Hypercalcemia following renal transplantation in a cat

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Possible causes of posttransplantation hypercalcemia include persistent hyperparathyroidism, resorption of extraskeletal mineralizations, hypophosphatemia, vitamin D toxicosis, preoperative dialysis, a decrease in the dosage of corticosteroids being administered, and a parathyroid adenoma.

Treatment of posttransplantation hypercalcemia is controversial; however, surgery should be considered if the condition is a result of a parathyroid adenoma.

An 11-year-old 3.0-kg (6.6-lb) neutered male Persian was referred to the University of Pennsylvania School of Veterinary Medicine for renal transplantation. Two years previously, polycystic kidney disease and renal insufficiency had been diagnosed. Prior treatment included administration of lactated Ringer's solution (150 ml SC, q 24 h), erythropoietin* (300 units, SC, 3 times a week), cimetidine hydrochloride* (5 mg/kg [2.3 mg/lb] of body weight, PO, q 12 h), aluminum hydroxide* (400 mg, PO, q 24 h), nitroglycerine ointment* (1/4 inch/ear, topically, q 12 h if systolic blood pressure > 200 mm Hg), and a vitamin supplement* (1 ml, PO, q 12 h).

The day prior to renal transplantation, serum biochemical abnormalities included high urea nitrogen (65 mg/dl; reference range, 15 to 29 mg/dl), creatinine (4.6 mg/dl; reference range, 0.5 to 2 mg/dl), and phosphorus (7.6 mg/dl; reference range, 2.5 to 6.0 mg/dl) concentrations. Serum total calcium concentration (12 mg/dl; reference range, 9.0 to 11.6 mg/dl) was also slightly high, and the albumin concentration was in the low end of the reference range (2.8 g/dl; reference range, 2.7 to 3.9 g/dl). Results of a CBC were unremarkable, and the urine specific gravity was 1.012. Radiographically, mineralization of both kidneys and the T11-T12, T12-T13, L4-L5, and L5-L6 intervertebral disks was evident (Fig 1).

Additionally, a 1-cm diameter calcified mass was evident in the caudal aspect of the left shoulder joint.

Renal transplantation was performed 1 week later. Administration of cyclosporine* (2 mg/kg [0.9 mg/lb], PO, q 12 h) was instituted 24 hours prior to surgery, and administration of prednisone (2.5 mg, PO, q 12 h) was instituted the morning of surgery. The ionized calcium concentration just prior to surgery was within reference limits (1.4 mmol/L). One day after surgery, serum urea nitrogen concentration was 65 mg/dl, serum creatinine concentration was 3.1 mg/dl, serum phosphorus concentration was 7.2 mg/dl, serum total calcium concentration was 10.1 mg/dl, serum ionized calcium concentration was 1.27 mmol/L, and serum albumin concentration was 2.3 g/dl. Two days after surgery, serum urea nitrogen concentration was 52 mg/dl, serum creatinine concentration was 2.5 mg/dl, serum phosphorus concentration was 6.2 mg/dl, serum total calcium concentration was 10.9 mg/dl, and serum albumin concentration was 2.7 g/dl, but the cat was anorectic. The cat was discharged, because the owners thought the cat would not eat while hospitalized. During the next week, the anorexia persisted, and in addition, the cat began to strain to defecate. Results of serum biochemical analyses were within reference limits, except for a slightly high phosphorus concentration (6.4 mg/dl) and extremely high total and ionized calcium concentrations (13.3 mg/dl and 1.64 mmol/L, respectively). In addition, a small mass was palpable on the right side of the trachea at the level of the thyroid and parathyroid glands. The finding of a cervical mass in conjunction with hypercalcemia prompted measurement of serum concentrations of parathormone (PTH); PTH-related protein (PTH-rp), and 25-hydroxycholecalciferol.

