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Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy

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Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy.

Background. Calciphylaxis, historically considered rare, seems to be increasing in frequency. In our single center, 36 new cases have accumulated in seven years. The majority of these cases were non-ulcerating, which we believe to be early disease, in contradistinction to the vast majority of published cases that presented with ulcers.

Methods. Prospective data were collected on all patients with calciphylaxis. As well, a case control study, with two controls per patient, was performed on patients presenting with non-ulcerating plaques.

Results. The incidence of calciphylaxis in dialysis patients increased with a rate of 4.5/100 patient-years in the past three years. Eighty percent of cases presented with non-ulcerating subcutaneous plaques in the calves, easily confused with cellulitis. In those patients presenting with plaques only, the mortality rate was 33% at six months. Once ulceration develops, the mortality rate increased to above 80%. Bone scan was positive in 97% of patients. Steroid therapy appeared to be beneficial in some patients. Peritoneal dialysis, female sex and diabetes were risk factors. In the case control study of patients presenting with plaques only, serum phosphate (OR 2.6; 95% CI 1.05 to 6.45, $P = 0.038$) and Ca $\times$ P product (OR 1.46; 95% CI 1.02 to 20, $P = 0.038$) predicted the disease, as did being on calcium salts + vitamin D (OR 4.05; 95% CI 1.14 to 14.5, $P = 0.03$).

Conclusions. Calciphylaxis is no longer rare. It is usually non-ulcerating and can be diagnosed clinically in all patients. These patients have a high mortality, especially once ulceration occurs. Calcium salts plus vitamin D, as well as serum Ca $\times$ P product and high serum P increase the chance of the diseases. Therefore, the disease may be preventable. Steroids may be of benefit to some patients.

Calciphylaxis, historically considered rare, is often a fatal complication of end-stage renal disease [1–3]. It occurs in both peritoneal and hemodialysis patients and can occasionally occur pre-dialysis [4, 5]. Ulceration has usually been considered to be the hallmark sign of the condition. However, we have previously described a series of patients presenting with dense, non-ulcerating plaques in the calves [6] and this appears to be the most common mode of presentation in our center. In the past seven years, we have encountered 36 patients with the condition, only 20% presenting with ulcers. Those with ulcers have a very high mortality rate [7]. Others have also noted an increasing frequency of the disease [8]. The subcutaneous calcium deposition can usually be detected by bone scan [6, 9].

Various putative risk factors have been reported. High serum Ca $\times$ P product has been implicated by some [10, 11] but not others [4, 12]. Female gender seems to be a risk factor [4, 13, 14]. The parathyroid hormone (PTH) level may [15] or may not be [4] a risk factor. Oral $CaCO_3$ dose has been reported as increasing the likelihood of the disease [4, 9] but this was not the case in a recent study [11]. Part of the above discrepancies lie in the relatively small numbers of patients with the disease in many of these studies.

This study details our entire experience of calciphylaxis in one center over seven years, and describes the role of various diagnostic tests and patient outcomes. A case control study was performed on these patients, but excluded patients presenting with ulcers on the basis that ulceration probably represents later disease that therefore cannot be matched for time of onset. This decision was based on two observations. Asymptomatic plaques are often picked up on routine physical examination in our clinics, and plaques often subsequently develop into ulcers. Therefore, many patients with ulceration may have had non-ulcerating disease for a significant time prior to diagnosis.

Key words: hyperphosphatemia, calcium salts, dialysis, end-stage renal disease, kidney calciphylaxis, phosphate-lowering therapy.

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METHODS

Patient selection

After observations were analyzed in our first five patients [6], we prospectively collected data on all cases of calciphylaxis in our unit, which at present has 200

peritoneal dialysis and 160 hemodialysis patients. In the initial case control study of 8 patients, controls were matched only for duration of dialysis [4]. However, because female sex and peritoneal dialysis were risk factors for the disease in that study, subsequent controls, two per patient, have been controlled for dialysis modality, duration of dialysis and sex. Control patients must have started dialysis within three months of the test case starting dialysis.

Hemodialysis patients were usually dialyzed against 1.6 mmol/L Ca^{++} bath. Kt/V was greater than 1.1. Peritoneal dialysis patients were either on 4 to 5 cycles per day (75%) or cycler dialysis. The peritoneal dialysate Ca^{++} has been 2.5 mEq/L since 1996.

