

## Case Report

# IDIOPATHIC SPORADIC TUMORAL CALCINOSIS OF THE HIP: SUCCESSFUL ORAL BISPHOSPHONATE THERAPY

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### ABSTRACT

**Objective:** To report the case of a woman with idiopathic sporadic tumoral calcinosis treated successfully with orally administered bisphosphonates.

**Methods:** We report the clinical, laboratory, and imaging findings and describe the clinical course of tumoral calcinosis. The literature was reviewed for the pathophysiologic features and strategies for treatment of tumoral calcinosis. In addition, we specifically reviewed the use of bisphosphonates in tumoral calcinosis and the possible pharmacologic basis for the therapeutic benefit.

**Results:** A 45-year-old woman presented with a 6-week history of left-sided pain in the hip in conjunction with stiffness after a trivial fall 4 weeks before the onset of symptoms. The findings on conventional radiology of the hip joint were consistent with tumoral calcinosis of the left hip. The biochemical profile of the patient was unremarkable. Oral treatment with alendronate, 70 mg once a week, yielded alleviation of symptoms within 12 weeks. Radiology of the left hip repeated after a period of 15 months revealed notable regression of the calcified lesion.

**Conclusion:** Bisphosphonate therapy may be considered as an alternative to surgical treatment in patients with idiopathic sporadic tumoral calcinosis. (**Endocr Pract.** 2007;13:000-000)

### Abbreviations:

**FGF-23** = fibroblast growth factor-23; **FTC** = familial tumoral calcinosis; **TC** = tumoral calcinosis

### INTRODUCTION AND BACKGROUND

Tumoral calcinosis (TC) was a term first used by Inclan et al (1) in 1943 to describe a dense, nodular, calcareous mass in the periarticular subcutaneous tissue. The mass most often occurs around the hips, elbows, shoulders, or feet but may occasionally be found elsewhere. The calcification usually takes the form of calcium hydroxyapatite crystals surrounded by a foreign body giant cell and histiocytic reaction. There seem to be 3 distinct varieties of TC with considerably different biochemical profiles and pathophysiologic features. The first type is the sporadic variety, in which no biochemical abnormalities or family history of a similar illness is elicited. The second type of TC is usually attributable to metabolic disturbances associated with the calcium  $\times$  phosphate solubility product, the common causes being chronic renal failure, hypervitaminosis D, and very rarely primary hyperparathyroidism. The third type, which is familial, is associated with a definitive gene defect on the long arm of chromosome 2. Biochemically, patients with the familial variant of the disease have abnormal serum phosphate levels and increased 1,25-dihydroxycholecalciferol levels.

The idiopathic sporadic variety is uncommon, and no definitive treatment has been suggested other than surgical excision, which is associated with the risk of recurrence of the tumor. When the disease is caused by renal failure, various management strategies, including dietary phosphate restriction, phosphate binders, intensification of dialysis, dialysis with use of a low-calcium dialysate, and parathyroid excision, have been attempted with some success. In at least 3 reports in the literature, bisphosphonates were used with some success in the treatment of renal failure-associated TC.

In this report, we describe the successful treatment of a middle-aged woman with idiopathic sporadic TC involving the hip with the use of orally administered alendronate during a period of 15 months.

### CASE REPORT

A 45-year-old woman presented with a 6-week history of pain and stiffness of the left hip joint. Movements of the left hip were painful, and she could not lie on her left

Submitted for publication February 19, 2006

Accepted for publication June 13, 2006

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side because of the pain. She related a history of a minor fall onto her left side, which she had sustained 4 weeks before the onset of her symptoms. She had no systemic symptoms. On examination, the left hip joint was tender, and movements of the left hip were considerably restricted. Findings on general physical examination were unremarkable.

Conventional radiology of the hip joint revealed chunky calcification adjacent to the lateral margin of the left hip joint. No underlying destruction of bone, periosteal resorption, or soft tissue swelling was noted. The fat planes around the joints were not displaced (Fig. 1).

The findings on radiography of the hip were consistent with TC. The patient denied having any previous episodes of joint pains or any family history of similar disorders. She had no clinical evidence of hyperparathyroidism, renal disease, or systemic sclerosis. On laboratory studies, she had normal results of renal function tests and normal fasting serum calcium and phosphate levels (Table 1).

Bisphosphonate therapy was initiated in the form of orally administered alendronate, 70 mg given on a once-weekly basis. On follow-up examination after 3 months of therapy, the patient was free of pain. Bisphosphonate treatment was continued, and her case was reviewed after a period of 1 year. She continued to be free of symptoms.

Radiography of the left hip done at that time revealed appreciable regression of the calcification, with only a minimal residue of the initial pathologic finding (Fig. 2).

