Tertiary Hyperparathyroidism Following Successful Renal Allografting

RONALD G. LATIMER, M.D., JAMES RENNING, M.D.,
LAWRENCE E. STEVENS, M.D., J. D. NORTHWAY, * M.D.,
KEITH REEMTSMA, M.D.

From the Department of Surgery, University of Utah College of Medicine, Salt Lake City, Utah

"AUTONOMOUS" hyperparathyroidism was first suggested as a disease entity in 1956 by Davies *et al.*, when hypercalcemia developed in a steatorrheic patient.[5] The synonymous title of "tertiary" hyperparathyroidism was suggested by W. T. St. Goar in 1963.[19] The chain of events which leads to the development of this disorder of calcium metabolism is now clearly understood. Poor absorption of calcium occurs in chronically uremic patients, presumably from inhibition or antagonism of the calcium absorbing action of vitamin D upon the intestinal mucosa.[15] As hypocalcemia ensues, defective bone mineralization follows, producing either osteomalacia in the adult or rickets in the child. Massive doses of vitamin D given at this time may reverse these bone lesions. Persistent hypocalcemia (the serum level of ionic calcium being the determinant) stimulates an increased production of hormone from the parathyroid glands. The resulting calcium mobilization from the bone leads to the typical lesions of ostetitis fibrosa cystica which are commonly noted in primary hyperparathyroidism. The parathyroid glands become enlarged and hyperplastic and the circulating levels of parathyroid hormone often reach higher values than in patients with primary adenomas.[2, 20] This situation featuring bone lesions and low normal to normal levels of serum calcium makes up the clinical picture of secondary hyperparathyroidism. If the hypersecretion of parathyroid hormone persists at high levels despite the compensatory mechanisms of secondary hyperparathyroidism and hypercalcemia thereby is produced, the criteria for a diagnosis of tertiary hyperparathyroidism have been fulfilled.[8]

The postoperative development of tertiary hyperparathyroidism following correction of the uremic state by successful renal allografting has been reported in 17 patients, the first case by McPhaul in 1964.[1, 10, 16, 17, 21] Tertiary hyperparathyroidism seen after renal transplantation is characterized by hypercalcemia and hypophosphatemia. Histologically, the enlarged parathyroid glands show diffuse chief cell hyperplasia. Many believe that this is simply a pre-existing tertiary hyperparathyroidism unmasked by normal renal function rather than developing *de novo*.[16] Recently, Alfrey *et al.*, reported that in nine of 17 renal transplant patients this pre-existing hyperparathyroidism was revealed by phosphate deprivation. Deprivation resulted from a steroid induced increase in phosphate clearance and from intestinal phosphate binding by aluminum hydroxide antacids.[1]

Two unusual complications (renal stone formation and symptomatic acute hyper-

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* Department of Pediatrics, University of Utah Medical Center.

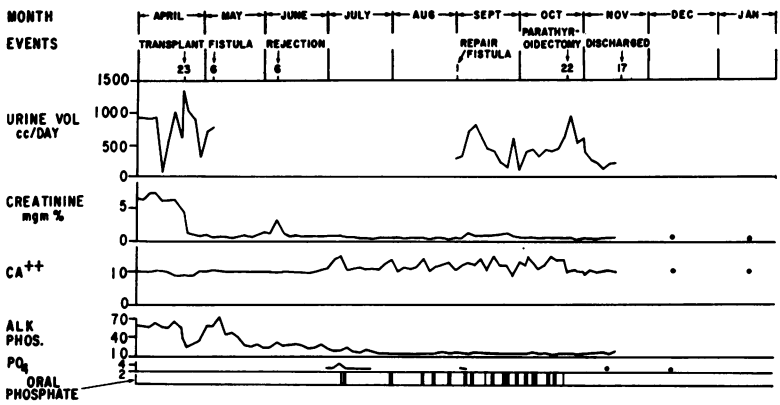

FIG. 1. Case history. J. B. UUMC 1-20-44-45.

calcemia) of postrenal allograft tertiary hyperparathyroidism are herewith reported.

Case History

(J. B., UUMC 1-20-44-45) A 10-year-old girl was first seen in the University of Utah Medical Center on March 1, 1966, with history for 5 years of recurrent urinary tract infections. Intravenous and retrograde pyelograms, cystopanendoscopy, and open kidney biopsy were performed, confirming the diagnosis of congenital polycystic kidney disease. A voiding cystourethrogram demonstrated a normal lower urinary tract.

