Periarticular Tumoral Calcinosis and Hypercalcemia in a Hemodialysis Patient Without Hyperparathyroidism: A Case Report

Brian Eisenberg, Antonios H. Tzamaloukas, Michael F. Hartshorne, Margaret B. Listrom, Elizabeth R. Arrington, and Donald J. Sherrard

Services of Nuclear Medicine, Medicine, Radiology, and Pathology, VA Medical Center, Albuquerque, New Mexico and Department of Medicine, VA Medical Center, Seattle, Washington

We present a case of a 58-yr-old male to illustrate the scintigraphic, roentgenographic, clinical, and pathologic features of periarticular tumoral calcinosis that occurred in a hemodialysis patient. Soft-tissue calcifications developed 3 yr after onset of hemodialysis, became progressively larger during the ensuing five years, and culminated in voluntary withdrawal from dialysis because of the extreme discomfort and lack of mobility that resulted from the calcinosis. Histologically, an aplastic disorder was present with very low bone formation. On bone scintigraphy, intense calcium uptake in soft tissues implied that it was metabolically active. We hypothesize that this high metabolic activity contributed to the persistent hypercalcemia observed during the patient's last year of life.

$\mathbf{M}$etastatic calcifications of soft tissues are complications of chronic renal failure (*1*). Unlike vascular calcifications, which are common in hemodialysis patients and are considered by many to be the result of dystrophic changes in the vascular wall (*2,3*), calcifications in other soft tissues are uncommon and are considered to be the result of either high calcium-phosphorous product (*2,4*), or calciphylaxis. Calciphylaxis is a syndrome of ischemic necrosis of tissues (fingers and toes) associated with extensive calcification in soft tissues, including vessels, and usually responding favorably to parathyroidectomy (*5*). Hyperparathyroidism is the disorder usually associated with metastatic calcifications, including tumoral calcinosis, in dialysis patients (*4*). Tumoral calcinosis consists of extensive calcifications of periarticular tissues, primarily around the large joints, manifested clinically by palpable and visible

tumors. Another form of tumoral calcinosis is seen in patients without advanced renal failure, is familial, and is thought to result from a defect in phosphate handling in the proximal tubules (*6*). We present a case report of a patient who was not hyperparathyroid, yet developed massive soft-tissue calcifications three years after the onset of hemodialysis. The calcifications were associated with aplastic bone disease and severe hypercalcemia. These soft-tissue calcifications, highly metabolically active on bone scintigraphy, combined with the aplastic bone disease on bone biopsy, imply that the increased calcium turnover from the soft tissues and the inability of the aplastic bone to incorporate the excess calcium may have been a potential step in the pathogenesis of hypercalcemia in this patient.

CASE REPORT

A 50-yr-old male began hemodialysis in December 1981. His medical history showed only hypertension, which was diagnosed in 1979. At that time his BUN was 19 mg/dl. He was treated with hydrochlorothiazide, captopril, and metoprolol. The patient presented in December 1981 with poorly controlled blood pressure, decreased appetite, nausea, vomiting, weight loss, weakness, and exertional dyspnea. On admission, his serum creatinine was 16.9 mg/dl. The kidneys were small by ultrasound measurement. No cause of renal failure was detected. Renal biopsy was not performed.

The early course of dialysis was characterized by poor control of serum phosphorus with persistent hyperphosphatemia and by the development in 1984 of persistent ascites, managed by a Le Veen shunt. Tumoral calcinosis was detected in 1985. Bone biopsy performed at that time revealed adynamic uremic osteodystrophy with minimal aluminum content. The tumoral calcinosis progressed.

In 1987, the serum parathormone (PTH, middle molecule, New Mexico Reference Laboratory, Albuquerque, NM) was 4,990 pg/ml [normal range (nr) 100-360]). Hypercalcemia was noted for the first time at the beginning of 1988, and became progressively worse. In January, 1989, the patient was transferred to the Albuquerque VA Medical Center from another institution with mental confusion and the following lab values:

serum calcium 13.1 mg/dl (nr 8.5-10.5); phosphorus 4.5 mg/dl (nr 2.8-4.6); albumin 2.4 gm/dl (nr 4.0-5.5); alkaline phosphatase 71 U/L (nr 30-115); bilirubin 0.4 mg/dl (nr 0.4-1.1); SGOT 32 U/L (nr 5-35); serum PTH (IRMA, Nichols, CA) 11 pg/ml (nr 10-65); serum 1,25 dihydroxycholecalciferol (New Mexico Reference Lab, Albuquerque, NM) 8 pg/ml (nr 20-76); and random serum aluminum level 103 ng/ml (Mayo Clinic, Rochester, MN). Of note is the normal PTH value at this time and throughout the remainder of the patient's life.