Investigations

Serum calcium, phosphate and PTH were measured by the usual laboratory methods; the upper limit of PTH in our laboratory is 66 ng/L. Bone scan was performed using ^{99m}Tc-MDP. Records of calcium salt and vitamin D (calcitriol) ingestion were obtained by chart review.

Statistics

Statistics were performed on the cases and their paired controls for all data using multivariate conditional logistic regression for matched case-controls using the SAS (6.12) program (SAS, Cary, NC, USA). Data are expressed as mean ± SD where applicable.

RESULTS

Incidence

Since our first case seven years ago, a total of 36 patients have presented with clinical features of calciphylaxis, and 79% of these cases have appeared in the past 40 months. This gives a frequency of approximately 4% of our PD population/year.

Clinical features

On presentation, 80% of patients were diagnosed with subcutaneous indurated plaques in the legs. These plaques varied from a couple of centimeters to involving most of the calf (Fig. 1). The most common site of initial involvement was 2 to 5 cm above the Achilles tendon. It is important to note that the plaque-only presentation may be indistinguishable from cellulitis (that is, tender, red, and warm). However, with experience, it becomes easy to feel the plaques. In almost all cases, the plaques were tender. When patients presented with ulcers, they were usually very painful, often necessitating strong analgesics. The condition was almost always bilateral.

The ulcers in those patients who presented with ulceration alone (17%) or ulceration plus plaque (3%) with usually large confluent ulcers on the legs were usually located below the knees and most often with considerable eschar. Other patients presented with multiple small (1 to 3 cm) lesions on legs, lower abdominal wall and arms (Fig. 1).

The condition was far more common in females ($P < 0.02$), peritoneal dialysis (PD) patients ($P < 0.001$) and diabetics ($P < 0.02$) than the dialysis population at risk (Table 1). Age and duration of dialysis were not different in cases compared with the dialysis population. Two patients were pre-dialysis.

Investigations

The white blood cell (WBC) count was elevated in some patients (15%). The bone scan showed abnormal uptake in 97% of patients. This uptake was almost always subcutaneous and in the clinically apparent diseased areas, but in one patient the distribution seemed to be at a deeper level. However, in two cases with deep ulceration affecting more than 50% of the surface area of the legs below the knee, no uptake was found in the legs but was marked in the lungs (Fig. 2). Only one patient had a clearly negative scan (on 2 occasions) in spite of a positive x-ray and biopsy. X-ray films of the legs were normal in 29% of patients with confirmed disease (Table 2). The x-ray patterns varied from a diffuse, fine reticular pattern to a very coarse reticulo-nodular appearance (Fig. 3). Often vessel calcification was very prominent and included the small hand vessels.

Biopsies

The diagnosis was confirmed in all four subjects (3 with plaques only, 1 with extensive ulceration) who were biopsied. However, in one patient the first two biopsies were negative; only the third biopsy gave a definite diagnosis. This patient had extensive ulceration. Two non-ulcerated patients developed extensive ulceration near the biopsy site within a few weeks.

Natural history and therapy

Thirty-three percent of the patients presenting with plaques-only progressed to ulceration with an extremely high mortality rate (89%). The overall mortality rate (all patients) at 6 and 12 months was 39 and 45%, respectively, 33% if presenting with plaques only, and 67% when presenting with ulcers (Table 3). Ulcers at any time increased the mortality rate to 80%; all of these deaths were related to calciphylaxis. No ulcers at any time conferred a good outlook with zero mortality at six months. Calciphylaxis related causes of death included sepsis, weight loss or malnutrition (often related to large doses parenteral analgesia), and discontinuation of dialysis.

