The pathogenesis of calciphylaxis, which has a rising incidence in the chronic dialysis population and a high mortality rate, is poorly understood. Abnormalities in the calcium–phosphorus–parathyroid axis are clinically related to calciphylaxis, but alone, they cannot explain this condition. Here, we present two patients who had chronic inflammatory conditions and hyperparathyroidism and who developed calciphylaxis.

A 41-year-old white woman on hemodialysis following scleroderma, hepatitis C, liver transplant, and failed kidney transplant, developed progressive ulcerative lower extremity calciphylaxis lasting more than 3 years. She had evidence of severe hyperparathyroidism and elevated serum C-reactive protein (CRP).

A 39-year-old white woman on continuous ambulatory peritoneal dialysis for 6 years for renal failure secondary to lupus nephritis, with sustained lupus activity during the dialysis period, developed rapidly progressing ulcerative calciphylaxis of the lower and upper extremities not responding to adequate treatment of hyperphosphatemia and hyperparathyroidism. Her condition culminated in death within 2 months of the appearance of the skin lesions. Her serum CRP was elevated on a sustained basis before the development of the calciphylaxis and rose to a very high level after appearance of the skin lesions.

Inflammation may assist in the development of calciphylaxis through depression of serum levels of fetuin-A, an endogenous inhibitor of calcification that is also a negative acute-phase reactant. The interactions between inflammation-mediated changes in the levels of endogenous inhibitors of calcification and abnormalities in calcium–phosphorus metabolism merit intensive study in the future as potential mechanisms of calciphylaxis.

Key words
Calciphylaxis, inflammation, C-reactive protein (CRP), systemic lupus erythematosus, scleroderma

Introduction
Calciphylaxis (calcific uremic arteriolopathy) is characterized histologically by small-vessel wall calcification and intimal hypertrophy, associated with small-vessel thrombosis and panniculitis (1). It manifests clinically as bilateral painful violaceous plaques starting in the lower extremities or as painful necrotizing skin lesions with ulcerations, which have a mortality of approximately 80% (2,3), usually from supervening infections. Various therapeutic approaches have not produced consistent results (1).

The incidence of calciphylaxis has increased recently (3). In three studies employing multivariate methods, the following predictors of calciphylaxis development were identified: hyperphosphatemia, high Ca×P product, and use of vitamin D and calcium salts (3); white race, obesity, and low serum albumin (4); and female sex, hyperphosphatemia, high serum alkaline phosphatase, and low serum albumin (5).

The pathogenesis of calciphylaxis remains unclear. The concept of a pathogenetic association between calciphylaxis and inflammation has emerged from recent developments in the topic of extra-osseous calcification. We present 2 patients that illustrate the latter concept.

Case reports

Patient 1
A 41-year-old white woman was treated for calciphylaxis for several years. She had been diagnosed with...
scleroderma in 1990. Cirrhosis, apparently caused by hepatitis C, led to a liver transplant in 1992. In 1993, she started maintenance hemodialysis because of renal failure attributed to scleroderma. She received a renal graft in 1998 and returned to hemodialysis in 2001 because of transplant loss. Her medications at that time included prednisone, cyclosporine, amlodipine, and omeprazole. She had also been treated with both calcium salts and vitamin D preparations.

In November 2002, this patient developed painful, hyperpigmented, indurated plaques on the anterior thighs and buttocks. Skin biopsy revealed calcification of the walls of the small vessels, and a bone scan revealed cutaneous calcifications in the legs and chest wall. She was treated with wound care, a low-phosphorus diet, sevelamer, and cinacalcet. Her lesions have slowly progressed, with several ulcerations and several admissions with cellulitis.

Recent measurements include body mass index (BMI) 19.7 kg/m²; calcium 7.3 ± 2.1 mg/dL with no hypercalcemia \((n = 14)\); phosphorus 4.9 ± 1.4 mg/dL, with 4 samples (29%) showing levels above 6.0 mg/dL; Ca×P product 39 ± 10, with no sample exhibiting a value greater than 55; and parathyroid hormone (PTH) 1003 pg/mL (whole molecule; normal range: 10 – 65 pg/mL). Parathyroidectomy is contemplated. Serum C-reactive protein (CRP), obtained after the appearance of the skin lesions of calciphylaxis, was 4.2 mg/dL (normal: <1.0 mg/dL).

**Patient 2**

A 39-year-old white woman developed painful, violaceous plaques with vesicular eruptions on the anterior surfaces of both thighs in April 2005. She had been diagnosed with systemic lupus erythematosus (SLE) with lupus anticoagulant in 1996 and had been on continuous ambulatory peritoneal dialysis (CAPD) since 1999 for renal failure caused by diffuse proliferative lupus glomerulonephritis. Her course on CAPD had been characterized by several episodes of peritonitis and two major lupus flares, the second of which, in 2003, resulted in a myocardial infarction, thought to be secondary to vasculitis, with left ventricular aneurysm and thrombus treated with warfarin. She had taken calcium salts for 4 years in the past and oral calcitriol for a few months. Her medications at presentation included sevelamer, prednisone, cyclophosphamide, and warfarin.