Over the following 23 months renal function gradually deteriorated until she required repeated peritoneal dialysis. On April 23, 1968, a cadaveric renal allotransplant was placed in her right iliac fossa. Immunosuppressive therapy consisted of prednisone 40 mg. (2.0 mg./Kg.), azathioprine 50 mg. (2.5 mg./Kg.) and antilymphocyte serum (60 mg. in globulin form) each day. In the following 24 hours after transplantation urine output was 10–20 ml./hr., and this flow increased to 50 ml./hr. by the 5th post-transplant day. Concomitantly, serum creatinine fell from 10 to 0.9 mg. per 100 ml. On the 10th post-transplant day she developed a subcutaneous wound infection requiring incision and drainage. By the 25th post-transplant day, a uretero-vesico-cutaneous urinary fistula developed and attempts to close the fistula with superficial sutures failed. A rejection episode beginning the 44th post-transplant day was successfully reversed by increasing the steroid dosage and by irradiatiating the graft with 150 rads daily for 4 days.

Before transplantation serum calcium values were consistently 8.3 to 8.4 mg. per 100 ml. with serum phosphorous from 13.2 mg. to 15.2 mg. per 100 ml. (Fig. 1). By the 75th post-transplant day serum calcium level reached a peak of 15.7 mg. per 100 ml. She complained of frequent headaches and a loss of appetite. Irritability and hypertension were noted. Until this point she had been treated prophylactically with the antacid Mylanta,* which was discontinued and Phosphaljel ** substituted. In addition, she was given oral Fleets Phosphosoda *** 1 tsp. twice or three times a day to combat episodes of hypercalcemia. This intermittently reduced serum calcium levels to normal. In the following 6 weeks, however, the frequency of the symptomatic hypercalcemic episodes increased to 2 to 3 times per week, although still controlled by increased dosages of oral phosphates.

On the 127th post-transplant day the urinary fistula was operated upon and necrosis of the distal ureter disclosed. A revision of the transplant ureter anastomosis into the bladder was accomplished. The pelvis of the transplanted kidney was opened to facilitate passage of a splinting catheter and several yellow calculi up to 4 mm. in diameter were removed. By chemical analysis the stones were composed of calcium phosphate. X-ray examination of her bones showed early reabsorption from the lateral ends of the clavicles. On examination of the cornea by slit lamp there were no calcium deposits.

Because of progressively more frequent hypercalcemic episodes and calcium phosphate calculi in the transplanted kidney pelvis subtotal parathyroidectomy was performed on the 181st post-

* Stuart Products, 3360 E. Foothill Blvd., Pasadena, California.

** Wyeth Laboratories, P. O. Box 8299, Philadelphia, Pennsylvania.

*** Fleet Company, Inc., C. B. 4615 Murray Place, Lynchburg, Virginia.

transplant day. Four large parathyroid glands were located and 3⅔ of the four glands were excised (1.8 Gm. of tissue). Following this procedure serum calcium levels slowly returned to normal. Her appetite improved, blood pressure returned to normal, headaches and irritability vanished and her mood improved. Pathologic examination of the excised parathyroid tissue showed diffuse chief cell hyperplasia.

She was discharged on the 202nd post-transplant day and has continued to do well. Thirteen months post-transplant serum creatinine is 0.3 mg. per 100 ml., BUN 29 mg. per 100 ml., calcium 10.4 mg. per 100 ml. and hematocrit 37 per cent.

Immunosuppressive therapy consists of azathioprine 25 mg./day, and prednisone 5 mg./day. She is in school full time and is progressing well.

Discussion

The problem is whether to treat tertiary hyperparathyroidism arising after successful renal allografting by subtotal parathyroidectomy or by oral phosphate therapy. The decision is difficult because it is impossible to predict (1) which chronic uremic patients will develop hyperparathyroidism postoperatively (2) which of those patients in whom tertiary hyperparathyroidism will resolve spontaneously and (3) how long an allograft can tolerate hypercalcemia, without permanent and irreversible damage.