For those who presented without ulceration; steroid therapy (prednisone 30 to 50 mg p.o. o.d. × 3 to 8 weeks) was administered to one half of the patients. In the early years we did not use this therapy but now use it regularly

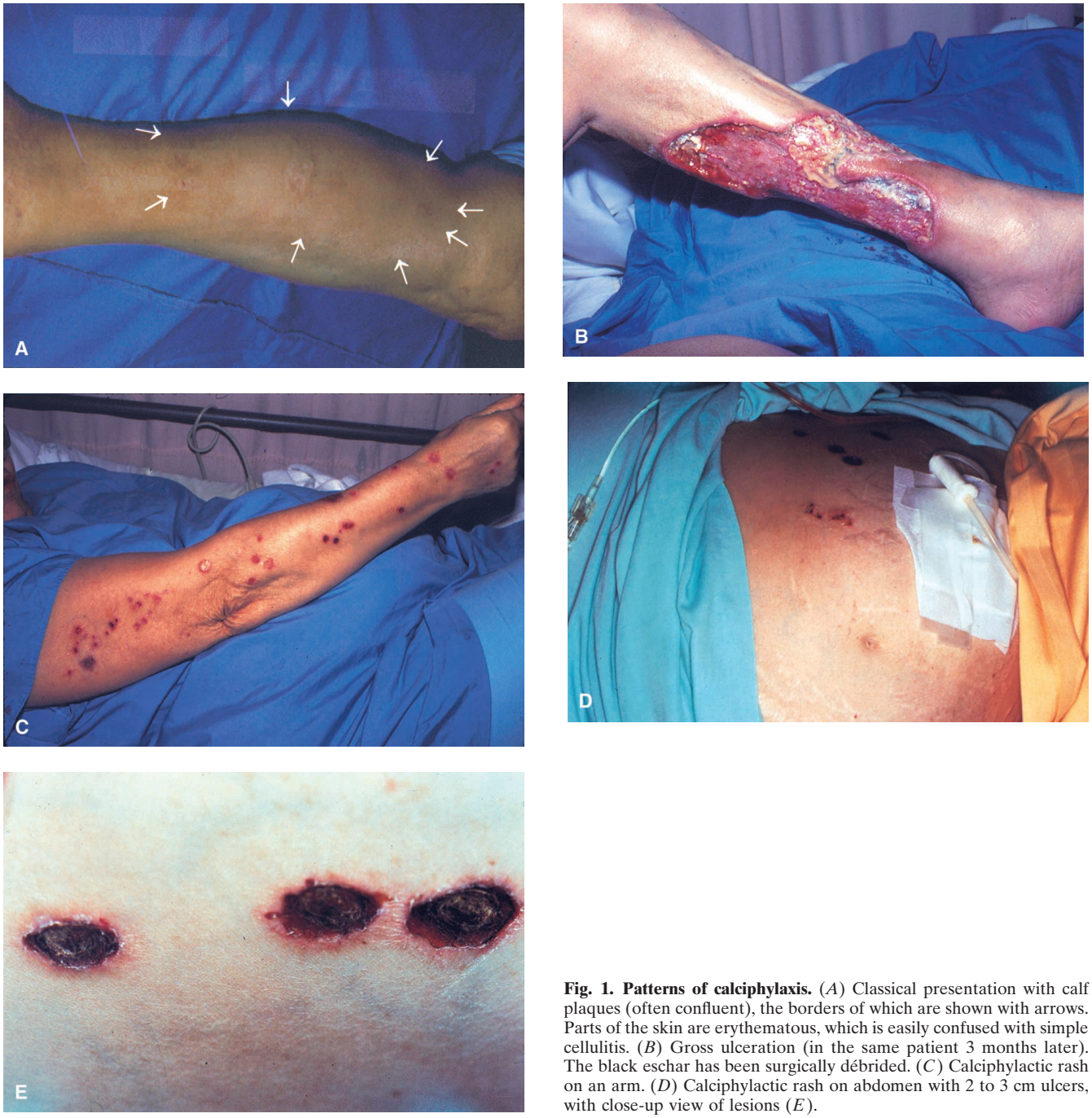

Fig. 1. Patterns of calciphylaxis. (*A*) Classical presentation with calf plaques (often confluent), the borders of which are shown with arrows. Parts of the skin are erythematous, which is easily confused with simple cellulitis. (*B*) Gross ulceration (in the same patient 3 months later). The black eschar has been surgically débrided. (*C*) Calciphylactic rash on an arm. (*D*) Calciphylactic rash on abdomen with 2 to 3 cm ulcers, with close-up view of lesions (*E*).

because of our having seen many dramatic responses. Our contraindications to steroid therapy included ulceration anywhere (related to PVD or calciphylaxis) or high risk of infection. Eighty percent of the treated patients improved (Table 4). In two of these 11 patients, the good response lasted two to six months, but the condition then relapsed into ulcerating disease. In the majority of responders, an improvement or cure was often rapid (3 to 60 days), whereas in those patients not given any specific therapy, any improvement was far more gradual (2 to 8 months). Of these untreated patients, 55% worsened and died of ulcerating disease.