In the 2 years preceding the development of the painful skin plaques, this patient’s serum calcium \((41\) measurements) averaged 7.0 ± 0.7 mg/dL, with no values in the hypercalcemic range; serum phosphorus was 6.7 ± 1.9 mg/dL, with 25 values (61%) above 6.0 mg/dL; Ca×P product was 56 ± 17, with 19 values (46%) above 55; serum albumin \((n = 33)\) was 3.5 ± 0.4 g/dL; serum PTH \((n = 6)\) was 516±177 pg/mL; and serum alkaline phosphatase (normal range: 38 – 126 U/L) rose steadily to 222 U/L from 54 U/L. Her BMI was 24.6 ± 0.7 kg/m² in the 2 years before the development of the calciphylaxis and 21.8 kg/m² on admission. Serum PTH was 1243 pg/mL on admission; levels of proteins C and S were normal; and immunoglobulin G antiphospholipid antibodies against cardiolipin, phosphatidic acid, phosphatidylglycerol, and phosphatidylserine were positive. She was also found to be antinuclear antibody–positive by indirect immunofluorescence, but negative for anti-dsDNA and anti-chromatin auto-antibodies by ELISA. Bone scan revealed cutaneous calcifications in the thighs and upper extremities. Skin biopsy showed small vessel clots and no vasculitis.

The patient was treated with local wound care, systemic antibiotics, a low-phosphorus diet, sevelamer, cinacalcet, and sodium thiosulfate \((6)\). Serum phosphorus decreased rapidly, to an mean value of 4.1 ± 1.8 mg/dL \((n = 14)\); Ca×P product decreased to 29 ± 14, with no value exceeding 55; and serum PTH \((n = 4)\) decreased to 58 ± 33 pg/mL. However, the skin lesions progressed rapidly, with extensive necrotic eschars in the thighs, buttocks, and eventually the hands. She expired within 2 months of admission. Serum CRP levels were 4.5 ± 3.6 mg/dL \((n = 7)\) in the 2 years before the development of calciphylaxis and more than 15 mg/dL after admission with calciphylaxis.

**Discussion**

The association between inflammation and calciphylaxis demonstrated by the patients in the present report may suggest causation through the effect of inflammation on the property of serum to inhibit precipitation of calcium phosphate. Inflammation reduces serum levels of fetuin-A, a circulating 62 kD \(\alpha_2\)-glycoprotein synthesized in hepatocytes. Fetuin-A is both an inhibitor of calcification and a negative acute-phase reactant \((7)\). In a preliminary report, serum fetuin-A was 0.26 ± 0.08 g/L in 8 patients with calciphylaxis and 0.61 ± 0.15 g/L in 15 normal controls \((p < 0.001)\), and inhibition of precipitation of calcium
phosphate in a meta-stable solution was substantially less with addition of serum from patients with calciphylaxis than of serum from normal subjects. The defect in inhibition of calcification of the serum from patients with calciphylaxis was corrected with addition of fetuin-A (8).

The evidence linking low serum fetuin-A levels to calciphylaxis would be stronger if it could be shown that low levels of serum fetuin-A precede the appearance of calciphylaxis, because the development of calciphylaxis is, itself, a cause of severe inflammation (see the CRP levels in patient 2 in this report). In this regard, the fact that the 2 patients in the present report had, before the development of calciphylaxis, diseases causing sustained inflammation (documented in the second case by persistently elevated serum CRP levels) provides indirect evidence further supporting a causative association between inflammation and calciphylaxis.

Calciphylaxis in association with inflammatory conditions and renal failure has been reported in a number of patients with SLE (9–12). In addition, calciphylaxis has been reported in small numbers of patients without chronic renal failure. Primary hyperparathyroidism was present in some of these patients; in other cases, calciphylaxis without chronic renal failure developed in patients with conditions strongly associated with inflammation (13–18).

Abnormalities in the calcium–phosphorus–PTH axis, although apparently important in calciphylaxis, are not sufficient to explain the condition, primarily because of the discrepancy between the number of end-stage renal disease patients with sustained hyperphosphatemia or hyperparathyroidism, or both, and the number of patients developing calciphylaxis. Inflammation probably plays an important role in the pathogenesis of calciphylaxis through its interaction with abnormalities in serum calcium and phosphorus. Other factors, including abnormalities in serum clotting proteins (16), which can affect the level of matrix Gla protein—an inhibitor of calcification in the wall of the vessels (7)—and auto-antibodies directly or indirectly affecting the vessels (19,20) have been associated with calciphylaxis and may have been operative in the second patient reported here. That patient was on chronic warfarin therapy and had antiphospholipid antibodies. Numerous reports have shown the heterogeneity of the antiphospholipid antibodies, which bind to various anionic antiphospholipids, proteins, or to phospholipid–protein complexes. The combination of these antibody subgroups seems to be a stronger predictor for pathologic changes (21), but so far, the frequency of the reported calciphylaxis in antiphospholipid syndrome is too low to permit statistical or pathogenic evaluation. Further studies may reveal antiphospholipid specificities that are important as markers for risk of developing calciphylaxis.

Conclusions

The critical steps in the pathogenesis of calciphylaxis remain to be determined. Future studies of this disease entity should evaluate the interaction between inflammation and abnormalities in calcium and phosphate metabolism, and also the role of the clotting mechanism, vessel wall biology, local trauma, sex, body habitus, and genetic factors.

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