Calciphylaxis:

Etiology of Progressive Vascular Calcification and Gangrene?

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PROGRESSIVE generalized vascular calcification, severe enough to produce arterial insufficiency and ischemic tissue necrosis after successful renal homotransplantation, is rare. When this degree of calcification has been reported, it has been associated with secondary or tertiary hyperparathyroidism. The calcifications usually regress almost completely within 2 months of transplantation.[12] In the remaining patients, subtotal parathyroidectomy has been followed by regression of vascular calcification and healing of ischemic ulcers.[5,9] The case reported here is unique due to the generalized vascular calcification which developed and progressed in the absence of hypercalcemia. Subtotal parathyroidectomy, despite producing hypocalcemia, failed to arrest progression of the vascular calcifications and tissue necrosis. The vascular lesions resulted in severe ischemia and peripheral gangrene which finally caused amputation of three extremities.

Calciphylaxis has been proposed as a possible mechanism in the pathogenesis of soft tissue and vascular calcification in chronic renal disease.[5,6] In this process, as defined by Selye,[10,11] local or generalized calcinosis followed by inflammation and sclerosis may be produced by prior tissue sensitization by a systemic calcifying factor such as parathyroid hormone, vitamin D, or hypercalcemia followed by treatment with another agent at some later critical period. This need not be at a time when the plasma calcium level is high since the challenging agents may act as a mordant to prepare the already sensitized tissues for the deposition of calcium. It is possible, as proposed by Massry,[5] that prednisone acting as a challenger, may lead to calciphylaxis in tissues previously sensitized by high levels of endogenous parathyroid hormone. Corticosteroids have been shown to aggravate or produce calciphylaxis under some circumstances in experimental animals.[10]

Case Report

A 23-year-old woman was first seen in December 1966, because of progressive renal failure secondary to diffuse exudative glomerulonephritis. Blood urea nitrogen was 170 mg./100 ml., serum calcium 8.3 mg./100 ml., *ionized calcium 4.5 mg./100 ml.*, and phosphorus 11.7 mg./100 ml. Bone survey x-rays were normal with no vascular or soft tissue calcifications. Bone biopsy showed osteosclerosis. A Scribner shunt was placed in the right arm to facilitate chronic hemodialysis. Three months later a cadaveric renal homotransplantation was performed; however, renal function was never sufficient to permit cessation of dialysis, so the graft was removed 6 weeks later.

Over the next 12 months she was treated by hemodialysis using both the twin-coil and the parallel flow dialyzers. Standard dialysate mixed with nondeionized tap water was used two to three times per week for a total of 12 to 20 hours per week. Predialysis serum calcium levels averaged 9.6 mg./100 ml., serum phosphorus 9.2 mg./100 ml., with a calcium phosphorus product of 88 and serum alkaline phosphatase 12.7 Shinowara-Jones units (normal range 2–9). Post dialysis serum calciums averaged 12.2

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mg./100 ml., serum phosphorus 5.1 mg./100 ml., with a calcium phosphorus product of 63 (Table 1). Slight osteoporosis of the lumbar spine was noted months after admission, and for the first time soft tissue calcifications adjacent to the lateral humeral epicondyle were seen.

A second transplant was performed 12 months later. Postoperatively her endogenous creatine clearance stabilized at 30 ml./min., at which time her mean calcium phosphorus product was 54. Drug therapy included azothiaprine and prednisone. Skeltetal x-rays at this time revealed bursal calcification about the head of the left humerus, with tapering of the lateral aspect of the left clavicle, suggestive of subperiosteal reabsorption. Repeat x-rays 18 months after the initial study revealed extensive metastatic calcification in both elbows, wrists, and hands. Dental films showed alveolar reabsorption with slight crown erosion. Painful ischemic ulcers of the right lateral gluteal region and thigh developed and gradually extended in the ensuing months despite intensive local therapy.

