Improved hypercalcemia after debulking of Uremic Tumoral Calcinosis in a parathyroidectomized patient

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Abstract

Uremic Tumoral Calcinosis (UTC) is a rare complication of chronic kidney disease on dialysis, characterized by large periarticular calcification. Among some cases, hypercalcemia with no conventional etiologies has been reported. We present a case of UTC in which hypercalcemia occurred after parathyroidectomy and introduction of low-calcium containing dialysate. Work-up of hypercalcemia did not reveal any conventional etiology, but hypercalcemia resolved after debulking of the tumor. This change in serum calcium gives us an insight into the mechanism of hypercalcemia, occasionally seen among cases with UTC.

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Introduction

UTC is a complication of chronic kidney disease on dialysis. Its prevalence appears to have increased recently[1,2]. Although histologically benign, UTC is generally progressive, may result in significant pain, immobilization, skin ulceration[3], secondary infection and even death[1,4]. The pathogenesis of UTC is not fully understood. Among some cases, hypercalcemia with no conventional etiologies has been reported. It is hypothesized, in those cases, that UTC can be an endogenous supply of calcium[3], mobilizing calcium into serum. To our knowledge, our case is the first report in the English literature to describe post-excisional improvement of hypercalcemia in UTC.

We review the literature regarding the pathogenesis of UTC, its association with hypercalcemia, and treatment.

Case Report

47 year-old multiethnic-Hawaiian woman began peritoneal dialysis in 1993 because of progression of idiopathic glomerulonephritis. She received a living-related renal transplant in 1997. However, she suffered a rejection in 1999, and subsequently started on hemodialysis (3hr 30min Dialysate: Ca 2.5mEq/L, K 2.0mEq/L, Dialyzer MCA 160, Blood Flow Rate 350cc/minute) with the following medications; calcium carbonate 1g (=400mg of elemental calcium) orally, 3 times a day, calcitriol 1mcg intravenously, 3 times a week on each HD, (subsequently switched to oral form), Epogen 10,000 units subcutaneously, 3 times a week on each HD. Three days after, laboratory data were as follows: total calcium (Ca) 7.5 mg/dL, phosphate (P)7.4mg/dL, albumin 3.5 g/dL.

She was discovered to have a large calcified mass around the right hip in December 2001 (Figure 1) but refused further evaluation. The laboratory results one month prior were as follows: intact parathyroid hormone (iPTH) 390pg/mL (reference range 12.6-53.5pg/mL), K 5.9mEq/L, Cl 96mEq/L, HCO_3 20mEq/L, BUN 92mg/dL, Cr 10.2mg/dL, Ca 10.1 mg/dL, P 7.3mg/dL, albumin 3.8 g/dL, alkaline phosphatase (ALK-P) 147 U/L (reference range 39-117U/L). Because of increased Ca×P product, calcitriol was discontinued, and calcium carbonate was switched to sevelamer 800mg, orally, 3 times a day. Diet restriction, especially phosphate restriction was discussed. Repeat renal transplantation was suggested to the patient as an option, but she was reluctant because of her previous reaction to steroids (i.e. palpitations, and demonic dreams). She was not always compliant to medications and diet restriction. As a result, her indices for secondary hyperparathyroidism did not improve as represented in the following: iPTH 306 pg/mL, Ca 9.2 mg/dL, P 7.8mg/dL in December 2002.

Her pain around the right hip slowly progressed to the point where she opted for total parathyroidectomy in an attempt to obtain symptomatic relief. Despite the operation performed in February 2003, her pre-dialysis serum calcium level remained high: Ca 11.0 mg/dL, P 8.4mg/dL, albumin 3.1g/dL, ALK-P 173 U/L. Therefore, beginning February 2003, calcium concentration of dialysate was lowered from 2.5mEq/L to 2.0mEq/L (3hr 30min, Dialysate: Ca 2.0mEq/L, Dialyzer F70NR, Blood Flow Rate 400cc/minute). However, the mass remained unchanged, and her serum calcium appeared to even increase to 11.9 mg/dL.

