectomy with autotransplantation.1 The transplanted gland is commonly placed in the forearm12 or sternocleidomastoid muscle.1 Kerby et al1 found both surgical procedures adequate for the treatment of tertiary hyperparathyroidism. However, several studies have suggested that only selective resection of enlarged glands is equally efficient.8,9,13 As a rule, our department uses subtotal parathyroidectomy in patients with tertiary hyperparathyroidism, and during surgery, a thorough search is made for all parathyroid glands in the neck. In the present series, 2 patients had markedly asymmetric enlargement of some of the glands, and only the enlarged glands were resected.

Our pathohistological results were similar to those reported in other studies.1,14 Most of the glands showed diffuse hyperplasia, with occasional oxyphil cells, clear cells, and fibrosis. Mostly nodular hyperplasia was identified in 4 of 18 patients; the remainder had a combination of diffuse and nodular hyperplasia.

The pathophysiologic of persistent posttransplant hyperparathyroidism has received some attention over the years, yet remains unclear. Researchers hypothesize that in renal (secondary) hyperparathyroidism, the glands grow diffusely, as well as polyclonally at first, and may later switch to a more aggressive and autonomous nodular pattern of growth.15-20 After renal transplantation, the glands are expected to involute. Our pathology and laboratory results, in addition to the above-mentioned studies, suggest that the glands first regress to a diffuse hyperplastic pattern, but some may reach a plateau without any further regression to complete involution. These patients may eventually need parathyroidectomy. Factors such as pretransplantation PTH levels,21 dialysis duration,22,23 and renal function21 were suggested to be important predictors of persistent hyperparathyroidism after renal transplantation. Other researchers suggested reduced phosphate reabsorption in the implanted kidney,24 skeletal resistance to PTH, and low density of calcitriol receptor in the parathyroid gland25 to be the causes of persistent hyperparathyroidism. Theories of genetic predisposition18 and monoclonality25 require further investigation.

According to previous studies, a high PTH level on follow-up may be attributable to a hypertrophic remnant, supernumerary glands, or resection of fewer than 3.5 glands.11,26 Pattou et al26 reported a 32% incidence of supernumerary glands as a cause
of persistent or recurrent hyperparathyroidism after surgery. However, the significance of high PTH level after surgery has not been thoroughly addressed. In our study, on follow-up, most of the patients (55%) had a high PTH level (>60 pg/mL), but only 3 patients also had hypercalcemia (>10.5 mg/dL). It stands to reason that the high PTH level is caused by a hyperfunctional parathyroid residue which produces an elevated level of PTH in response to a certain calcium level. This raises doubts regarding the current supposition that subtotal excision is sufficient for the treatment of tertiary hyperparathyroidism. At the same time, there was no significant difference on follow-up in calcium and PTH levels between patients treated by limited resection under PTH monitoring or patients who had selective resection and patients in whom 3.5 glands were resected. We do not have enough experience with total parathyroidectomy to compare it to the subtotal procedure. Nevertheless, given our morphological and clinical data, we suggest that tertiary hyperparathyroidism is a stepwise but heterogeneous process which includes a broad spectrum of clinical manifestations, from adenomatous hyperplasia of only 1 or 2 glands to advanced hyperactivity of all individually existing parathyroid cells, which do not fit the standard surgical concepts.

Postoperatively, 35% of the patients had symptoms related to hypocalcemia (finger tingling, muscle twitching), of whom 20% had true hypocalcemia. This could be related to the “hungry bone syndrome” described as a metabolic response to parathyroid surgery and characterized by avid calcium retention by demineralized bone. 27

In our study, the kidney transplant recipients were more likely to have systemic complications than were the primary and secondary hyperparathyroidism groups, and a longer hospitalization time than the primary hyperparathyroidism group. The chronic disease state and immunosuppressive regimens may explain, at least in part, this group’s greater “fragility.” Thus, it is mandatory that a nephrologist actively participates in every decision involving these patients.

In conclusion, the management of tertiary hyperparathyroidism requires further investigation. We recommend that in renal transplant patients with hyperparathyroidism, the search for all parathyroid glands should be thorough, and the use of intraoperative PTH monitoring should be considered. Our study suggests that the subtotal procedure alone may be insufficient. Special attention should be addressed to these patients preoperatively and postoperatively owing to their distinctive requirements and characteristics.

REFERENCES