Parathyroidectomy was performed in three patients with PTH values greater than 4 × normal. In all cases an improvement or cure occurred. A tissue sample from the calciphylactic area in an amputated leg and a piece of

Table 1. Patient characteristics in 36 consecutive patients with clinically apparent calciphylaxis

	All cases $N = 36$	Dialysis population at risk *patient-years* $N = 1620$	Presentation	
			Plaques $N = 29$	Ulcers $N = 7$
Age	54 ± 15	58 ± 14	55 ± 12	50 ± 14
Female	27 (75%)	858 (53%)[b]	23 (79%)	5 (71%)
PD	28 (78%)	923 (57%)[b]	23 (79%)	5 (71%)
Diabetes	24 (67%)	470 (29%)[a]	18 (62%)	6 (86%)
Dialysis duration *months*	28 ± 20	30 ± 15	33 ± 23	29 ± 20

[a] $P < 0.001$, [b] $P < 0.02$, all cases vs. entire dialysis patient population at risk

Table 2. Diagnostic tests for calciphylaxis

	Positive	Negative	Equivocal	Notes
X-ray $N = 7$	5	2[a]		[a] Both had +ve scans, 1 had +ve biopsy
Bone scan $N = 36$	34[a]	1[b]	1	[a] 2 of these pts had −ve uptake in areas of severe ulceration but +ve in lungs [b] X-ray +ve, biopsy +ve
Biopsy $N = 4$	4[a]			[a] In one of these patients first and second biopsy were −ve, the third one +ve