At that point, an extensive workup was completed for her hypercalcemia. The results, including serum vitamin D levels, parathyroid hormone related peptide, serum protein electrophoresis and bone scan, were unrevealing (Table1). Hypercalcemia appeared to be due to mobilization of calcium from the large calci-

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fied mass. Serum calcium levels taken from different venous sites failed to demonstrate differences between the sites (Table1).

In June 2003 the patient presented with a complaint of right hip pain after a fall and was subsequently admitted for pain control. MRI showed a 27×14×17 cm calcified mass with fluid-filled loculations, which is characteristic for UTC[5], in the soft tissues of the right hip and proximal femur (Figures 2, 3). Compared to the previous film in 2001, the mass was essentially unchanged. The patient continued to have intractable pain refractory to opioids. She elected to undergo an excision of the mass because of the pain. Pre-operative core needle biopsy showed calcification and benign soft tissue fragments with no evidence of neoplasm.

In July 2003, excision and debulking of the mass was performed. Because of too much intermingling of the soft tissue with the mass, a clean dissection could not be performed. Histological findings showed calcifications surrounded by fibro-fatty tissue and skeletal muscle without evidence of neoplasm. Eleven days after the surgery the patient was discharged in good condition.

Twenty-three days after the surgery, however, the patient presented with fever, chills and increased pain at the surgical site. Foul-smelling, purulent material was draining from the incision site. She was admitted and intravenous antibiotics were started. Her regular medications were not changed. Débridements of the right thigh were carried out on multiple occasions because of non-healing wound infection. Wound cultures grew *Proteus mirabilis* and *Enterococcus* species. Despite vigorous treatment, her wound never healed. On post-operative day #67, she died from sudden cardiopulmonary arrest. Autopsy was not performed. Her post-operative calcium levels had dropped from 10.8mg/dL (post-operative #1) to 8.5mg/dL (post-operative #34). Her serum albumin levels remained stable 2.9g/dL (post-operative day #8), 3.2g/dL (post-operative #23), 3.2g/dL (post-operative #65).

Table1.— Findings on Workup for Hypercalcemia.

	Result	Reference Range
Ca (mg/dL)	13	8.4-10.2
Phos (mg/dL)	5.6	2.6-5.4
Albumin (g/dL)	3.5	3.5-5.0
VitaminD (25-OH) (ng/mL)	<5	20-57
VitaminD (1,25(OH)2) (pg/mL)	9	15-75
serum Aluminum (mcg/L)	6	<30
PTHrP (pmol/L)	0.7	<1.3
intact PTH (pg/mL)	<1	7-53
Cosyntropin Stimulation Test		
Serum Cortisol levels	21.3 (baseline)	2-24
(mcg/dL)	28.5 (30min)	
	27.5 (60min)	
Serum Ca levels from the different sites (mg/dL)		
Right antecubital vein	11.3	8.4-10.2
Right femoral vein	11.3	8.4-10.2
Left femoral vein	11.6	8.4-10.2
Serum Protein Electrophoresis:	Normal	
Bone scan	No tumor	

