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TREATMENT OF CALCINOSIS WITH DILTIAZEM

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Objective. **To test the hypothesis that the calcium antagonist diltiazem is effective in the treatment of calcinosis.**

Methods. **Diltiazem, 240–480 mg/day, was given to 4 patients with idiopathic or CREST-related (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) calcinosis for 1–12 years. Serial radiographs of the affected areas, using identical technique, and clinical evaluations were obtained. A fifth patient, who did not tolerate diltiazem, received verapamil, 120 mg/day for 18 months.**

Results. **All patients taking diltiazem had a reduction or disappearance of the calcific lesions, with striking clinical improvement. One patient's case was followed for 12 years. The response to diltiazem during the first 5 years of treatment has been previously reported in detail; however, over 7 years of additional treatment, there was further reduction of the lesions. One patient developed a large calcific lesion while receiving verapamil for hypertension, and after verapamil was replaced with diltiazem, there was a dramatic response. Verapamil was ineffective in the fifth patient, who did not tolerate diltiazem.**

Conclusion. **Long-term treatment with diltiazem, but not verapamil, is effective in calcinosis.**

Pathologic calcification of soft tissues occurs in a wide variety of systemic disorders (1). In one group, soft tissue calcifications are the result of disorders of calcium and/or phosphate metabolism, such as primary and secondary hyperparathyroidism, sarcoidosis, and hypervitaminosis D. In these patients correction of the underlying condition usually leads to a reduction in calcification. The other group includes conditions characterized by normal calcium and phosphate metabolism, such as connective tissue diseases (scleroderma, CREST syndrome [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias], systemic lupus erythematosus, and polymyositis), and are known as calcinosis or dystrophic calcification (1). Calcinosis may also be idiopathic. The process typically involves mineral accumulation within matrix vesicles and sometimes within mitochondria (2). Deposits of calcium salts are formed in the extracellular space and often drain to the exterior as a whitish, thick material. This drainage occurs intermittently without significant reduction in the size of the calcific masses.

The factors that ultimately lead to the formation of calcium deposits are poorly understood, and no reliable therapy for calcinosis is currently available. Systemic administration of steroids is generally ineffective (3,4); intralesional administration of steroids appears to produce some benefit in calcinosis confined to the skin (5,6). Chelating agents, such as disodium EDTA (3,4), and diphosphonates (7,8), have yielded unimpressive results in clinical trials. In a few patients, probenecid (9,10) and colchicine (11) have appeared to be beneficial. More recently, low-dose warfarin therapy was advocated for mild cases of calcinosis universalis (12,13), but it was ineffective for more advanced cases (14).

We have reported the arrest and radiographic regression of multiple lesions in a patient with calcinosis, during 5 years of treatment with diltiazem (15). In the present communication we report on an additional 7-year followup of the same patient and the beneficial effect of long-term diltiazem administration in 3 additional cases of calcinosis, as well as the lack of

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Table 1. Clinical presentation and response to treatment in 5 patients with calcinosis

	Patient				
	1	2	3	4	5
Sex/age (years)	F/68	F/62	F/57	F/37	F/77
Race	Afro-American	Caucasian	Caucasian	Afro-American	Caucasian
Definable connective tissue disease	None	None	None	CREST*	None
Duration of calcinosis prior to treatment (years)	Unknown	11	1	23	2
Diltiazem treatment					
Daily dose/months	360 mg/27	240 mg/24	240 mg/12	240–480 mg/144	60 mg/2
Clinical response	All symptoms disappeared	Less drainage	All symptoms disappeared	Improvement	Unchanged
Radiographic changes	Total resolution	Reduction in size; no new lesions	Total resolution	Reduction in size; no new lesions	Unchanged
Treatment with other Ca antagonists	No	No	Verapamil, 1 year prior to treatment with diltiazem†	No	Verapamil, 18 months

* Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias.
† The patient developed calcinosis while taking verapamil (see text).

improvement in a fifth patient who did not tolerate this drug, but received verapamil, another Ca antagonist.

CASE REPORTS

Table 1 summarizes the clinical presentation and response to treatment of all patients.

Patient 1. A 68-year-old African-American woman was admitted to the hospital with a history of several weeks of severe neck pain. She noticed progressive weakness in the extremities, particularly in the upper extremities, with inability to abduct both shoulders. The neurologic diagnosis was spastic quadriparesis. Her medical history revealed a fracture of the left proximal femur at age 56, and at age 62, a motor vehicle accident caused laceration of her left knee with joint involvement, which required drainage and antibiotic treatment. At that time, radiographs of the cervical spine showed degenerative changes, but no masses or calcinosis.