Six months after transplant, the patient was admitted with ischemic rest pain in the ring and middle fingers of the right hand. Examination of the right hand revealed pallor, pain, and hypothermia with no pulses felt distal to the brachial. The circulation improved with intravenous heparin and low molecular weight dextran therapy. X-rays of the right hand and forearm obtained at this time showed extensive small and large vessel vascular arterial calcification as well as widespread soft tissue calcifications (Fig. 1). Two months later she was rehospitalized because of progressive ischemia of both hands, as well as progression of the lesions on the right thigh. X-rays at this time showed widespread vascular calcification and diffuse soft tissue calcifications including calcific bursitis of both shoulders. Right brachial angiography revealed occlusion of both radial and ulnar arteries with multiple calcified vessels in the hand which did not visualize on delayed serial views.

Pertinent blood chemistries following transplantation included a mean serum calcium of 10.0 mg./100 ml. (range: 9.0–11.7), mean serum phosphorus 5.2 mg./100 ml. (range: 3.8–5.8), and calcium phosphorus products ranging from 49–57 (Table 2). Endogenous creatinine clearance remained stable at 25–30 ml. per

TABLE 1. *Pretransplant Clinical Course*

Date	Initial Data 12/66	Hemodialysis 12/66–1/68	
		Pre-Dialysis	Post-Dialysis
Ischemic Symptoms	None	—	None
X-ray Findings	Normal	—	Normal
CCr	5	5	—
Serum Calcium: Mean (mg./100 ml.)	8.3	9.6	12.2
(Range)	—	(7.7–12.1)	(11.4–14.3)
Ser. Phosphorus: Mean (mg./100 ml.)	11.7	9.2	5.1
(Range)	—	(4.3–14.4)	(3.9–7.0)
Ionized Calcium (mg./100 ml.)	4.5	6.0	7.9
Alkaline Phosphatase*	—	12.7	—
Ca × P	97.1	87.7	63.0

*Shinowara-Jones Units

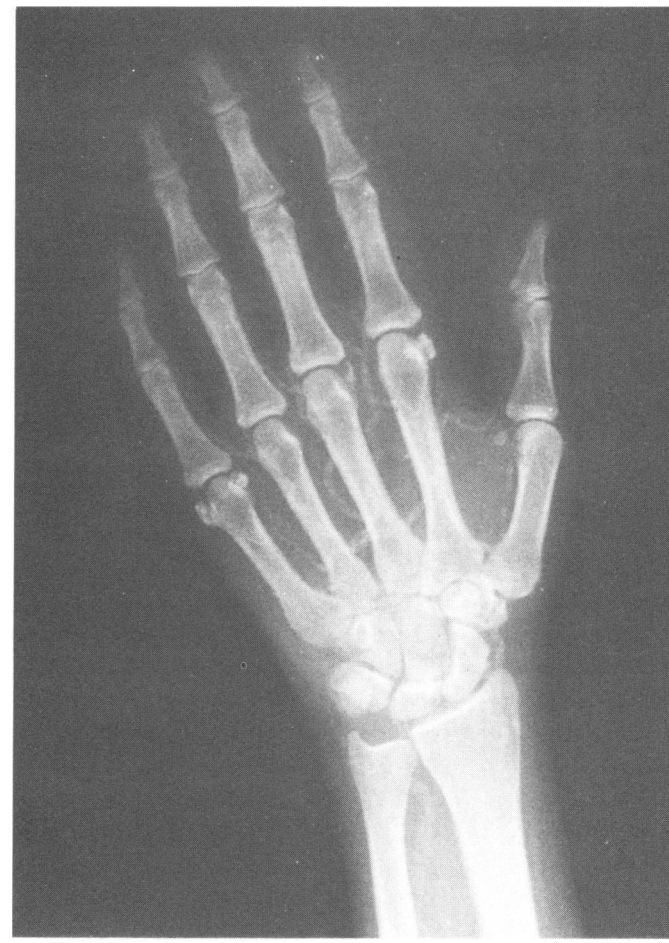

FIG. 1-a. Diffuse soft tissue and vascular calcification of small and medium sized arteries of hand with sever ischemia secondary to fibrous obliteration of lumen of vessels.