The cat was treated with fluids (0.9% NaCl, IV, at a rate of 2 ml/kg/hr [0.9 ml/lb/hr]) and furosemide (1 mg/kg [0.45 mg/lb], IV, q 6 h); however, serum total and ionized calcium concentrations continued to increase (15.5 mg/dl and 1.71 mmol/L, respectively), and the cervical mass had increased in size so that it was now visible as a protuberance underneath the skin. Serum PTH concentration was 1.7 pmol/L (reference range, 0 to 4 pmol/L), serum 25-hydroxycholecalciferol concentration was 107 nmol/L (reference range, 65 to 166 nmol/L), serum PTH-rp concentration was 0 pmol/L (reference range, < 0.2 pmol/L), and serum

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ionized calcium concentration was 1.95 nmol/L. Exploratory surgery of the ventral aspect of the neck was performed, and a 1.5 x 1-cm right external parathyroid mass was removed (Fig 2).

One hour after surgery, the serum ionized calcium concentration was within reference limits (1.06 mmol/L), and the serum calcium concentration remained normal for the next 14 months without any specific treatment. The gross and histologic appearance of the mass, combined with the rapid decrease in serum calcium concentration following its removal, confirmed that the mass was a functional parathyroid adenoma.

Hypercalcemia is a common postoperative complication in human patients undergoing renal transplantation, with a reported incidence of 8.5 to 53%.1,2 A variety of mechanisms are thought to contribute to the development of posttransplantation hypercalcemia, including persistent hyperparathyroidism, resorption of extraskeletal mineralizations, hypophosphatemia, vitamin D toxicosis, dialysis treatment, and a decrease in the dosage of corticosteroids being administered.

Parathyroid gland hyperplasia with secondary hyperparathyroidism often accompanies chronic renal failure.3,4 This hyperplasia may persist for long periods after renal transplantation and contribute to posttransplantation hypercalcemia. Theoretically, reversal of parathyroid gland hyperplasia can be expected after successful renal transplantation. However, some patients have tertiary hyperparathyroidism with autonomous excretion of excess PTH after successful renal transplantation.1,2,5

Because of the palpable cervical mass, parathyroid hyperplasia or a parathyroid adenoma was suspected to be the likely cause of the hypercalcemia in the cat described in the present report. Serum PTH concentration was within reference limits; however, it was unclear whether this should have been considered abnormal, in that concentration would typically be low with severe hypercalcemia. This finding was similar to findings for dogs with parathyroid hyperplasia.6

Mobilization of metastatic mineralizations can be an important factor contributing to posttransplantation hypercalcemia.3,5,8 Posttransplantation hypercalcemia is more common in human patients that had soft-tissue mineralization prior to surgery. Soft-tissue mineralization was evident prior to surgery in the cat described in the present report and involved both kidneys, the left shoulder joint, and multiple intervertebral disks. Interestingly, on abdominal radiographs obtained 9 months after renal transplantation, the amount of mineralization of the kidneys was unchanged, but only 1 of the intervertebral disks was still mineralized (Fig 3).

Hyperphosphatemia is common after renal transplantation and may contribute to and aggravate posttransplantation hypercalcemia.3 Hyperphosphatemia may result from hyperparathyroidism or exogenous administration of corticosteroids at large dosages or may possibly be a consequence of primary renal phosphate loss.3,7 It has also been suggested that phosphate malabsorption secondary to antacid administration may be a factor in posttransplantation hyperphosphatemia.4,6,10 In the cat described in the present report, however, this was not a consideration, because serum phosphorus concentration was consistently normal or slightly high during the time that the cat was hypercalcemic.

Vitamin D toxicosis was also unlikely to be the cause of the hypercalcemia in this cat. The cat was receiving a vitamin supplement prior to renal transplantation; however, if the supplement had contributed to the hypercalcemia, one would expect that the cat would have been hypercalcemic prior to surgery. Additionally, the 25-hydroxycholecalciferol concentration was 107 nmol/L, which is within reference limits for cats.