At admission, her temperature was 36.6°C, pulse was 80 per minute, and blood pressure was 140/80 mm Hg. Radiographs of the cervical spine revealed extensive, large globular soft tissue calcifications posterior to C2, C3, and C4. There was normal alignment throughout the cervical spine (Figure 1A).

A bone scan showed intense uptake in the cervical spine (Figure 1B, top). Magnetic resonance imaging showed abnormal signal intensity and expansion of the posterior elements at C2–C5. The expansion resulted in spinal canal narrowing, most severe at C3. At this level, the subarachnoid space was obliterated and the cervical cord was compressed, with a canal measurement of 7 mm (Figure 1C). Expanded vertebral bodies with low signal intensity on T1 and multiplanar gradient echo imaging were consistent with calcifications and sclerosis. Following administration of gadolinium, there was partial enhancement of the expanded vertebrae and the associated soft tissue mass. Computed tomography of the cervical spine revealed expansion of bone of C2 through C6, with sclerosis of the posterior elements of the vertebral bodies and a calcified mass posterior to the vertebrae.

Laboratory tests showed mild normochromic normocytic anemia, with a hemoglobin level of 10.8 gm/dl. The red blood cell (RBC) count was 4.46 million/mm^3. The white blood cell (WBC) count was 4,500/mm^3 with a normal differential cell count. Serum chemistries were within normal limits, and her blood level of ionized Ca was 4.76 mg/dl (normal 4.3–5.3). Serum calcidiol and calcitriol levels were within normal limits. Serum protein electrophoresis showed elevation of acute-phase globulins. Antinuclear (ANA), anticentromere (ACA), and anti–Scl-70 (anti–topoisomerase I [anti-topo I]) antibodies were within normal limits. Bone marrow aspiration and biopsy were nondiagnostic.

During exploratory surgery of the cervical spine, extrusion of whitish, thick, creamy material was observed after dividing the ligamentum nuchae. The whitish material extended down to the dura at the level