minute. On the basis of the clinical, radiological, and biochemical findings subtotal parathyroidectomy was performed in an attempt to control the morbid calcinosis. Also, cervicodorsal sympathectomy was done hoping to improve digital blood flow. The three and one-half parathyroid glands removed showed minimal hyperplasia. Postoperatively, serum calcium decreased to 8.3 mg./100

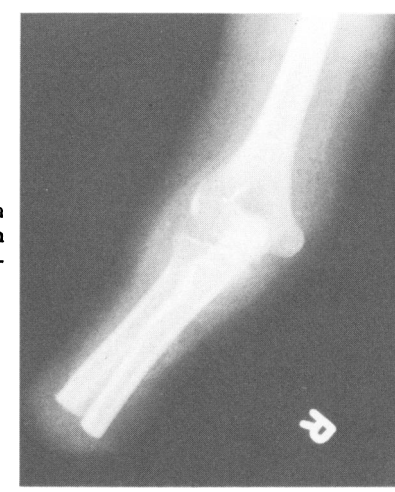

FIG. 1-b. Amputation stump and upper arm show similar calcifications.

TABLE 2. *Post-transplant Clinical Course*

Date	Pre-Parathyroidectomy 12/67–10/69	Post-Parathyroidectomy 10/69–5/70 Period I	Post-Parathyroidectomy 6/70–9/70 Period II
Ischemic Symptoms	6/68—Ulcerations Buttock & Thigh 6/69—Ischemic R. Hand	10/69—Amp. R. Hand 4/70—Amp. L. Hand	9/70—Amp. L. Leg 9/70—Death
X-ray Findings	4/68—Bursal Calcification 6/68—Widespread Soft Tissue Calcification 6/69—Progressive Arterial & Soft Tissue Calcification 9/69—Occlusion R. Radial & Ulnar Arteries	3/70—Extensive Arterial Calcification	
CCr	25–30	22.0	7.6
Serum Calcium: Mean (mg/100 ml)	10.0	8.8	8.2
(Range)	(9.0–11.7)	(7.3–10.8)	(8.1–8.4)
Ser. Phosphorus: Mean (mg/100 ml)	5.2	5.5	5.8
(Range)	(3.8–5.8)	(4.2–7.6)	(5.6–6.5)
Ionized Calcium (mg/100 ml)	4.6	4.3	4.3
Alkaline Phosphatase*	—	4.2	5.9
Ca × P	49–57	48.5	47.0

* Shinowara — Jones Units

ml., serum phosphorus 5.6 mg./100 ml., and alkaline phosphatase 3.4 units with a calcium phosphorus product of 48. *Calculated ionized calcium levels were essentially unchanged.* Relentless progression of gangrene of the right hand required mid forearm amputation 2 weeks after the parathyroidectomy. There was extensive medial calcification with marked intimal and subintimal thickening of the radial and ulnar arteries, with fibrous obliteration of the lumen. She then developed gangrene of the index and middle fingers of the left hand requiring amputation of these fingers 1 month later (Fig. 2). X-rays at this time showed almost complete calcific visualization of the medium and small sized arteries of the extremities, trunk, and chest. She next developed arterial insufficiency of the left foot which progressed, and below the knee amputation of the left leg became necessary. Following this, she went downhill and died 3 years after the onset of renal failure and 21 months post-transplantation.