Duration of pretransplantation dialysis has been associated with posttransplantation hypercalcemia in people.1,2,5,8,10 In one report,10 54% of patients receiving dialysis for <6 months prior to renal transplantation developed secondary hyperparathyroidism after surgery, whereas 100% of patients receiving dialysis for >12 months did. The aluminum in the dialysate solution is thought to bind phosphorus resulting in hyperphosphatemia. The cat described in the present report did not undergo dialysis prior to renal transplantation.
Another important cause of increases in serum total calcium concentration during the first 6 months after renal transplantation in humans is increases in serum albumin concentration.11 The rate of albumin degradation is markedly increased by corticosteroids, and high doses of corticosteroids given early after transplantation are likely to cause low albumin concentration.12 As the dosage of corticosteroids is decreased with prolonged graft survival, plasma albumin concentration increases.13 In the cat described in the present report, however, hypercalcemia was observed within 1 week after renal transplantation, the prednisone dosage had not been changed, and the plasma albumin concentration had increased only minimally, from 2.7 g/dl to 3.0 g/dl.

The severe hypercalcemia that developed following renal transplantation in this cat appeared to be related to a functional parathyroid adenoma and not persistence of renal secondary hyperparathyroidism (tertiary hyperparathyroidism). The presence of a single enlarged parathyroid gland during surgery, rather than symmetrical involvement of all parathyroid glands, was indicative of an adenoma. Additionally, histologic evaluation of the mass indicated that it was well-demarcated from the adjacent thyroid tissue by a capsule. Other findings that suggested that the mass was an adenoma, rather than a result of hyperplasia, included the identification of neoplastic cells with nuclei exhibiting a mild degree of pleomorphism, the more abundant eosinophilic cytoplasm in these cells, and the presence of oxyphil-like cells. It is important to note that mild hypercalcemia was present in this cat prior to surgery. During the weeks after surgery, the parathyroid mass increased in size in conjunction with a worsening of the hypercalcemia. It is possible that the cat had a parathyroid adenoma prior to renal transplantation that contributed to the mild hypercalcemia prior to surgery. If this were the case, however, an explanation for the rapid increase in size of the parathyroid mass after surgery is not readily apparent.

In humans, development of a parathyroid adenoma following renal transplantation is rare, with only 2 cases reported in the literature.1,12 In these cases, it was thought that development of the parathyroid adenoma represented sporadic primary hyperparathyroidism, rather than tertiary hyperparathyroidism.

In humans and animals, renal failure can result in blunting of end-organ responsiveness to PTH, and posttransplantation hypercalcemia may represent an improvement in responsiveness of the end-organs to PTH. Management of posttransplantation hypercalcemia remains controversial, because the condition may resolve spontaneously, and the effect of hypercalcemia on renal graft function is uncertain. Controversy exists regarding the calcium concentration at which parathyroidectomy should be considered.1 Some experts suggest that mild to moderate hypercalcemia (12 mg/dl) of long duration does not seem to have an adverse effect on the graft or the patient. Others suggest that surgery should be reserved for patients with symptomatic hyperparathyroidism and those with a total serum calcium concentration > 12.5 mg/dl > 1 year after renal transplantation.13 A rapid deterioration in renal function and development of skeletal fractures are clear indications for parathyroidectomy.14,15 In human patients, the best surgical treatment for secondary hyperparathyroidism is open to debate. Resection of 3 of the parathyroid glands with hemicruresis of the remaining gland and total parathyroidectomy with parathyroid gland autografting are effective means of restoring serum calcium concentrations to normal.14,15 In the cat described in the present report, the abnormal right cranial parathyroid gland was removed, and the 3 remaining parathyroid glands were left intact. If hypercalcemia in this cat had been a result of parathyroid hyperplasia, a surgical procedure similar to one of those described for human patients would likely have been more appropriate.

Unlike human patients, the incidence of hypercalcemia following renal transplantation in cats appears to be low. In people, parathyroid hyperplasia with secondary hyperparathyroidism appears to be the most common cause of posttransplantation hypercalcemia, and treatment of these patients remains controversial. In the cat described in the present report, the parathyroid mass was a parathyroid adenoma and not parathyroid hyperplasia. Because of the increasing calcium concentration, continued anorexia, and enlarging cervical mass despite medical management, surgical resection was performed. Fourteen months after surgery, the cat’s serum calcium concentration remains normal, and the cat continues to be free of clinical signs. Although this complication is uncommon, surgeons caring for cats that have undergone renal transplantation should be aware of its possible development, as early recognition and treatment may be important in the successful management of affected cats.

References