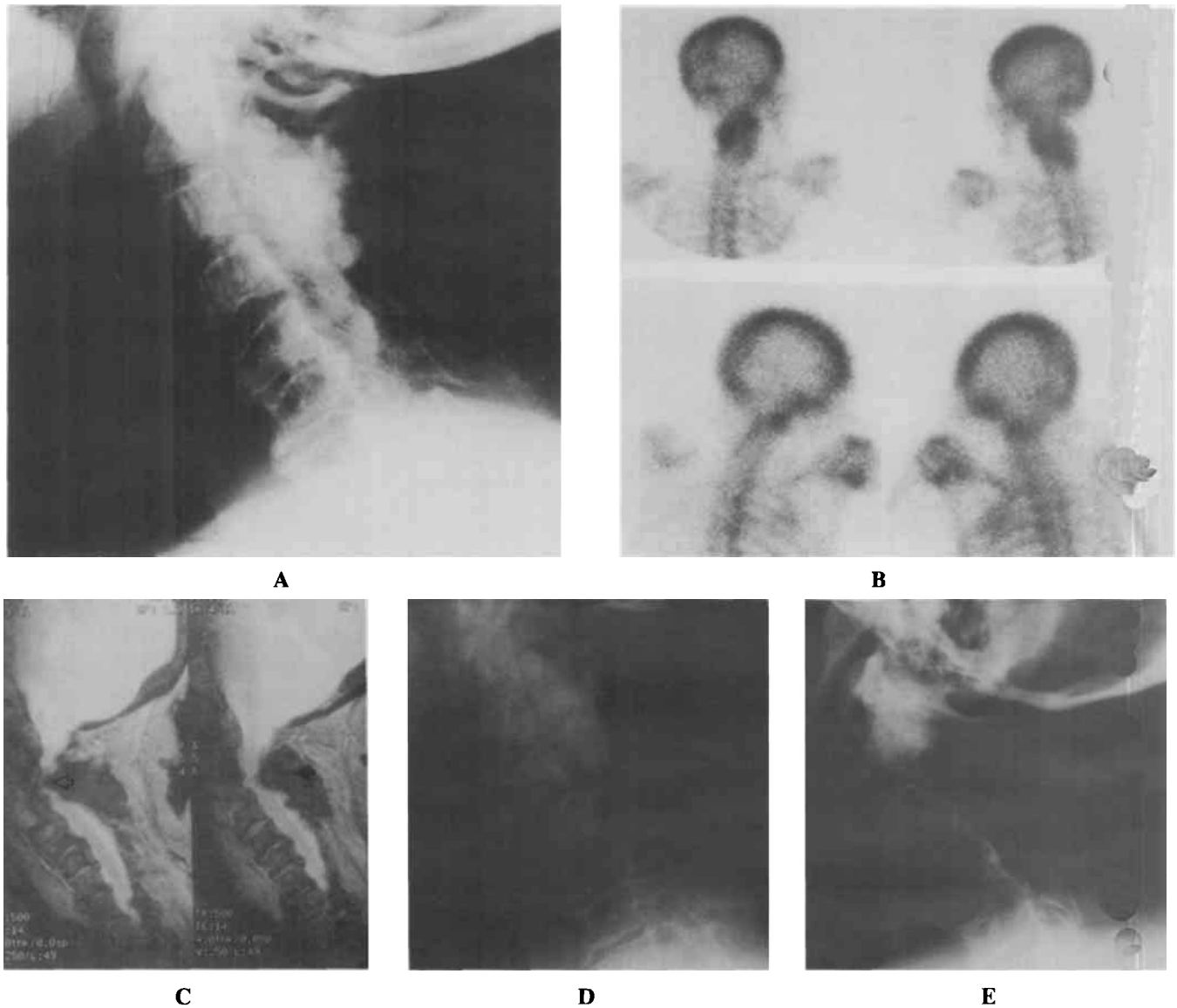
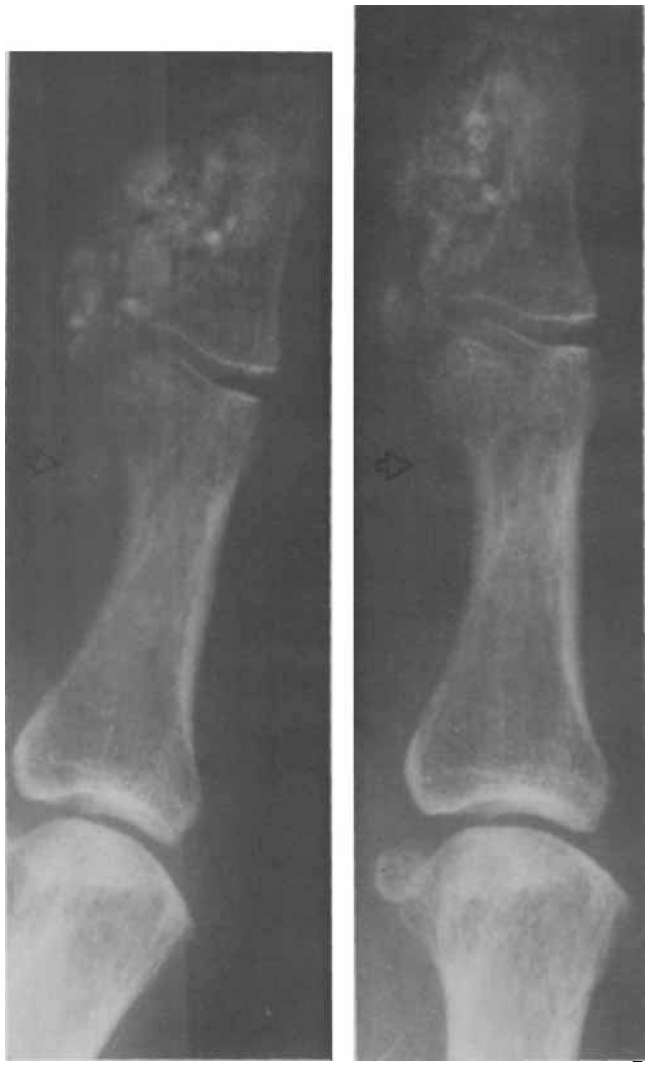


Figure 1. Patient 1. **A,** Lateral view of the cervical spine, showing extensive soft tissue calcification posterior to the C2, C3, and C4 vertebral bodies. **B,** Oblique views of technetium diphosphonate bone scans, showing increased radionuclide uptake in the posterior neck (top), and marked improvement after 2 years of diltiazem treatment (bottom). **C,** Sagittal T1-weighted (500/14) magnetic resonance images of the neck, showing extensive soft tissue calcification (**solid arrow**) and severe narrowing of the spinal canal (**open arrow**). **D,** Lateral view of the cervical spine 1 week after surgery, showing extensive residual calcification adjacent to the posterior elements of C2, C3, and C4. **E,** Lateral view of the cervical spine after 2 years of treatment with diltiazem, showing no residual calcification. The C3 and C4 vertebrae are now fused, and there is partial posterior subluxation of C4 and C3.