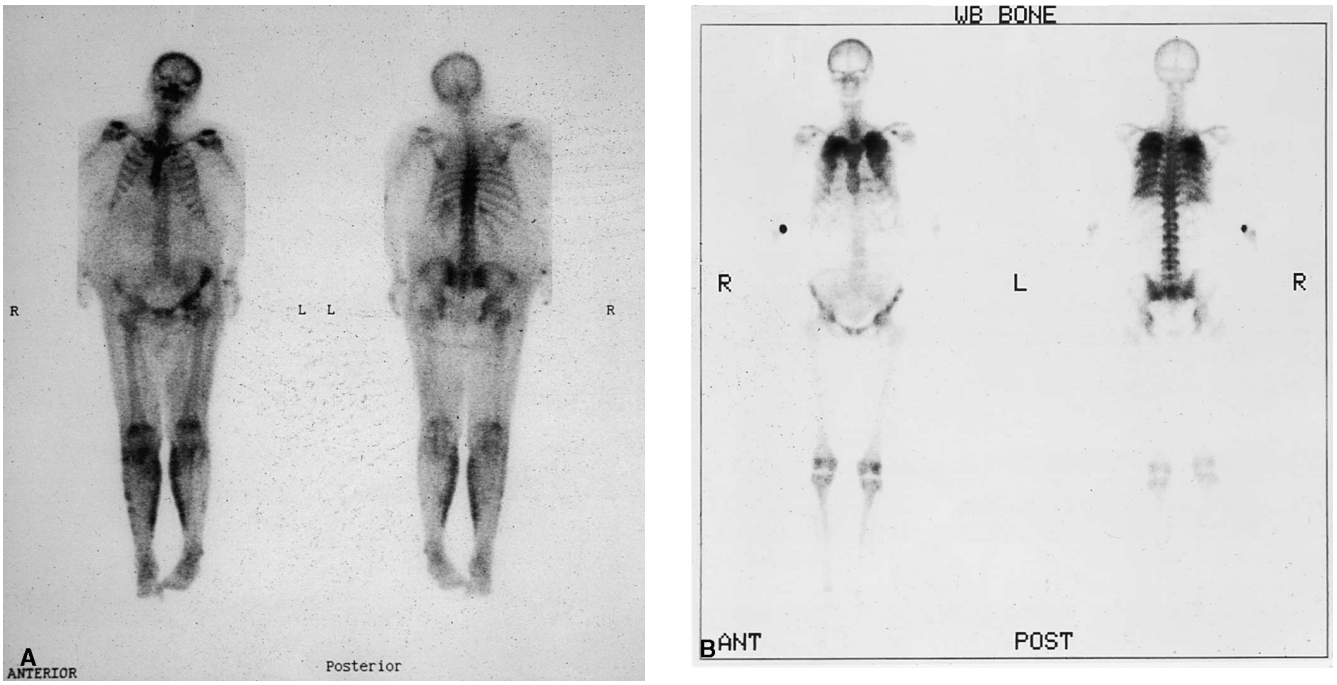

Fig. 2. Bone scan abnormalities in calciphylaxis. (*A*) Classical calf calcification. (*B*) There is strongly positive lung calcification but negative uptake in lower legs. At the time of the scan, both lower legs had gross ulceration from popliteal fossa to ankles. Other types are discussed in the **Results** section.

a grossly atherosclerotic vessel from a non-renal patient were analyzed by Fouriere-transformed infrared spectroscopy (Nicolet 510 P, Nicolet Instrument Corp., Madison, WI, USA). In both, calcification was in the form of carbonate apatite.

Risk factors

In the case control study of patients presenting with plaques-only, serum phosphate and Ca × P product were significant risk factors for calciphylaxis (univariate and multivariate; Table 5). Therapy with both Ca salts and vitamin D three and four months prior to onset increased the likelihood of getting the disease (univariate OR 3.25; 95% CI 1.009 to 10.520; $P = 0.048$) and multivariate OR 4.05; 95% CI 1.14 to 14.5; $P = 0.031$) with similar data for one month of this treatment. PTH levels and coumadin administration were not different between cases and controls.

DISCUSSION

Our results, to our knowledge the largest single unit experience reported, demonstrate that calciphylaxis is far more common in dialysis patients than the literature suggests. Contrary to the literature, most cases present with non-ulcerating plaques, which we believe to be the early form of the disease, that may respond to steroids. Once ulceration develops, the six-month mortality rate drastically increases. Serum phosphate, Ca × P product and combined therapy with calcium salts and vitamin D