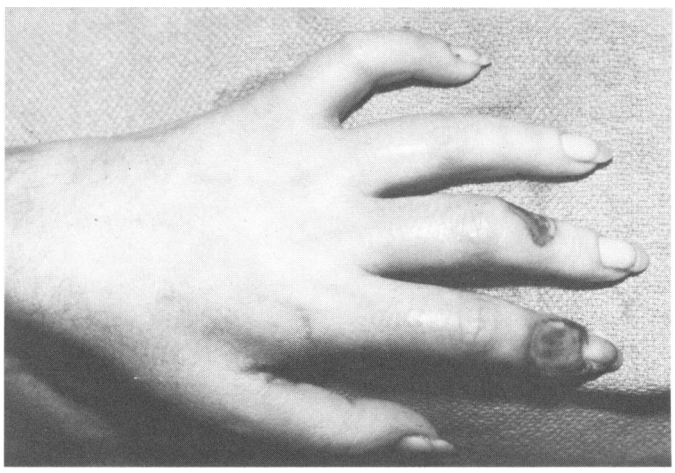

FIG. 2. Gangenous areas of index and middle fingers of left hand which eventually required digital amputation.

Autopsy revealed generalized medical calcification with fibrous obliteration of the lumen of all vessels studied, extensive interstitial and vascular calcifications within the myocardium, and marked pulmonary interstitial calcifications (Fig. 3.) The patient's own kidneys showed diffuse medial calcification of the muscular arteries with widespread glomerular calcification (Fig. 4). Abnormal calcifications were not present in the transplanted kidney.

Discussion

Metastatic soft tissue calcification in uremia is usually attributed to chronic elevation of the plasma calcium-phosphorus product. When this value is more than 60 plasma solubility is exceeded and precipitation of calcium salts occurs. Local, as in the kidney, and systemic, as after hemodialysis, increases in pH may predispose to this precipitation.[6] In our patient, metastatic calcification became apparent after renal function had been restored and when the calcium phosphorus product was minimally elevated.

Vascular calcifications are frequently seen in patients with chronic renal failure. Radiologic evidence of vascular calcification was reported by Katz[3] in 38 of 195 patients with chronic renal failure, and by Friedman[2] in eight of 20 patients treated with chronic hemodialysis. Pendras found vascular calcification in 20% of patients without evidence of hyperparathyroidism on chronic hemodialysis; this figure rose to 58% in patients who developed secondary hyperparathyroidism, and to 75% in those with autonomous or tertiary hyperparathyroid-

ism.[1,4,7] Despite the frequency of vascular calcification, arterial insufficiency and tissue necrosis associated with chronic renal failure or chronic hemodialysis has been present in only a few isolated cases.[3,5,8,9]

Arterial calification in uremia is usually localized to the tunica media, resulting in a pipestem pattern of calcification, such as is seen in Monckebergs' arteriosclerosis.[6] Intimal calcification, as seen in atheromatous plaques, is rare in uremia, thus explaining the usual lack is ischemia in spite of marked roentgenographic abnormalities. Occasionally, however, fibrous obliteration of the lumen develops, perhaps in response to the medial calcification; thereby producing ischemia as in our patient.

Progression of vascular calcification resulting in tissue necrosis after successful renal transplantation is extremely rare with only two cases reported.[5,9] In both, significant hypercalcemia was present following renal homotransplantation. In one, subtotal parathyroidectomy resulted in progressive regression of the vascular calcifications over a period of 1 year.[9] The second patient died of sepsis 39 days after subtotal parathyroidectomy. Postoperatively, the serum calcium returned to the normal range without signs of clinical improvement.[9]

In contrast, our patient did not exhibit hypercalcemia following successful renal transplantation. Nevertheless, vascular calcification, which had not been detectable while she was on dialysis, appeared and progressed to cause widespread arterial insufficiency and peripheral gangrene. Subtotal parathyroidectomy failed to halt the progression of her vascular disease during the remaining 11½ months of life. Amputations were required of three extremities. During this entire period, serum calcium remained in the low normal or hypocalcemic range (Table 1).

Microscopic vascular calcifications which occur prior to transplantation may have predisposed to calciphylaxis and the addition of prednisone therapy post-transplantation precipitated the calcinosis, even though hypercalcemia no longer existed. Calciphylaxis, once underway, may not be reversible by restoration of renal function or by parathyroidectomy. If so, parathyroidectomy may not be advisable in similar cases of severe vascular and soft tissue calcification without hypercalcemia in the post-transplant patient.