## DISCUSSION

TC is a rare clinical disorder of unknown origin. It was first mentioned as the so-called progressive lipocalcinogranulomatosis by Teutschlaender (2) in 1935. The main clinical signs are calcium deposits in the soft tissues around the joints, often at multiple sites but not always concomitantly, with an asymptomatic increase in size. Symptoms, if present, are related to functional impairment or mechanical neural irritation. There is no evidence of a malignant lesion or bone involvement. The sporadic category of TC manifests as a diagnostic challenge to the clinician. Patients with the sporadic presentation have no history of renal disease and no family history of TC; thus, the diagnosis is difficult. In such cases, careful attention to the plain radiographic features of amorphous calcification should alert clinicians to the possibility of this disease. In cases in which the imaging studies are not diagnostic, a biopsy is necessary.

### Pathophysiology of TC

The exact pathophysiologic process in TC is not clear. The most likely explanation is that the process is initiated

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**Fig. 1.** X-ray film of hips at time of presentation of study patient, revealing chunky calcification adjacent to lateral margin of left hip joint. L = left side.

**Table 1**  
**Laboratory Values of Study Patient**  
**at Time of Presentation and After 15 Months**  
**of Treatment With Alendronate**

Serum measurement	Baseline	After 15 months	Normal range
Calcium (mg/dL)	9.8	9.4	8.3-10.4
Phosphate (mg/dL)	3.1	3.2	3.5-5.0
Albumin (g/dL)	3.8	3.6	3.5-5.0
Alkaline phosphatase (U/L)	104	95	40-125
Creatinine (mg/dL)	0.8	0.7	0.5-1.4

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by microtrauma in the periarticular tissues, causing small hemorrhages. The patient described in this report had a trivial fall preceding the diagnosis, which may have initiated the process. Subsequently, foamy histiocytes aggregate around these microhemorrhages. The histiocytes initiate tissue damage, including collagenolysis, which leads to the formation of cystic cavities containing degraded products of the damaged tissue. These cavities are subsequently lined by osteoclastlike giant cells and histiocytes. The key factors for this transformation seem to be movement and friction, both of which are generated because of the periarticular location of the lesion. The damaged tissue and degraded cell membranes form a nidus for calcium phosphate binding. Calcium phosphate may be deposited as hydroxyapatite crystals or in its amorphous form. Ultimately, the cavities fill with calcified material, become encapsulated by fibrous tissue, and ossify. The osteoclastlike giant cells are pivotal in this process of calcification. Eventually, the process becomes self-sustaining. The calcified deposits themselves cause tissue trauma, resulting in an increasing mass of calcified material (3).

Calcium phosphate by itself is a fairly insoluble compound. It is precipitated in tissues only when its solubility product exceeds  $70 \text{ mg}^2/\text{L}^2$ . Any metabolic condition that increases either the serum concentration of calcium or, more frequently, the serum concentration of phosphate can lead to ectopic deposition of calcium phosphate in the tissues. This is the explanation for the formation of tumors in the presence of renal failure and vitamin D toxicosis. Therefore, TC may be a primary sporadic phenomenon, occurring as a response to microtrauma, or it may be related to metabolic conditions that increase the calcium  $\times$  phosphate solubility product (4).

Familial TC (FTC) is a severe autosomal recessive disorder, which is common among people of African descent. The biochemical nature of the metabolic abnormality is only partially understood. This condition, however, is associated with 2 genetic defects, the first of which



**Fig. 2.** X-ray film of left hip after 15 months of bisphosphonate therapy, documenting notable regression of ectopic calcification. *L* = left side.

has been mapped to chromosome 2q24-q31. This region of the chromosome includes the gene *GALNT3*, which encodes a glycosyltransferase responsible for initiating mucin-type *O*-glycosylation (5). The genetic defect in FTC was identified as biallelic loss-of-function mutations

in the *GALNT3* gene. Recently, Benet-Pages et al (6) reported a homozygous missense mutation (S71G) in the *FGF23* gene in a boy with hyperphosphatemia, renal phosphate retention, and painful swelling of the elbows. Shortly thereafter, Larsson et al (7) reported the same biallelic *FGF23* (S71G) mutation in 2 sisters with FTC.

Fibroblast growth factor-23 (FGF-23) is a novel agent implicated in the regulation of phosphate homeostasis. Most of the evidence for the role of FGF-23 in phosphate regulation has been derived from studies among patients with tumor-induced osteomalacia. The increased levels of FGF-23 secreted from the tumor have been postulated as the cause of phosphaturia from the kidneys and the development of subsequent bone disease. FTC would be considered the metabolic opposite of tumor-induced osteomalacia, with low levels of FGF-23 being associated with phosphate retention and subsequent increase in the serum phosphate levels being responsible for ectopic calcification (8). Biochemically, this condition is associated with high serum phosphate and high 1,25-dihydroxycholecalciferol (vitamin D) levels.