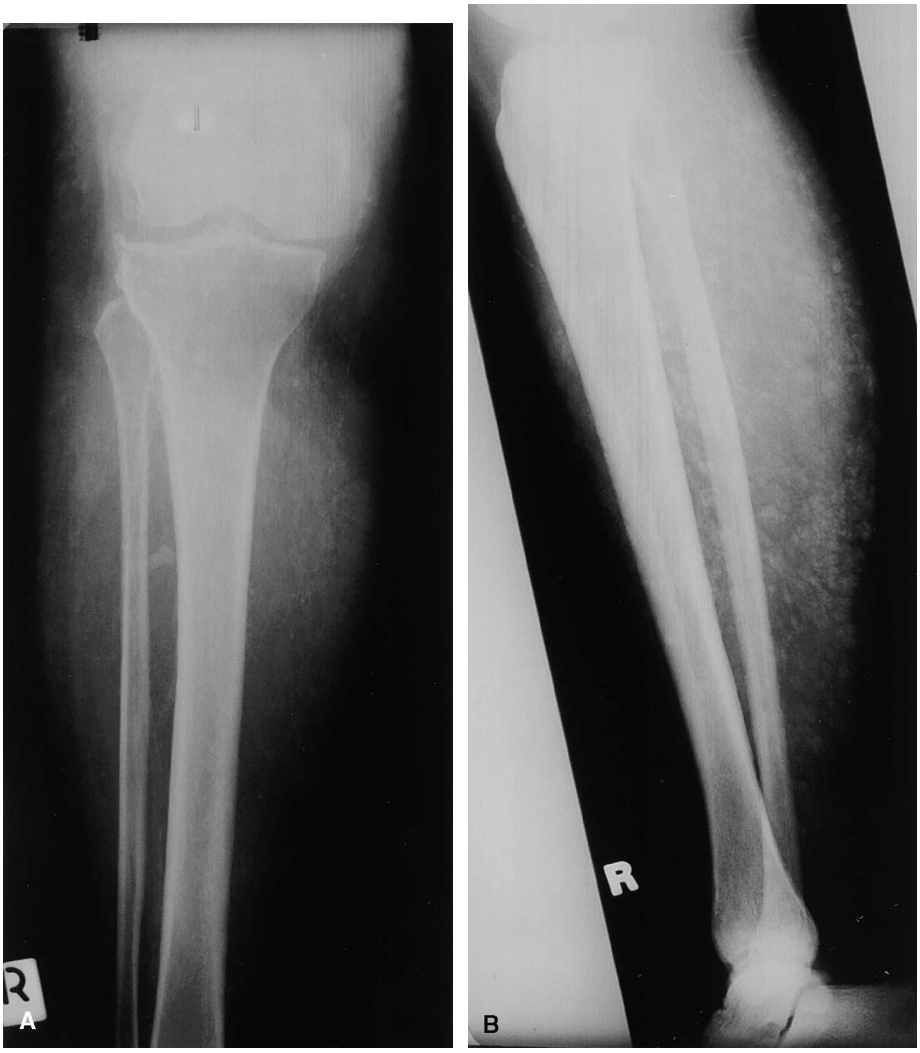

Fig. 3. Patterns of x-ray abnormalities in calciphylaxis. (*A*) Diffuse reticular pattern (with heavily calcified vessels). (*B*) Gross confluent patches of calcification. Other variants are discussed in the **Results** section.

Table 3. Mortality in 33 patients with calciphylaxis in relation to their clinical findings

		Deaths		% Deaths related to calciphylaxis	
Method of presentation	Number	6 months	12 months	6 months	12 months
Plaques only	27	9 (33%)	11 (41%)	89	73
Ulcers ± plaques	6	4 (67%)	4 (67%)	100	100
All patients	33	13 (39%)	15 (45%)	93	93
Subsequent clinical status					
Plaques→ulcers	9	8 (89%)	8 (89%)	100	100
Ulcers at any time	15	12 (80%)	12 (80%)	100	100
No ulcers at any time	18	0	3 (17%)		66

are risk factors for the disease, as well as female sex, diabetes and peritoneal dialysis.

The term calciphylaxis is based on the original description in experimental non-uremic rats, in which animals were sensitized by various measures and subsequently injected with albumin or traumatized [16]. The animals developed severe calcification at the injection site as well as in the atrium of the heart. Calcification was found in the subcutaneous tissues but without vessel calcification, the hallmark of calciphylaxis in humans. The experimental design and histology bear little resemblance to the human situation. Hence, the variety of nomenclature in the literature includes calcifying panniculitis, calcific uremic arteriolopathy, necrotizing panniculitis and calcinosis cutis. The condition as described in over 98% of all reported cases is characterized by cutaneous painful ul-

Table 4. Disease progression and response to treatment in 27 patients with calciphylaxis presenting with plaques-only

	Outcome		Death within 12 months calciphylaxis	
Therapy	Worse	Improved/stable	Related	Not related
Nil				
$N = 11$	6 (55%)	5 (45%)	6 (100%)	0
Steroids				
$N = 14$	3 (21%)	11 (79%)	3 (60%)	2 (40%)
Parathyroidectomy				
$N = 3$		3†	0	0

[a] Two of these patients obtained significant improvement over 2–6 months but then relapsed, and 1 other patient had steroid therapy
[b] Parathyroidectomy
[c] One patient had both steroid therapy and parathyroidectomy

cers, usually with eschar, usually on the legs, occurring in dialysis or post-transplantation patients. Marked calcification of blood vessels is often found radiologically.

Several years ago, we described non-ulcerating plaques in the calves as the major presenting feature in five patients [6]. Very rare reports of similar plaques had been described previously [1, 17, 18]. It is clear from the present study that presentation with non-ulcerating plaques is far more common than presenting with ulcers. It is important to recognize that these lesions are easily missed by the physician, who often makes an alternative diagnosis of cellulitis. After the experience of several cases, however, the diagnosis can be made rapidly. The condition has now become so prevalent in our peritoneal dialysis population that we often routinely examine for and find the condition at clinic visits in early asymptomatic patients.