He was treated by lowering the dialysate calcium concentration from 7 mg/dl to 2 mg/dl. Serum calcium decreased to 9.5 mg/dl immediately post-hemodialysis and 11.0 mg/dl predialysis, while serum albumin remained at 2.4-2.7 g/dl. His mental state improved. In the face of severe hypoalbuminemia, serum calcium between 9.5 and 11.0 mg/dl represents hypercalcemia (7). Repeated PTH (IRMA, Nichols, CA) 2 wk after lowering of serum calcium was 8 pg/ml. In February 1989, a repeat bone biopsy was performed in a standard manner (8), and again disclosed an adynamic disorder, but aluminum was present. The bone histology revealed a decrease in osteoid, decreased numbers of osteoblasts, absent tetracycline uptake, and a moderate increase in aluminum staining (15%-20% of cancellous bone surfaces). Vitamin D preparations were not prescribed or taken by the patient at any time while he was on hemodialysis. There was no family history of tumoral calcinosis.

Bone scintigraphy and radiographs obtained during the last admission revealed multiple areas of dramatic soft-tissue calcification, which, for the most part, corresponded to clinically palpable areas. A total-body bone scan was performed after the intravenous administration of 25 mCi of technetium-99m-

methylene diphosphonate (^{99m}Tc-MDP). Images revealed extensive bone agent uptake in the soft tissues surrounding the shoulders, right chest wall, hips, and left fibular head (Fig. 1). A limited plain film view of the fibula with corresponding scintigraphic image showed extensive vascular calcification as

FIGURE 1
Anterior view from total-body bone scan reveals extensive soft-tissue uptake around the hips, shoulders (left greater than right), the right chest wall, and the left fibular head.
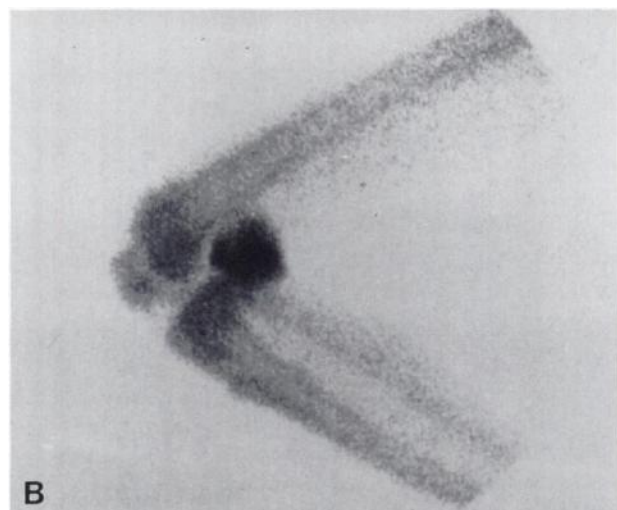

