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Iatrogenic Hypercalcemia Postrenal Transplantation

Yvelynne P. Kelly[1], Ana Onuchic-Whitford[1], Ivy A. Rosales[2] and Winfred W. Williams[1]

[1]Department of Nephrology, Massachusetts General Hospital, Boston, Massachusetts, USA; and [2]Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence: Yvelynne P. Kelly, Department of Nephrology, Massachusetts General Hospital, Boston, MA 02114, USA. E-mail: ypkelly@bwh.harvard.edu

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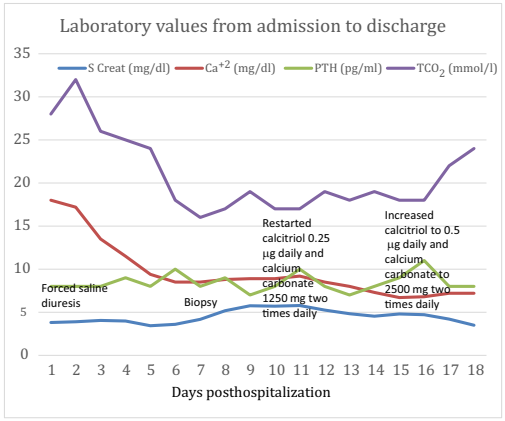
CASE PRESENTATION

A 62-year-old Indian woman with a history of end-stage kidney disease due to hypertension and diabetes, and who had a solitary kidney, presented 3 months after deceased donor renal transplantation with fatigue, bilateral lower extremity pain, and weakness. She had been unable to eat and drink for 2 days before admission, but had remained compliant with her immunosuppressive regimen. She had previously experienced an episode of rhabdomyolysis in the first month posttransplantation due to a calcineurin inhibitor−statin interaction, but had not restarted a statin since then. She denied chest pain, cough, shortness of breath, back pain, headache, visual symptoms, speech difficulties, nausea, vomiting, diarrhea, fever, chills, or rigors. The patient described pain in her thighs bilaterally without overlying skin changes. She denied sick contacts at home and had been voiding without difficulty.

Her laboratory results were notable for a serum calcium of 18.0 mg/dl (4.5 mmol/l), with an ionized calcium of 2.26 mmol/l and a low parathyroid hormone level (PTH) at 8 pg/dl (0.85 pmol/l) and creatinine of 3.9 mg/dl (345 μmol/l). Her oral calcium dosage was increased after her episode of acute rhabdomyolysis because of hypocalcemia associated with hyperphosphatemia during this episode. There was approximately a 3-month interval between the onset of the rhabdomyolysis and the symptomatic hypercalcemia and acute kidney injury (AKI). Pretransplantation, her serum calcium was 9 mg/dl (2.25 mmol/l), with a serum phosphorus of 4.3 mg/dl (1.39 mmol/l), alkaline phosphatase of 82 U/l, and magnesium of 2 mg/dl (0.82 mmol/l). Her last recorded urinalysis several months before transplantation was positive for 1+ leukocyte esterase and 2+ protein with a pH of 5. Posttransplantation, her nadir serum creatinine was 1.1 mg/dl (97 μmol/l), with a serum calcium of 9.3 mg/dl (2.33 mmol/l), phosphorus of 4.7 mg/dl (1.52 mmol/l), magnesium of 1.4 mg/dl (0.58 mmol/l), and alkaline phosphatase of 65 U/l. Her most recent urinalysis before admission was positive for 1+ leucocyte esterase but negative for protein, with a pH of 7.0.

Her medical history was noteworthy for recurrent renal calculi, and she underwent a left native nephrectomy in India in 2012 due to symptomatic obstructive uropathy. Following this, she later underwent a thyroidectomy for a multinodular goiter in 2016, with incidental removal of 2 adenomatous parathyroid glands. Her PTH had dropped from 300 pg/ml (32 pmol/l) to 9 pg/ml (0.95 pmol/l) postoperatively and remained suppressed since that time. The etiology of her precipitous drop in PTH was uncertain, but might have been related to atrophy or absence of the remaining 2 parathyroid glands. She commenced regular oral calcium carbonate supplementation after this, with a substantial increase in her dose (from 500 to 2500 mg 3 times daily) with the addition of regular oral calcitriol of 0.5 μg daily after the recent episode of rhabdomyolysis. During the intervening period, her serum calcium remained within normal limits until her proton pump inhibitor (PPI) was stopped several weeks before admission. Her losartan dose was also up titrated at the same time.