The apparent increased incidence of this condition may, therefore, be partially related to increased physician awareness. Others, though, have noted an increase in incidence of ulcerating calciphylaxis in the past few years [8, 19, 20]. The basics of dialysis therapy have changed little over the past two decades, other than changing clearance targets, but our therapy of renal bone disease has changed dramatically. Hyperphosphatemia has assumed increasing importance as a direct stimulator of PTH production in dialysis patients [20] and has recently been shown to be a predictor of mortality [21]. Calcium salts have replaced aluminum salts as phosphate binders and the usage of vitamin D has increased. Our finding that the use of calcium salts plus vitamin D increases the risk of developing calciphylaxis suggests that the disease may be preventable by using non-calcium containing phosphate binders, or even calcimimetics [22]. Interestingly, it has recently been shown that coronary artery calcification increases in young dialysis patients related to calcium-salt ingestion [23], but this does not progress when changed to non-calcium phosphate binders [24]. Our results confirm a very recent report in which high serum phosphate and Ca × P product increased the risk of calciphylaxis [25].

The diagnosis is made clinically. For example, we have not yet encountered a patient who we considered to have the condition who had negative investigations. The bone scan is almost always positive and in most cases, the abnormal uptake is in the clinically obvious areas. Comparable to the clinical situation, radiologist experience of the disease increases the sensitivity of the test, especially when the changes are subtle. We have encountered only one patient with clinically obvious disease who had a negative bone scan (which on a repeat scan 2 months later, was still negative). The diagnosis in this case was confirmed by x-ray and biopsy. Of the limited number of patients who had x-rays ($N = 7$), two were negative in spite of grossly obvious disease. Overall, therefore, bone scan is the test of choice for calciphylaxis.

With regard to bone scan, it is interesting to note that in two of our worst patients, with florid and widespread deep ulceration of the lower legs, right down to the muscle (similar to Fig. 1B), there was zero uptake in the legs but strong uptake in the lungs. It seems probable that the complete denudation of subcutaneous tissue rids the limbs of calcium-containing tissue.

There is seldom a need to perform a biopsy, and in our experience, this can be hazardous. In two of our four biopsies, both in non-ulcerating patients, ulceration developed in the region of the incision, within two to six weeks. The ulceration, surprisingly, did not develop at the exact biopsy site but 2 to 3 cm away. Both patients died of rapidly progressive disease. Others have noted poor healing post-biopsy [26]. A single biopsy may be negative in the presence of the disease. In one patient three biopsies had to be taken. The first biopsy did not contain subcutaneous tissue. The second biopsy was negative for calciphylaxis, in spite of large amounts of subcutaneous tissue in the sample. Only the third biopsy confirmed the diagnosis. We have encountered a similar patient in another hospital who needed three biopsies to make the diagnosis. The diagnosis was pursued by repeated biopsies on account of the attending physician being unfamiliar with the condition. Thus, biopsies overall gave no new information to the nephrologist (except in the first biopsy, which was on our index case). Because they can be hazardous, biopsies should be discouraged.

The role of parathyroidectomy in this condition is unclear and our report does little to expand current knowledge in this area. Some dramatic results have been reported [15] but there is clearly a publication bias for positive reports. In a review of 47 patients, outcome was unchanged following parathyroidectomy [14]. However, all patients in these studies have had ulcerating disease. In our case control study, all three patients had resolution of subcutaneous plaques, although in one of these patients, concurrent steroids were given. In our in-

Table 5. Case control study of 24 patients with calciphylaxis presenting as plaques-only with two controls per patient

			Univariate		Multivariate	
	Cases	Control	OR ± 95% CI	P	OR ± 95% CI	P
Phosphate *mmol/L*	2.15 ± 0.79	1.8 ± 0.53	2.40 (1.009–5.714)	0.048	2.6 (1.05–6.45)	0.038
Ca *mmol/L*	2.39 ± 0.25	2.34 ± 0.23	2.51 (0.042–3.74)	0.42	2.62 (0.3–21.7)	0.37
Ca × P *mmol/L*	5.23 ± 1.8	4.26 ± 1.48	1.43 (1.013–2.02)	0.042	1.46 (1.02–20.9)	0.038
PTH *ng/L*	527 ± 323	585 ± 670	1.0 (0.999–1.001)	0.68	1.0 (0.99–1.01)	0.79
$CaCO_3$						
3 & 4 months			4.0 (1.07–14.92)	0.039	3.92 (0.98–15.6)	0.053
Vitamin D						
3 & 4 months			2.6 (0.818–8.26)	0.55	2.51 (0.78–8.06)	0.62
Ca + Vitamin D						
3 & 4 months			3.25 (1.009–10.529)	0.048	4.05 (1.14–14.5)	0.03
Ca + Vitamin D						
1 month			2.86 (0.96–8.6)	0.060	3.56 (1.0–12.66)	0.05