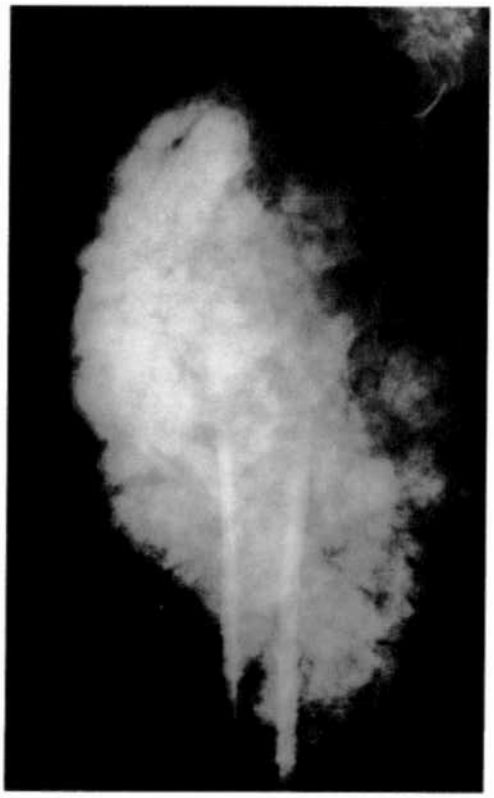
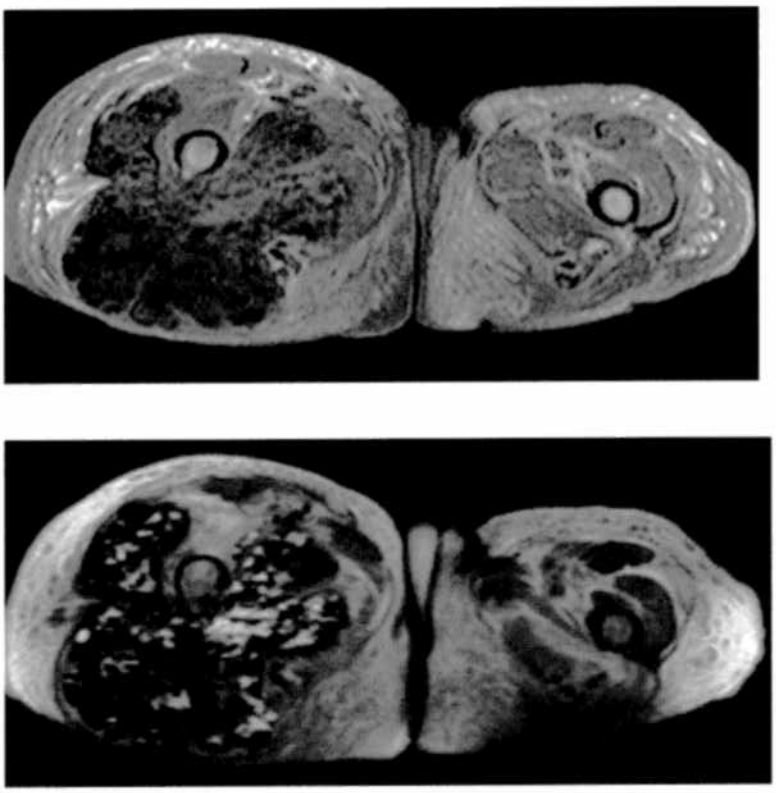


Figure 1.— X-ray of the hip: Extensive soft tissue calcification around the right hip and over the region of the right upper sacro-iliac area.

Discussion

Tumoral calcinosis (TC) is characterized by massive calcium-phosphate deposits, usually periarticular in location. The etiology may be divided into two categories: primary and secondary. Primary TC is postulated to be an autosomal recessive disorder[6]. Secondary TC, known as uremic TC (UTC), is well recognized in patients with chronic kidney disease on dialysis.

The exact pathogenesis of UTC is not fully understood. The following factors are associated with UTC[4,7-9]: 1)increased calcium-phosphate product (Ca×P), 2)impaired mineralization of the bone (renal osteodystrophy), 3)secondary hyperparathyroidism, 4)aluminum overload, 5) local factors, such as tissue



Figures 2.3.— MRI showed a calcified mass with fluid-filled loculations in the soft tissues of the right hip and proximal femur.

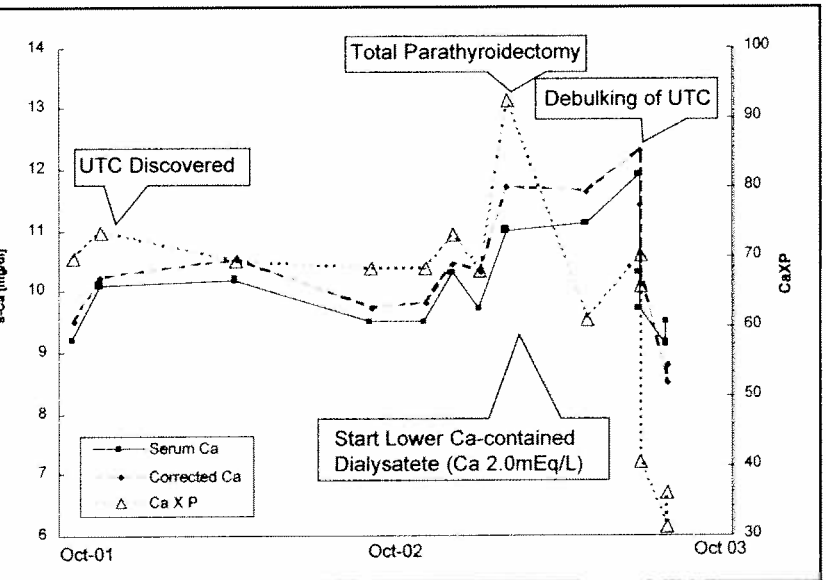


Figure 4.— Serial changes in serum Ca, corrected Ca by serum albumin (corCa), and Ca×P.