She commenced vigorous saline rehydration with gradual improvement in her total serum calcium and ionized calcium levels. I.v. bolus doses of furosemide were added once she became euvolemic to bring about a forced diuresis. Her calcium levels continued to correct slowly with these measures, and her mental status improved accordingly. She did not require any additional measures to reduce her serum calcium level. However, despite her robust urinary response to high-dose diuretics, her AKI (as measured by creatinine



Pre-admission: calcitriol 0.5 µg daily calcium carbonate 2500 mg three times daily

Figure 1. Graph of serum creatinine (S Crea), calcium (Ca^{+2}), parathyroid hormone level (PTH), and total amount of carbon dioxide (TCO_2) during hospital admission.

clearance) was slow to resolve. Tacrolimus trough levels were at the target of 5 to 7 ng/ml throughout this time. Renal ultrasound revealed new renal calculi within the transplant allograft associated with mild hydronephrosis. However, a subsequent nuclear medicine renogram showed prompt uptake of tracer but delayed excretion consistent with acute tubular necrosis (ATN), but there was no definite evidence of significant obstruction seen. A further workup for hypercalcemia revealed a suppressed PTH at 8 pg/ml (0.85 pmol/l), a 25-OH-vitamin D level of 10 ng/ml, a PTH-related peptide level of 0.9 pmol/l, normal serum protein electrophoresis, and a serum free light chain ratio of 1.14. Her thyroid-stimulating hormone was notably elevated to 16 mIU/l, for which her levothyroxine dose was appropriately increased. Her urinalysis became positive for 1+ protein during the admission, but did not develop any further abnormalities in conjunction with this. She subsequently became hypocalcemic after aggressive saline rehydration and loop diuresis, so calcitriol and calcium carbonate supplementation were re-introduced at approximately 50% of the initial dose (Figure 1).

Her hospital course was further complicated by the development of *Escherichia coli* urosepsis, which required a short critical care admission for antibiotics and i.v. fluid resuscitation. Her mycophenolate mofetil dose was reduced in the setting of associated leukopenia. Her renal allograft function continued to decline, and a renal biopsy was performed. This revealed 2 areas of calcium deposition in the tubules with ATN and interstitial inflammation, which raised the possibility of borderline rejection (Figure 2). There were no acute vascular or glomerular changes. She was given an oral pulse of prednisone in response to this, and her target tacrolimus trough level was increased to 8 to 10 ng/ml, with a gradual increase in mycophenolate mofetil as her leukopenia improved. Her serum creatinine eventually returned to an excellent baseline, with a nadir of 0.8 mg/dl (70 µmol/l). There was no further recurrence of hypercalcemia; however, her PTH level remains suppressed at <10 pg/ml (<1.06 pmol/l) to date.

DISCUSSION

Iatrogenic hypercalcemia due to vitamin D and calcium supplement intoxication is becoming more common because patients frequently use over-the-counter preparations that can vary significantly in terms of concentration and dosage (Table 1).[1] Patients often take more vitamin D than they were prescribed,[2] and sensitivity to vitamin D toxicity might be genetically determined.[3] Hypervitaminosis D, in this case caused by iatrogenic use of oral calcitriol (with a low vitamin D3 level), increases intestinal calcium absorption and causes hypercalcemia. Acute hypercalcemia leads to AKI by direct renal vasoconstriction and by decreases in extracellular fluid volume due to anorexia, nausea, vomiting, and decreased ability to concentrate urine. If chronic, hypercalcemia can lead to the formation of renal calculi and the onset of nephrocalcinosis.[4] In this case, we also hypothesized that an existing AKI, such as that caused by an excessive dosage increase of an angiotensin receptor blocker in the setting of volume depletion, could also have contributed to her acute hypercalcemia by reducing calcium filtration at the glomerulus.[5]

Several studies that directly examined the effect of PPI therapy upon calcium absorption suggest that omeprazole therapy might impair dietary calcium absorption due to hypochlorydia (Table 1). Using a validated single oral radio-tracer method, O'Connell *et al.*[6] showed that among women aged 65 years or older, omeprazole at a dose of 20 mg/d taken for 7 days significantly reduced the absorption of calcium carbonate taken under fasting conditions. Similarly, in a nested case–control study using the UK General Practice Research Database, Yang *et al.*[7] reported that long-term PPI therapy, particularly at high doses, was associated with a risk of hip fracture. This risk progressively increased with the duration of PPI treatment. Limited animal and human studies[8] showed that gastric acid secretion could enhance calcium absorption by facilitating release of ionized calcium from insoluble calcium salts. Calcium solubilization is believed to be important for calcium absorption. This might vary further according to whether a patient is fasting or taking a full oral diet,[9] which might help explain the sensitivity of our patient to hypercalcemia because she