FIGURE 2
(A) X-ray, anterior view of left knee region reveals extensive vascular calcification as well as extraosseous calcification around the left fibular head. (B) Left lateral view from total-body scan reveals soft-tissue uptake of ^{99m}Tc-MDP surrounding the left fibular head corresponding to the calcifications seen on plain film.
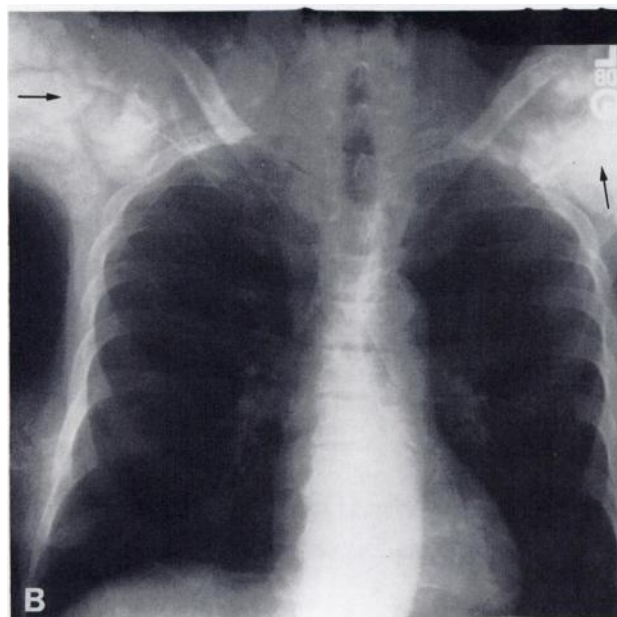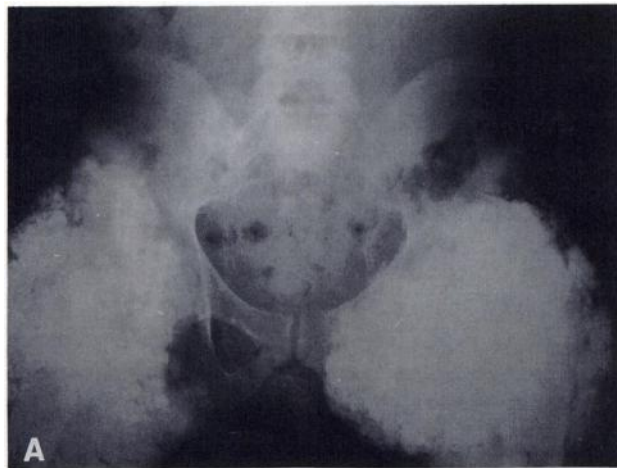
FIGURE 3
(A) Plain film of the pelvis reveals massive soft-tissue calcifications surrounding the hips. (B) Plain film of the chest reveals calcifications surrounding both shoulders (arrows).

FIGURE 4
Plain film of the abdomen showing splenic artery calcification in the left upper quadrant (arrowhead) as well as other abdominal vascular calcifications.

well as the noted soft-tissue abnormality (Fig. 2A-B). Plain films of the hips, (Fig. 3A) and the shoulders, (Fig. 3B) revealed the massive soft-tissue calcifications which explained the patient's lack of mobility in these joints. Plain films of the abdomen showed extensive arterial calcifications (Fig. 4). Hand x-rays revealed no evidence of erosions along the radial aspect of the middle phalanges (commonly seen in hyperparathyroidism), but did have extensive areas of vascular and soft tissue calcifications (Fig. 5).

The patient suffered from greatly restricted joint movement as a result of the widespread tumoral calcinosis and became bedridden. He subsequently developed a sacral decubitus ulcer. He decided soon after the second bone biopsy to discontinue hemodialysis. He died 2 wk later. At autopsy, metabolically quiescent bone was found in several sites, including ribs, humeral and femoral heads, and vertebrae. Osteitis fibrosa cystica was universally absent. Large periarticular deposits of calcium were found in the regions of hips, shoulders, knees,
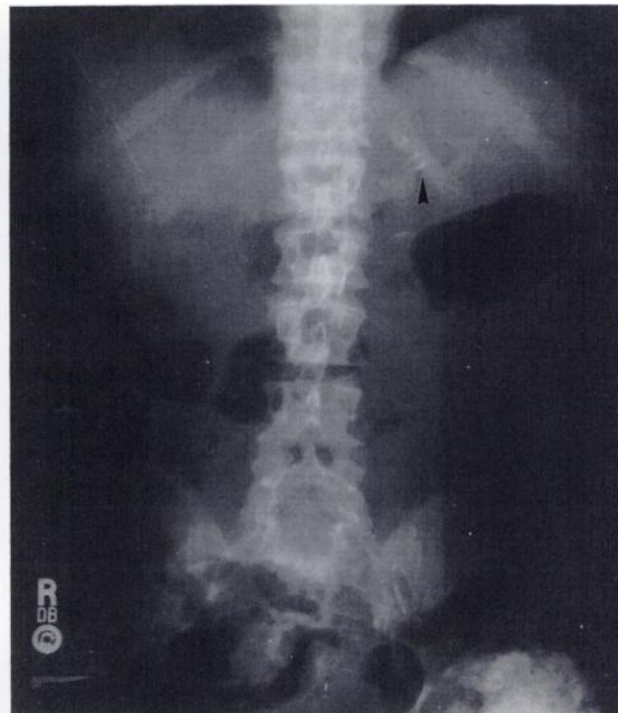
and elbows. Microscopically active and inactive phases of the calcified tissue could be distinguished (Fig. 6A-C). Extensive medial vascular calcification was also identified. The parathyroid glands were of normal size (diameter 0.3 mm–1.5 mm) and contained a variable amount of fat. The Le Veen shunt was occluded. There was no hepatic cirrhosis. Both kidneys were devoid of normal parenchyma and were considered "end-