Data on 3 patients were incomplete and are not included in the case control study.

dex case, the very extensive and confluent plaques extending throughout the entire calves (similar to Fig. 1A) started to resolve within two weeks of parathyroidectomy and within four months had completely resolved. We have not considered parathyroidectomy on extensively ulcerated patients because they are so often debilitated, have advanced disease and are in too poor a condition for surgery. Further studies are needed to define the role of parathyroidectomy.

The dramatic twofold increase in mortality when ulcers develop strongly suggests that all possible therapy should be entertained to prevent ulceration. The decision to treat some patients with steroids was initially prompted by a predominance of cellulitis-type symptoms and signs in several patients. In several patients, the response to treatment was dramatic, with reduction in pain and redness within 3 to 10 days. In many others, the disappearance of the lesions takes two to three months after therapy started. The majority of plaque-only patients develop ulceration (with an 89% mortality rate) when untreated as distinct from only 21% of those treated with steroids. However, the low numbers of patients and the arbitrary decision-making for steroid therapy do not allow valid statistical analysis. Only two patients in the literature have been given steroids [27, 28], with one patient obtaining a good response was obtained [27] but not the other. It is our recommendation that all patients with non-ulcerating disease be given a therapeutic trial of steroids, unless medical contraindications exist, but further studies are clearly needed.

Hyperbaric oxygen has been shown to reverse ulceration in some patients [29] and in support of this therapy, low skin oxygen tensions have been found in the limbs of patients with calciphylaxis [30]. We have no experience of its usefulness.

Part of the high mortality rate in these patients relates to the accompanying co-morbid conditions that include cardiovascular disease, poor nutrition and diabetes. However, these conditions are not prerequisite for the condition, as our three most severe cases had no known detectable vascular disease.

The female predisposition to calciphylaxis may be partially related to the increased fat mass in females because fat has less blood supply than other tissues. The increased frequency of diabetes in these patients could further compromise circulation. It is possible that the increased frequency of calciphylaxis in PD patients is due to the constant exposure to hyperphosphatemia compared to hemodialysis, where significant reductions in serum phosphate occur after each treatment.

Another factor could be that adynamic bone disease is more common in peritoneal dialysis patients and in diabetics [31, 32]. In this condition, the bones have a reduced buffering capacity for additional calcium, presumably leading to increased tendency for tissue calcification [33]. Parathyroidectomy in such patients with calciphylaxis is unlikely to be of any benefit. Although our results confirm previous reports of the lack of effect of PTH levels on onset of calciphylaxis [11, 25] this cannot be ruled out as a factor due to the recent finding that the 1-84 intact hormone assay may include a very significant amount of inactive 7-84 PTH [34]. Further studies of active PTH levels in calciphylaxis need to be performed.

We are convinced that plaque-only patients have calciphylaxis rather than a novel calcifying disorder for the following reasons. The histology and bone scans are the same whether ulcerating or not. One third of patients with plaques-only develop ulceration and many patients have both ulcers and plaques simultaneously. Plaque-only presentation probably reflects early, potentially treatable disease.

In conclusion, the frequency of calciphylaxis seems to be markedly increasing, probably related to long-term and wide usage of calcium salts plus vitamin D. The disease is clinically obvious but can be confirmed by bone scan. The vast majority of cases have non-ulcerating

plaques representing early disease. Steroids seem to be beneficial in reducing the development of ulceration, which carries an over 80% mortality rate. New phosphate-lowering therapies may prevent this condition in the future.

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NOTE

Since this article was accepted for publication, six new patients have been diagnosed with calciphylaxis (4 non-ulcerating and 4 on PD).

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