Attempting to unify these 2 molecular defects is challenging. A simple explanation would be to speculate that the glycosyltransferase coded by the *GALNT3* gene glycosylates FGF-23 and that appropriate glycosylation is critical for the stability, maturation, and function of FGF-23. Currently, however, there is no evidence to link these 2 defects (8).

### Therapeutic Options

With regard to therapeutic options, surgical excision has been recommended in patients with pain, recurrent infection, ulceration, and functional impairment attributable to TC of any cause. Surgical trauma itself, however, may stimulate further calcification, and recurrence is common after excision—especially in patients with FTC and secondary TC. In infants with sporadic TC, surgical treatment is the preferred management and is not associated with the same risk of recurrence as in adults (9).

Pharmacologic therapy for the tumors can be considered as an alternative to surgical excision. The therapeutic strategies for the medical treatment differ with the pathogenic mechanism of TC. In patients with renal failure, the primary goal of therapy is the lowering of plasma phosphate levels. Clinicians have attempted to achieve this goal with dietary phosphate restriction, use of phosphate binders, intensification of dialysis therapy, use of low-calcium dialysate, and parathyroidectomy in patients with severe secondary hyperparathyroidism (9). The role of parathyroidectomy is a controversial subject because benefits are not found in most cases, and progression of the neoplasm has been observed in a few cases (10) and partial remission in others (11). Various authors recommend subtotal parathyroidectomy as a standard indication in patients with TC, although its therapeutic benefit has yet to be substantiated (12). The definitive therapy for TC in

patients with renal failure would be renal transplantation (13).

In FTC, the focus of therapy to date has been to decrease the serum phosphate levels. Phosphate deprivation has been achieved by the use of aluminum hydroxide to bind dietary phosphates. Reports have suggested that the addition of acetazolamide to phosphate binders may further reduce serum phosphate levels by its phosphaturic actions on the kidneys (14).

### Use of Bisphosphonates and Possible Mechanism of Action

The ~~in vitro effect of bisphosphonates to inhibit calcium phosphate crystal formation~~ was demonstrated almost 4 decades ago (15). Subsequent work confirmed the effect of bisphosphonates in alleviating soft tissue calcification in experimental renal osteodystrophy. The first report to demonstrate clinical benefit of bisphosphonates was published in 1978; in that study, 1 patient among 5 treated with bisphosphonates had regression of uremic TC (16). A second study (in 1999) reported clinical benefit with use of etidronate in combination with calcitonin in TC in a patient with sarcoidosis and renal failure, demonstrating a reduction in the size of the tumor (17). Initial published reports regarding the use of bisphosphonates in metastatic calcification were disappointing. In 1998, Kuriyama et al (18) used bisphosphonates and calcitonin in combination with continuous ambulatory peritoneal dialysis and vigorous transient hemodialysis with use of a low-calcium dialysate for successful treatment of symptomatic TC associated with renal failure. Subsequently, Phanish et al (19) demonstrated therapeutic benefits of adding bisphosphonates to the therapy for a patient with TC and renal failure. We could not find any published reports of the use of bisphosphonates in the treatment of sporadic TC or FTC.

Bisphosphonates are synthetic compounds that have physiochemical effects very similar to polyphosphates. They bind to the surface of calcium hydroxyapatite crystals to inhibit further crystal formation and aggregation. This action inhibits further mineralization. Moreover, they may have additional physiochemical effects that can promote dissolution of the crystals already formed. In addition, bisphosphonates have multiple effects on the osteoclast cells, including the following: (1) direct inhibition of osteoclast activity, (2) decrease in the recruitment of osteoclasts, and (3) reduction of the survival of osteoclasts by apoptosis (20). The pathogenesis of TC involves the role of osteoclastlike giant cells in addition to histiocytes. A similar action on these giant cells as on normal osteoclasts has been postulated in forming the basis of the therapeutic role of bisphosphonates in TC (19).

Spontaneous regression of the tumor has been reported in 2 case reports involving infants with TC (21,22). No reports in the literature have described spontaneous regression of TC among adults with this disease.

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## CONCLUSION

Sporadic TC in adults is an uncommon disease with no known definitive pharmacologic therapy to date. The calcification in the periarticular soft tissue is mediated by osteoclastlike giant cells along with histiocytes. Surgical treatment, though definitive, is associated with the risk of recurrence of the tumor. Medical treatment of sporadic TC with bisphosphonates may be a safe option. The possible mechanisms of action of bisphosphonates are (1) the inhibition of the osteoclastlike giant cells and (2) the direct inhibition and regression of calcium phosphate crystallization. Hence, treatment with bisphosphonates should be attempted in patients with sporadic TC before surgical intervention is considered. Bisphosphonate therapy may also be of benefit in the familial variant of the disease because the pathophysiologic process of the tumor formation is very similar.

## DISCLOSURE

The authors have no conflicts of interest to disclose.

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