of C3. There was obvious erosion of bone, and in some areas the laminae were absent. Multiple biopsies of the wall of this cavity and the C2 vertebra were obtained. The pathologic diagnosis was calcinosis. There was no evidence of malignancy, and multiple cultures of the material obtained during surgery were negative for aerobic and anaerobic bacteria, acid-fast bacilli, and fungi.

Seven days after surgery, the patient was clinically unchanged and radiographs of the cervical spine showed a large area of calcification unchanged in comparison to the preoperative films (Figure 1D). Ten



A B

Figure 2. Patient 2. **A,** Anteroposterior view of the left thumb, showing a large area of punctate calcification in the soft tissues of the distal phalanx. Faint cloud-like calcification is present adjacent to the proximal phalanx (**arrow**). **B,** After 2 years of treatment with diltiazem, there is minimal decrease of the calcinosis of the proximal phalanx (**arrow**). However, there is no significant change in the appearance of the distal calcifications.

days after surgery, treatment with diltiazem was initiated, in increasing doses, from 60 mg/day to 360 mg/day in 4 divided doses, with close monitoring by a cardiologist. Ninety days after surgery, while taking 360 mg of diltiazem daily, the patient was markedly improved, and there was resolution of the quadriparesis.

She was followed up in the outpatient facilities for 2 years, and the dosage of diltiazem continued at 360 mg/day. Radiographs of the cervical spine at the completion of 2 years of treatment showed postoperative changes at C2–C3, with fusion of the intervertebral disc at this level and slight anterior subluxation of C2 on C3. There was complete resolution of the calcified mass (Figure 1E). A bone scan performed at that time showed marked improvement in the cervical spine (Figure 1B, bottom).

Patient 2. A 62-year-old Caucasian woman presented with an 11-year history of painless nodules in both hands and the right elbow, with spontaneous discharge of whitish, thick material from the elbow nodule every 1–2 months. Her medical history was negative for connective tissue diseases. Her weight was 65.5 kg, blood pressure 144/80 mm Hg, pulse 80 per minute, and temperature 36.0°C.

The physical examination yielded negative findings except for a 3-cm (diameter) palpable mass with white spots, compatible with calcinosis, on the patient's right elbow. Similar masses were observed on both thumbs, and very small masses were palpable on several other fingers. The nodules were not tender, but severely impaired the normal function of both hands.

Laboratory studies showed normal blood cell counts, serum chemistries, calcidiol, calcitriol, and ionized Ca. Serum protein electrophoresis was nondiagnostic; rheumatoid factor and anti–extractable nuclear antigen were negative. The erythrocyte sedimentation rate (ESR) was 13 mm/hour. The serum T4 level was 5.9 mg/dl, T3 uptake was 29.9%, and the free thyroxine index was 1.8 (all within normal limits). The serum thyroid-stimulating hormone (TSH) level, however, was elevated at 11.7 μIU (normal range 0.35–7.0). Serum osteocalcin was slightly elevated at 8.2 ng/ml (normal range 2–7).

Radiographs revealed punctate, closely clustered, globular soft tissue calcifications in both hands at the interphalangeal joints of both thumbs and adjacent to the distal phalanges (Figure 2A). Additionally, there were calcifications in the soft tissues of the left second and fifth digits. The bone scan showed increased uptake in both thumbs, the right elbow, and the distal areas of the left second and fifth digits. A biopsy of one of the nodules revealed calcinosis. No signs of inflammation were observed.

The patient was given diltiazem, 240 mg/day in 4 divided doses, and L-thyroxine, 75 μg/day, and there was gradual improvement. The frequency of episodes of spontaneous discharge of whitish material from the lesions diminished, and the serum TSH became normal and remained within normal limits for 2 years.