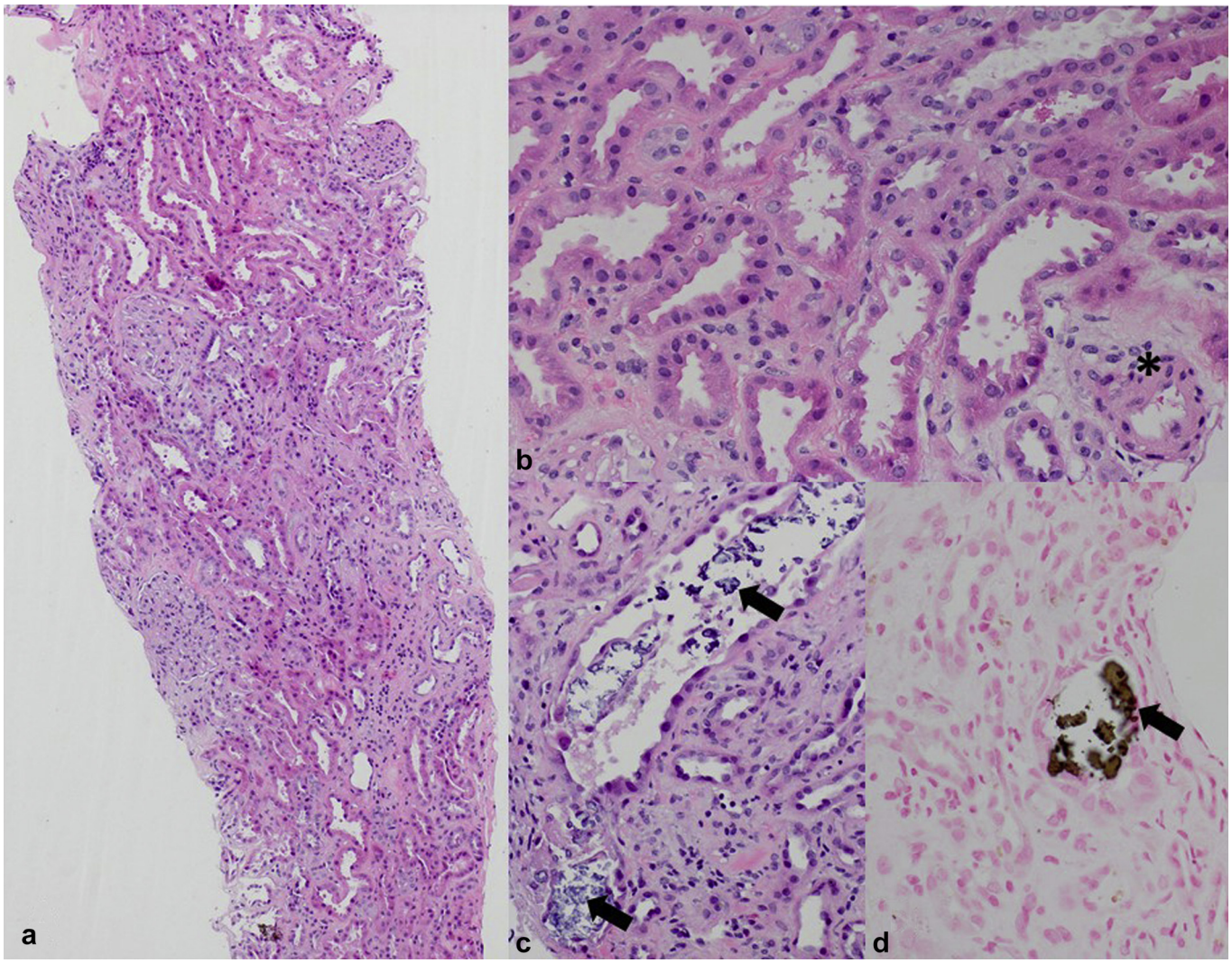


Figure 2. The transplant biopsy showed diffuse tubular injury (a). Interstitial inflammation was sparse (hematoxylin and eosin, original magnification ×10). The tubules showed loss of brush borders and flattened epithelial cells (b). An arteriole (asterisk) appears normal (hematoxylin and eosin, original magnification ×40). Focal areas of tubular injury also showed intratubular calcifications (arrows; hematoxylin and eosin, original magnification ×40; c). Intratubular calcifications (von Kossa, original magnification ×40; d).