FIGURE 5
Plain film of the hands shows soft-tissue calcifications around the left second digit, right wrist (along the ulnar aspect), and fifth right digit (along the radial aspect). Bilateral vascular calcifications are noted.
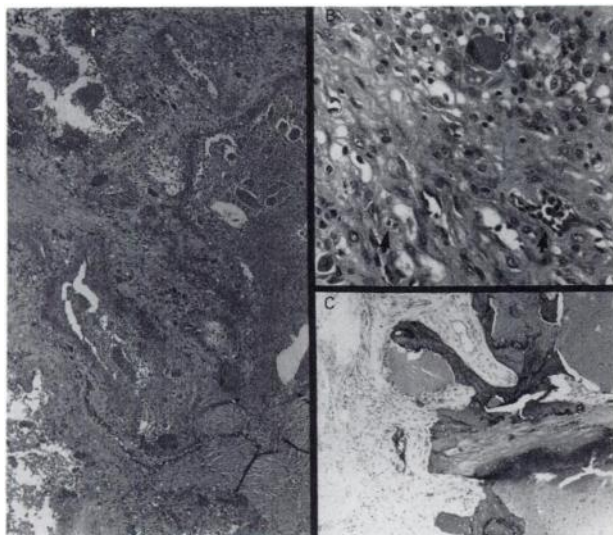
FIGURE 6
(A) Active phase of tumoral calcinosis. Amorphous calcified material bordered by florid proliferation of macrophages and the multinucleated, osteoclast-like giant cells (H&E, ×20). (B) Higher magnification of A. The surrounding stroma has numerous vascular spaces (arrows). A multinucleated giant cell is visualized in the upper right. (C) Inactive phase with minimal histiocytic response and surrounding dense fibrous material.

stage" kidneys. There was no evidence of any malignant tumor or granulomatous disease.

DISCUSSION

Although calcifications of periarticular tissues are frequent in patients on chronic dialysis (9), tumoral calcinosis is rare. The frequency of tumoral calcinosis in the patients dialyzed in this institution between 1968 and 1988 was 2/381 (0.5%). A calcium-phosphorous product in the serum greater than 65-75 (4,10) and hyperparathyroidism secondary to renal failure (4) are factors known to predispose to tumoral calcinosis. Calciphylaxis has also been described in association with extensive soft tissue calcifications (5). Both decreasing serum phorphorous concentration and parathyroidectomy have been advocated for the management of soft tissue calcifications and calciphylaxis (4).

Factors other than serum calcium-phosphorous product and hyperparathyroidism can also predispose dialysis patients to tumoral calcinosis. Elevated serum 1,25 dihydroxycholecalciferol levels either after intake of this vitamin, or produced in granulomas such as sarcoid (11), may lead to rapid development of tumoral calcinosis in dialysis patients especially if serum phosphorous is elevated (12). Neither hyperparathyroidism, nor elevated 1,25 dihydroxycholecalciferol were present in the patient reported in this case. The identified factor predisposing this patient to extraosseous calcifications was an elevated calcium-phosphorous product. We suggest that adynamic bone disease, with its defective bone mineralization, may have been another predisposing factor. Osteitis fibrosa cystica resulting from hyperparathyroidism and osteomalacia represent the two major forms of renal osteodystrophy (13,14). Osteomalacia, characterized by a relative increase in unmineralized osteoid, can develop in dialysis patients by two mechanisms. The first mechanism is by increased rate of formation of osteoid. The second mechanism is by an osteoid mineralization rate which is less than the osteoid formation rate (15). The second (adynamic) form of osteomalacia is routinely present in hemodialysis patients with aluminum osteodystrophy (16). This lesion was recently described in patients on continuous ambulatory peritoneal dialysis in the absence of heavy body loads of aluminum (17). The incidence of the lesion in hemodialysis patients without heavy body loads of aluminum is not known. Adynamic disease (recently called "aplastic" disease) was present in both bone biopsies, taken four years apart, of the patient presented here. However, aluminum was almost absent from the first bone biopsy and present in large quantities in the second. These findings suggest that the adynamic lesion preceded the heavy deposition of aluminum in the bone. Hemodialysis patients are routinely exposed to high dialysate calcium concentration during each dialysis. The defect in bone mineralization present in this adynamic disorder may predispose such patients to extraosseous calcifications.