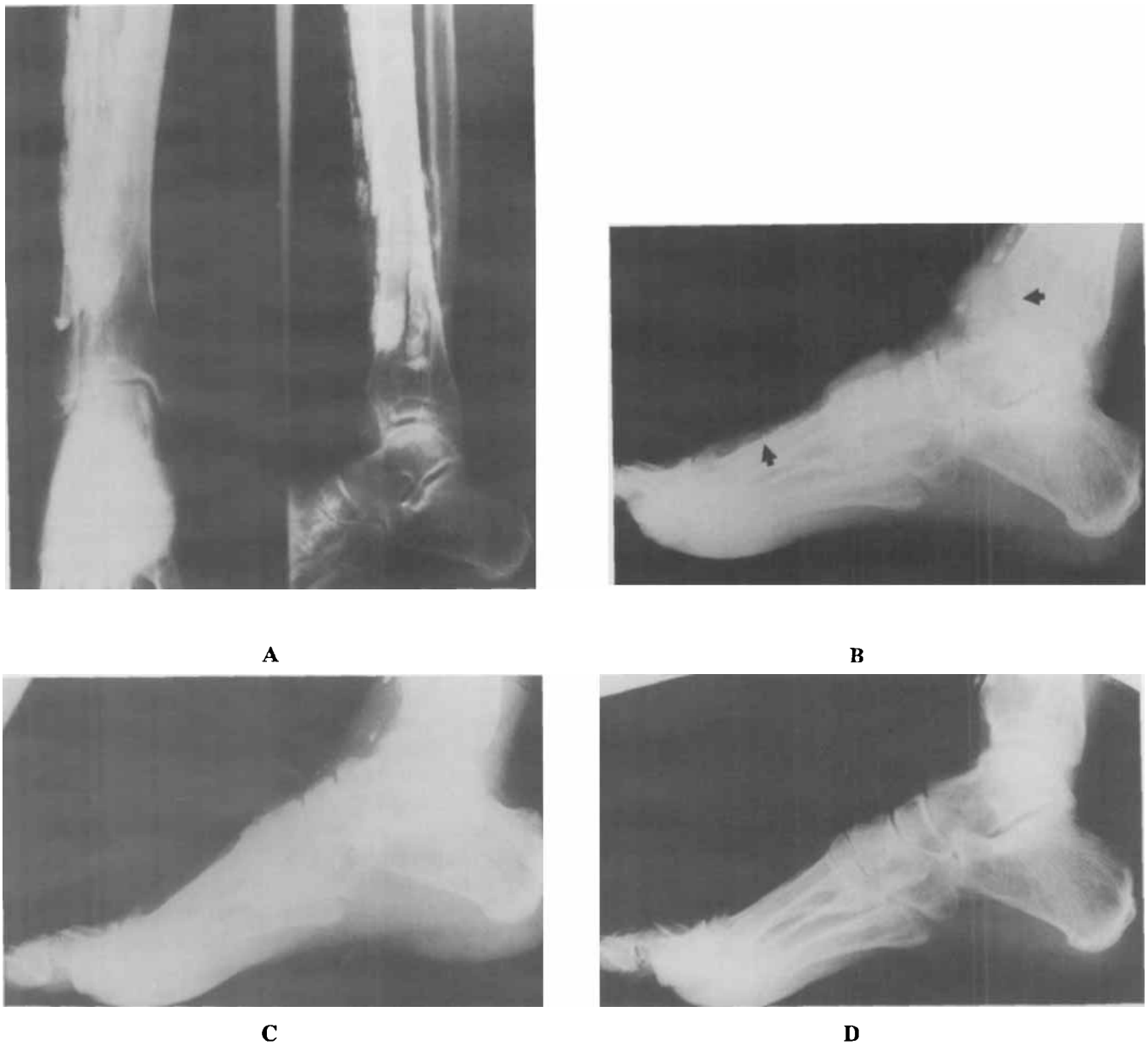


Figure 3. Patient 3. **A,** Anteroposterior and lateral views of the leg, showing extensive compartmental calcification characteristic of the calcific myonecrosis syndrome. **B,** Lateral view of the left foot, showing a faint, large, globular calcification anterior to the tibiotalar joint, with erosion of the anterior tibia (**upper arrow**). Similar smaller calcifications are also present in the soft tissues of the dorsal aspect of the foot (**lower arrow**). **C,** Lateral view of the left foot after 7 months of diltiazem treatment, showing a marked decrease in all calcifications. **D,** Lateral view of the left foot after 1 year of diltiazem treatment, showing complete resolution of the soft tissue calcifications.

Biannual radiographs of the hands for 2 years showed no new lesions and a reduction in the size of the preexisting calcific nodules in the soft tissues of the distal phalanx of the left thumb (Figure 2B).