Table 1. Learning points

• Acute hypocalcemia is generally transient after rhabdomyolysis; therefore, the dose of calcium supplementation should be monitored and adjusted accordingly.
• Iatrogenic hypercalcemia due to vitamin D and calcium supplement intoxication is becoming more common as patients frequently use over-the-counter preparations that can vary significantly in terms of concentration and dosage of active ingredients.
• Acute kidney injury can contribute to hypercalcemia by reducing calcium filtration at the glomerulus.
• Patients with adynamic bone disease after parathyroidectomy are at greater risk of hypercalcemia due to decreased bone capacity to buffer calcium and to handle a greater calcium load.
• Prolonged use of proton pump inhibitors can lead to hypochlorydia and reduced gastric absorption of calcium.
• Prolonged use of proton pump inhibitors can also lead to excess gastrin secretion and compensatory parathyroid gland hypertrophy and/or hyperplasia, which leads to increased calcium resorption from bones. This did not occur in this case because our patient had adynamic bone disease after a 2-gland parathyroidectomy.
• There is an estimated 1% incidence of *de novo* renal calculi after kidney transplantation. Hyperparathyroidism, hypercalciuria, hypocitraturia, hypophosphatemia, and urinary tract infection have been identified as the main risk factors for this. Renal calculi are not generally associated with decreased graft survival due to early diagnosis and intervention when needed.

stopped PPI usage in the setting of reduced appetite and poor diet.

PPI-induced hypergastrinemia can result in parathyroid hyperplasia and/or hypertrophy and increased PTH secretion, which can help to compensate for the reduction in calcium absorption by increasing osteoclastic activity and calcium mobilization from bones (Table 1). However, in this case, we presume that our patient experienced adynamic bone disease due to previous resection of 2 adenomatous parathyroid glands during a thyroidectomy, which led to long-term relative hypoparathyroidism and a need for regular calcium and vitamin D supplementation after surgery. Adynamic bone disease was therefore a further risk factor for the development of iatrogenic hypercalcemia in this case. This was similarly described by Osorio *et al*. (see Supplementary References) who reported a 12-year-old boy on long-term peritoneal dialysis who

developed severe hypercalcemia and pancreatitis in the presence of adynamic bone disease, as well as the use of vitamin D and calcium carbonate therapy. Meric *et al*. (see Supplementary References) also demonstrated this phenomenon in patients on long-term hemodialysis and patients with advanced chronic kidney disease and severe secondary hyperparathyroidism. Over time, patients can experience a rise in plasma calcium in association with adynamic bone disease and markedly reduced bone turnover. In such patients, hypercalcemia is due to a marked reduction in the bone uptake of calcium after a calcium load, such as calcium carbonate or calcium acetate to treat hyperphosphatemia, as in the case of our patient (see Supplementary References). This iatrogenic hypercalcemia can, in turn, act as a risk factor for the future development of calciphylaxis (see Supplementary References).

A recent meta-analysis (see Supplementary References) described a 1% incidence of *de novo* urinary calculi after renal transplantation, with a mean duration to diagnosis of kidney stones after renal transplantation of 28 $\pm$ 22 months. The main risk factors for development of renal calculi post-transplantation were hyperparathyroidism, hypercalciuria, hypocitraturia, hypophosphatemia, and urinary tract infection (Table 1). Our patient had presumed hypercalciuria in the setting of acute iatrogenic hypercalcemia and subsequently developed a urinary tract infection. As with native kidneys, these calculi can cause AKI due to obstructive uropathy. However, recent studies (see Supplementary References) showed no association between *de novo* renal calculi and allograft survival, likely due to early diagnosis and intervention when needed to prevent progression of the associated AKI. In common with aluminium-related adynamic bone disease, non-aluminium adynamic bone disease is characterized by a tendency to develop hypercalcemia and metastatic calcification. By definition, the ability of bone to buffer a calcium load is reduced in adynamic bone disease. Kurz *et al*. (see Supplementary References) performed calcium kinetic studies using the double isotope technique, iliac crest bone biopsies for mineralized bone histology, histomorphometry, and determinations of serum indexes of calcium and bone metabolism. Patients with low turnover bone disease exhibited a normal or slightly decreased plasma calcium efflux and calcium accretion rate, together with disproportionately low calcium retention. This was particularly relevant for our patient, who received escalating doses of vitamin D and calcium salts as part of management of transient hypocalcemia in the setting of rhabdomyolysis.

In summary, our patient experienced acute, symptomatic, iatrogenic hypercalcemia, with associated AKI, and *de novo* renal calculi 3 months after renal transplantation, due to milk-alkali syndrome in the setting of adynamic bone disease, escalating doses of vitamin D and calcium salts after treatment of rhabdomyolysis, and abrupt cessation of PPI therapy.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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