Tertiary hyperparathyroidism can develop in from 3 days to 6 months following allografting and hypercalcemia has persisted as long as 13 months (Tables 1 and 2). Alfrey *et al.*, reported that seven of nine hypercalcemic patients became normocalcemic within 2 to 3 months following adoption of aluminum phosphate antacid therapy. Of the other two patients one required subtotal parathyroidectomy and the second was given long-term oral phosphate therapy.[1]

Hyperparathyroidism with hypercalcemia threatens normal renal function. Hueper[11] and Carone[4] found permanent epithelial damage, necrosis and calcification in the ascending loop of the Henle, in the distal

TABLE 1. *Hypercalcemia Following Successful Renal Transplant Operated*

Investigator	Year	Sex	Age	Time for Hypercalcemia to develop Post Tx	No. of Parathyroids Removed Operation	X-ray Bone Invo.	Calcium (mg./100 ml.)	Phosphorous (mg./100 ml.)	Complication	Duration of Hypercalcemia
Mc Phaul[7]	1964	M	19	56 days	3½	+	12.0	2.2		1 month
Wilson[11]	1965	M	32	60 days	3¾	+	14.2	0.9		2 months
Kastagir[12]	1965	M	32	142 days	4	+	12.4	3.5		
Mc Intosh[8]	1966	M	18	7 days	3¾	+	13.6	1.3		3 months
		F	37	13 days	3¾	0	13.0	1.8		1.6 months
		F	15	30 days	3¾	+	12.2	1.5		1 month
Alfrey[9]	1968	M	25	60 days	3¾	+	13.2	1.5		9 months
Latimer	1968	F	10	63 days	3⅔	+	15.7	2.8	Renal Calculus Formation in Tx	6 months

TABLE 2. *Hypercalcemia Following Successful Renal Transplant Non-operated*

Investigator	Year	Sex	Age	Time for Hypercalcemia to develop Post Tx	X-ray Bone Invo.	Calcium (mg./100 ml.)	Phosphorous (mg./100 ml.)	Complications	Duration of Hypercalcemia
Mc Intosh[8]	1966	F	23	14 days	0	12.0	1.6	Pulmonary metastatic calcification	Intermittent for 8 mos.
		M	21	3 days	0	11.8	1.8		13 months
Alfrey[9]	1968	M	25	182 days	0	13.0	1.0		2–3 months
		M	21	182 days	0	12.1	2.8		7–10 months
		F	20	150 days	+	12.0	3.1		2–3 months
		F	27	90 days	0	12.9	2.8		2–3 months
		M	25	90 days	0	11.9	2.9		2–3 months
		M	36	120 days	0	11.5	3.8		2–3 months
		M	24	90 days	0	13.9	2.8		7–10 months
		F	33	45 days	+	11.4	2.9		2–3 months

convoluted tubules and in the collecting tubules in animals made hypercalcemic by injections of parathyroid hormone. Similar findings have been confirmed in hyperparathyroid patients by Pyrah.[14] Furthermore, calcium nephropathy with advanced azotemia may result from intrarenal hydronephrosis even through glomerular destruction or tubular calcifications are absent.[7]

This is the second reported patient with tertiary hyperparathyroidism who developed symptoms of acute hypercalcemic toxicity, Alfrey *et al.*,[1] reported the earlier case. Acute hypercalcemia is an emergency with a mortality of 66 per cent.[13] Administration of oral and intravenous phosphate preparations have been advocated for acute hypercalcemia.[6, 9] These effective preparations exert their effect by exceeding the solubility product of calcium phosphate with resultant bone deposition.[10, 14] There is also a possibility of extraosseous metastatic calcification.[3] McIntosh[16] reports pulmonary metastatic calcification in a patient who was not taking phosphate therapy. As in our patient, resistance to oral phosphate therapy may develop and renal calculi can form.

Indications for subtotal parathyroidectomy in patients who develop tertiary hyperparathyroidism after renal allografting include:

1. Symptoms of acute hypercalcemia,
2. A threat of metastatic calcification or renal calculus formation after prolonged phosphate therapy,
3. Progressive unresponsiveness to phosphate therapy, and
4. Hypercalcemia persisting longer than 6 weeks despite therapy with oral phosphates.

Summary

Tertiary hyperparathyroidism developing following successful renal allografting may resolve spontaneously. Complications of

renal stone formation, acute hypercalcemic toxicity, metastatic calcification, and irreversible damage to the transplanted kidney may develop if tertiary hyperparathyroidism persists for too long. Subtotal parathyroidectomy should be considered to avoid these complications.

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