Patient 3. A 57-year-old Caucasian woman had a 1-year history of pain in the right ankle and foot, which had begun when she stumbled while walking. She developed a large globular mass on the dorsum of the right foot, which had the appearance of a large hematoma. Because of progressive enlargement of the mass, it was partially drained for diagnostic purposes, yielding ~1 ml of whitish material. Cultures for aerobic and anaerobic organisms were negative. The pathologic diagnosis was calcinosis.

One month later, the patient returned with more discomfort and had noticed increasing swelling of the previously drained mass. On palpation, the mass appeared to be slightly larger.

The patient's medical history was significant for a 10-year history of arterial hypertension, which had been well-controlled for more than 1 year with slow-release verapamil, 240 mg/day orally. There was no history of connective tissue diseases. At age 13, the patient had had a fracture of the right tibia following significant trauma, with uneventful healing; however, 44 years later, at the time of presentation for the right foot pain and swelling, radiographs revealed long, thick, linear calcifications in the anterior and lateral soft tissues of the right leg. The calcifications in the leg and foot were anatomically unconnected. The longitudinal thick, linear calcification was compatible with lower-extremity post-traumatic compartmental calcification of calcific myonecrosis (16–18). At age 40, the patient underwent surgery for degenerative arthritis of the cervical spine; at age 53, she underwent surgery for an intracranial aneurysm, with excellent results.

The patient's weight was 55.3 kg, blood pressure 122/64 mm Hg, and pulse 85 per minute. Physical examination findings were unremarkable, except for a 5 × 7-cm mass on the dorsum of the right foot. Laboratory studies showed a hemoglobin level of 14.7 gm/dl, a hematocrit value of 45.7%, an RBC count of 4.4 million/mm^3, and a WBC count of 6,900/mm^3, with 70% neutrophils and 24% lymphocytes. The ESR was 8 mm/hour. Serum chemistries were normal. ACA and ANA were negative.

Radiographs of the patient's left leg revealed compartmental calcification, with a pattern and distribution characteristic of calcific myonecrosis (Figure 3A). Lateral views of the left foot showed faint globular calcification in the dorsum of the foot (Figure 3B). A bone scan revealed increased uptake in the right foot and ankle, as well as in the lower right leg, particularly in the interosseous membrane.

Treatment with verapamil was discontinued and diltiazem, 240 mg/day in 4 divided doses, was begun. Six months after the initiation of treatment, the patient noticed increased mobility of her right foot and ankle and marked reduction in the size of the mass. Twelve months after initiation of treatment, she was totally free of symptoms and was engaged in normal activities. No masses were palpable in the right foot and ankle.

Repeat radiographs 7 months following treatment showed a marked decrease in the globular calcification since the previous study, as well as a marked decrease in the linear, more opaque calcifications (Figure 3C). Lateral views of the left foot 1 year after initiation of treatment showed complete resolution of the calcifications (Figure 3D).

Patient 4. A 37-year-old African-American woman with a 23-year history of progressive calcinosis and features of CREST syndrome, had been taking diltiazem, 240 mg/day in 4 divided doses, since 1983. The results of the first 5 years of treatment (from 1983 to 1988) were previously described in *Arthritis and Rheumatism* (15). During that time, no new lesions occurred and radiographs showed marked reduction in size of the existing lesions.

Radiographs were obtained every 6 months from 1988 to 1995, and demonstrated no new lesions and further reduction of the soft tissue calcifications (Figures 4a, b, and c). Because of a questionable enlargement of one of the lesions (December 1993), the diltiazem dosage was increased to 480 mg/day. The patient is currently in good health, without symptoms associated with the CREST syndrome. The arterial hypertension diagnosed prior to 1983 has remained under good control with diltiazem. Biannual cardiovascular evaluations have revealed no abnormalities. The most recent radiographs of the hands (obtained after 12 years of diltiazem therapy) showed continued resolution of the soft tissue calcifications adjacent to the distal interphalangeal joint of the right fourth finger (Figure 4d).

Patient 5. A 76-year-old Caucasian woman presented with a 2-year history of painful subcutaneous nodules in her hands. The nodules were first noted at the tips of her fingers and had gradually increased in size, occasionally extruding a whitish, chalky material, which microscopic analysis revealed to be calcium deposits. She denied having any tightness or thickening of the skin, Raynaud's phenomenon, or dysphagia. Her medical history was negative, except for chronic palpitations, for which she was taking verapamil, 80 mg/day.