The corrected Ca value is obtained from the following formula. corCa=0.8×(4-serum albumin) + measured Ca (Jacques Wallach. *Interpretation of Diagnostic Tests* 7th ed. Lippincott Williams&Willkins, Philadelphia, PA: 2000; 46)

injury, hematoma, infection, and injection. There are recent cases lacking evidence of hyperparathyroidism[1,8,10-12]. Therefore, many authors consider increased Ca×P to be the most important predisposing factor for recent cases of UTC. [1-4, 12, 13].

The prevalence of UTC appears to have increased to 3% in 1990-97[12] from 0.5% in the period of 1968-1988[8]. Some authors speculate that this increase may be due to increased use of calcium-based phosphorus binders and vitamin D, and long-term use of dialysate with relatively high Ca concentration, all of which could result in positive calcium balance[1,11,12].

Hypercalcemia is frequently observed in UTC[8,12]. As in our case, hypercalcemia in some UTC cases cannot be attributed to conventional etiologies such as hyperparathyroidism, excess of vitamin D, malignancy, or granulomatous diseases. It appears that UTC itself can cause hypercalcemia independent of parathyroid hormone, or vitamin D status. The postulated mechanism is increased release of calcium from UTC in the presence of adynamic bone disease, in which condition mineralization of calcium into bone is impaired [1,8]. This hypothesis is supported by the following facts: 1) Animal models demonstrated that calcium resorption from soft tissue calcification causes significant hypercalcemia in parathyroidectomized rats with normal and abnormal renal function[14]. 2) Transient increase in serum calcium and phosphate[2,10], as well as urinary excretion of calcium and phosphate[10], during regressions of UTC in cases on dialysis or with renal transplants. 3) Induction of a negative calcium balance appears to further facilitate mobilization of calcium from UTC [2]. Interestingly, it appears that the more aggressively a negative balance of calcium is induced, the faster UTC regresses but also the more likely severe temporal hypercalcemia may develop[2,13]. In retrospect, the worsened hypercalcemia in our case after total parathyroidectomy and introduction of low calcium-dialysate may be due to the same mechanism, although we did not observe any appreciable decrease in the size of UTC during the course.

To our knowledge, our case is the first report in the English literature to describe post-excisional improvement of hypercalcemia in UTC. Medications cannot explain this change, because calcium-containing medications and vitamin D were discontinued during the hospitalization prior to surgery, yet hypercalcemia persisted. In contrast, her serum calcium fell significantly after the debulking. We cannot exclude other possibilities for this drop, such as decreased oral intake postoperatively resulting in lower calcium and phosphorus intake. Mitigating against this possibility is the fact that her serum albumin levels had been stable postoperatively.

Treatment of UTC is not established[1]. Six cases of successful medical treatments with complete or

significant regression of UTC have been reported[2,3,11-13,15]. In these cases, combined modalities were used to induce a negative CaxP balance (i.e. extended dialysis time, including daily nocturnal home hemodialysis[3], use of high-performance membrane dialyzers, use of low calcium dialysate in most cases). Regression of UTC has also been reported in those who received renal transplants[10,12,15]. None of these cases has reported recurrence of UTC or treatment-related morbidity or mortality after the regression. Thus, treatment with the above calcium-reduction regimens appears to be safe and durable even though reported numbers are small.

In summary, UTC, although rare, is one of the potentially life-threatening complications of long-term dialysis. The prevalence is apparently increasing. This may be related to recent therapeutic modalities causing positive calcium balance. UTC itself may cause hypercalcemia independent of parathyroid hormone. Given its likely progression to a debilitating condition, aggressive medical treatment targeting negative calcium balance is recommended before contemplating surgery, particularly when the UTC is too large for complete excision.

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