Summary

A patient is described in whom progressive vascular calcification and severe peripheral ischemia developed after apparent successful renal homotransplantation. The progressive ischemia resulted in eventual gangrene, which required amputation of three extremities, finally ended in death. Subtotal parathyroidectomy with pro-

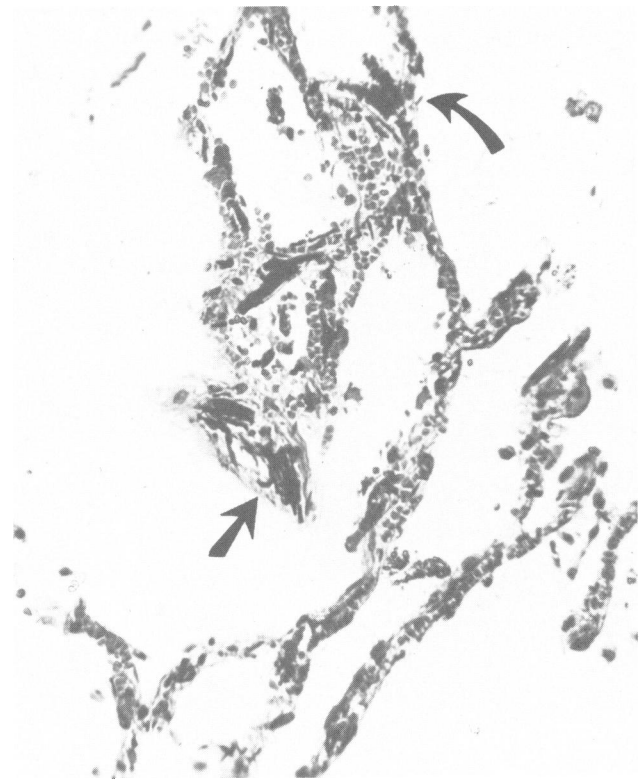

FIG. 3. Extensive pulmonary interstitial calcifications found at autopsy. Hematoxylin and eosin stain. Magnification 250×.

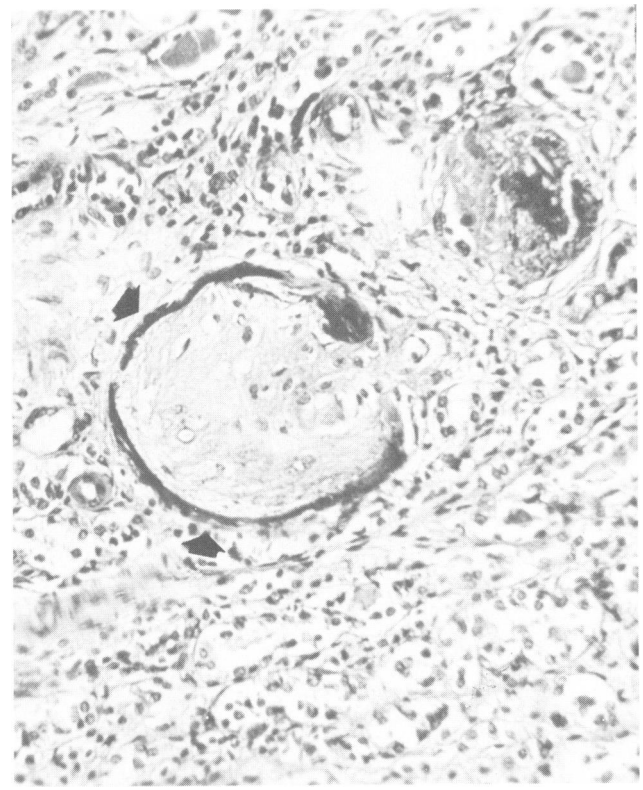

FIG. 4. Extensive calcification of glomeruli of patient's own kidney. Hematoxylin and eosin stain. Magnification 250×.

duction of hypocalcemia failed to produce regression or cessation of the progressive vascular and soft tissue calcifications. Calciphylaxis is proposed as a possible mechanism for this previously unreported sequence of events.

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