Hypercalcemia has been described previously in cases of aluminum osteodystrophy (18). We speculate that hypercalcemia could also be sustained by calcium from the calcified extraosseous tissue in the patient presented here.

REFERENCES

1. Parfitt AM. Soft tissue calcification in uremia. *Arch Intern Med* 1969; 124:544–546.
2. Ritz E, Krempien B, Mehls O, Malluche H, Strobel Z, Zimmerman H. Skeletal complications of renal insufficiency and maintenance hemodialysis. *Nephron* 1973; 10:195–207.
3. Ibels LS, Alfrey AC, Huffer WE, Craswell PW, Anderson JJ, Weil R III. Arterial calcification and pathology in uremic patients undergoing dialysis. *Am J Med* 1979; 66:790–796.
4. Ibels LS. The pathogenesis of metastatic calcification in uraemia. *Prog Biochem Pharmacol* 1980; 17:242–250.
5. Gipstein RH, Coburn JW, Adams DA, et al. Calciphylaxis in man: a syndrome of tissue necrosis and vascular calcification in 11 patients with chronic renal disease. *Arch Intern Med* 1976; 136:1273–1280.
6. Kirk TS, Simon MA. Tumoral calcinosis. *J Bone Joint Surg [Am]* 1981; 63:1167–1169.
7. Popovtzer MM, Knochel JP. Disorders of calcium, phosphorous, vitamin D, and parathyroid hormone activity, In: Schrier RN, ed. *Renal and electrolyte disorders*, 3rd edition. Boston: Little, Brown and Co.; 1986:251–329.
8. Sherrard DJ, Maloney NA. Single-dose tetracycline labeling for bone histomorphometry. *J Clin Path* 1989; 91:682–687.
9. Tattler GLV, Baillod RA, Varghese Z, et al. Evolution of bone disease over 10 years in 135 patients with terminal renal failure. *Br Med J* 1973; 4:315–319.
10. Eastwood JB, Bordier PJ, De Wardener HE. Some biochem-

ical, histological and clinical features of renal osteodystrophy. *Kidney Int* 1973; 4:128–140.

11. Mason RS, Frankel T, Chan YL, Lissner D, Posen S. Vitamin D conversion by sarcoid lymph node homogenate. *Ann Intern Med* 1984; 100:59–61.

12. Tzamaloukas AH, Gardner KR, Jr. Chronic Renal failure. In: Mandal AK, Jennette JC, eds. *Diagnosis and management of renal disease and hypertension.* Philadelphia: Lea and Ferbiger; 1988:448–471.

13. Coburn JW. Renal osteodystrophy. *Kidney Int* 1980; 17:677–693.

14. Chan YL, Furlong TJ, Cornish CJ, Posen S. Dialysis osteodystrophy. *Medicine* 1985; 64:296–309.

15. Evans RA, Flynn J, Dunstan CR, George CRP, McDonnell GD. Bone metabolism in chronic renal failure. *Mineral Electrolyte Metab* 1982; 7:207–218.

16. Ott SM, Maloney NA, Coburn JN, Alfrey AC, Sherrard DJ. The prevalence of bone aluminum deposition in renal osteodystrophy and its relation to the response to calcitriol therapy. *N Engl J Med* 1982; 307:709–713.

17. Hercz G, Goodman WG, Pei Y, Segre GW, Coburn JW, Sherrard DJ. Low turnover bone disease without aluminum in dialysis patients [Abstract]. *Am Soc Nephrol Abstracts* 1988; 21:230A.

18. Piraino BM, Rault R, Greenberg A, et al. Spontaneous hypercalcemia in patients undergoing dialysis. Etiologic and