On physical examination there was no evidence of sclerodactyly or telangiectasias. Her ESR was 22 mm/hour, and results of a complete blood cell count and serum chemistries were within normal limits. Fluorescent ANA was positive at a titer of 1:640, with a nucleolar pattern. ACA and anti–topoisomerase I were negative. Radiographs of the hands revealed extensive soft tissue calcinosis bilaterally, without bone destruction or an intraarticular component to the calcifications.

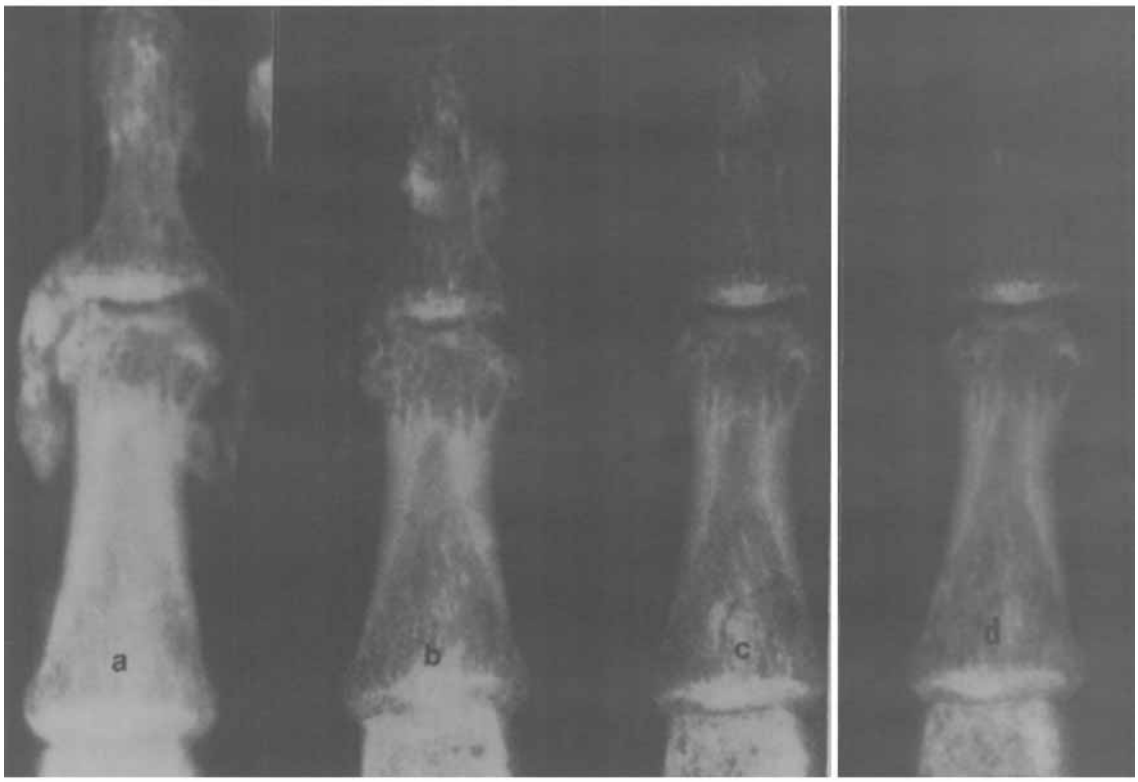


Figure 4. Patient 4. Posteroanterior views of the right fourth finger. Films taken in 1983 (**a**), 1984 (**b**), and 1988 (**c**) reveal a gradual decrease in the calcifications with diltiazem treatment. The most recent radiograph (**d**), taken in 1995, after 12 years of diltiazem therapy, shows virtually complete disappearance of the calcifications. (Figures a, b, and c were reproduced from ref. 15.)

Verapamil treatment was discontinued, and the patient was started on diltiazem, 60 mg/day. Two months later, diltiazem was discontinued because of increasing complaints of palpitations, and verapamil was reinstituted at 120 mg/day, which she continued to take for the following 18 months. The patient was unable to tolerate larger doses of verapamil because of exacerbation of palpitations. Cardiovascular evaluation failed to demonstrate organic heart disease. Radiographs obtained after 18 months of treatment with verapamil (120 mg/day) revealed no change in the appearance of the calcifications in both hands.

DISCUSSION

This report shows that long-term treatment with the Ca antagonist diltiazem results in subjective and objective beneficial effects in patients with calcinosis. In patient 4, who had features of the CREST syndrome, the effects of treatment were followed over 12 years. The most dramatic effects were noted during the first 5 years of treatment, as previously reported (15). During the last 7 years of observation, additional improvement occurred. In patients 1 and 3, radiographs showed disappearance of the lesions, and in patient 2, there was reduction in the size of the lesions. In patient 5, who did not tolerate diltiazem, no changes were observed after 20 months of observation, 18 months of which were with treatment with verapamil.

In only 1 patient, patient 4, was the calcinosis related to the CREST syndrome. In patient 3, tumoral calcinosis in the foot was associated, but was anatomically not connected, with calcific myonecrosis of the lower extremities, also known as compartment syndrome (16–18). In the remaining 3 patients, no cause of the calcinosis was found.

The pathophysiology of calcinosis is unknown. It is well established, however, that the Ca ion concentration in the extracellular fluid is $10^{-3}M$, and is

$10^{-7}M$ in the cytosol. This 10,000-fold gradient is maintained by the impermeability of the cell membrane to ionic Ca and by the presence of an energy-dependent calcium pump (19). Alterations of cellular Ca homeostasis have been demonstrated in several unrelated diseases (20). It is therefore not surprising that the therapeutic use of calcium antagonists has grown exponentially over the last 20 years.

Our rationale for using diltiazem to treat calcinosis was based on our studies of muscular dystrophy. Muscle from dystrophic hamsters (21) and from patients with Duchenne's muscular dystrophy (22) has shown ~3–10-fold elevation in muscle Ca content, as is also found in fetal muscle, before signs of necrosis are noticeable (23). Thus, it appears that the elevated cellular Ca may play a role in the pathogenesis of the dystrophic process (24). Diltiazem markedly reduced muscle Ca content in the heart, skeletal muscle, and diaphragm of dystrophic hamsters (21) and the number of Ca-positive muscle fibers in Duchenne's muscular dystrophy (25), and caused a positive trend in muscle function in this disease (26). There is no evidence suggesting any possible link between muscular dystrophy and calcinosis, although both conditions affect mitochondria (2,27). The response to diltiazem in these two unrelated conditions could suggest that perhaps in calcinosis, there is an intracellular Ca dishomeostasis in connective tissue cells, i.e., fibroblasts, that could accumulate and extrude Ca salts, with formation of large deposits (tumoral calcinosis) that eventually open their way to the exterior, with the characteristic whitish, chalky discharge. Diltiazem would then correct to a certain extent the cellular Ca disorder, diminishing the accumulation of Ca deposits. Readily available macrophages, congregated in the vicinity of areas of calcinosis, would scavenge the ectopic Ca deposits, recognized by macrophages as "foreign bodies." Thus, the balance of equation of "calcinosis-forming cells" and macrophages will be tilted in favor of the latter.

Patient 3 apparently developed the large globular lesion of calcinosis while receiving verapamil, and patient 5 did not respond to this agent. Verapamil and diltiazem are both calcium antagonists, but they differ in their structure and mechanism of action. Calcium antagonists are heterogeneous and fall into 3 major classes: the phenylalkylamines (verapamil), the dihydropyridines (nifedipine), and the benzothiazepines (diltiazem). Although all bind to the same large protein, they do not bind to the same receptor sites (28). Diltiazem appears to be the only Ca antagonist with an inhibitory effect in mitochondrial sodium–calcium exchange (29). Work done in our institution (30) has clearly shown that neither verapamil nor nifedipine has any effect on the exaggerated accumulation of muscle Ca in muscle dystrophy, while diltiazem causes marked diminution of muscle Ca, increased longevity, and histologic improvement in dystrophic hamsters. Since muscle mitochondria are seriously affected in muscular dystrophy (31), it is conceivable that the unique effect of diltiazem preserving mitochondrial Ca homeostasis could play a role in the pathogenesis of disorders characterized by exaggerated Ca accumulation.

Calcinosis is an uncommon and heterogeneous condition. Of the many connective tissue diseases that can lead to the formation of calcium deposits in the subcutaneous tissues, the CREST syndrome of scleroderma is the most common cause, and in some cases, the calcification is extensive and is the main feature of the disorder. No satisfactory treatment is available, and the rarity of this condition precludes single-center, large, prospective studies on the effect of any particular agent. Although limited to a few patients, only 1 of whom met the criteria for a definable connective tissue disease, the present study strongly suggests a beneficial effect of diltiazem in the treatment of calcinosis.

Addendum. After this article was accepted for publication, an article by Dolan et al appeared in the *British Journal of Rheumatology* (32), describing the remission of calcinosis in a patient with scleroderma taking diltiazem.

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