Calciphylaxis

Esteban Daudén, MD, PhD[a,*], María-Jesús Oñate, MD[b]

KEYWORDS

• Calciphylaxis • Vascular calcification
• Hyperparathyroidism • Calcium/phosphorus product

CALCIPHYLAXIS

Calciphylaxis has been classically considered a rare, life-threatening disease that is usually observed in patients with renal failure and is characterized by violaceous, reticulate areas of cutaneous necrosis and eschar, particularly in the extremities, raised calcium phosphorous product, an elevated parathyroid hormone (PTH) level, radiographic evidence of vessel and soft-tissue calcification, and the finding of mural calcification affecting small arteries and arterioles on histopathology.[1] Numerous controversial aspects of the disease are still unresolved, however.

Calciphylaxis: A Changing Concept

Calciphylaxis was first reported by Bryant and White in 1898, who described the association between cutaneous gangrene and vascular calcification.[2] The term "calciphylaxis" was coined by Selye and colleagues[3] in 1962 as a condition of systemic hypersensitivity induced by a sensitizing agent that resulted in metastatic calcification in various organs, analogous to anaphylaxis. They performed an experimental work, a two-stage process in laboratory rats. First, a period of sensitization was achieved by various methods (eg, high phosphate diet, exogenous vitamin D3, or biochemically induced hyperparathyroidism). This test was followed by a challenging agent (eg, egg white, metallic salts, local tissue trauma), which resulted in cutaneous calcification and necrosis.

A few years later, a syndrome characterized by peripheral ischemic tissue necrosis and cutaneous ulceration was reported in uremic patients, and because of the resemblance to the animal model of Seyle and colleagues, it was termed calciphylaxis.[4] At this point we should question whether the term is calciphylaxis appropriate. The truth is that although a similar clinical picture may be considered from the two processes, the histologic findings differ in significant ways. The hallmark of calciphylaxis in humans is calcium deposition in small and medium-sized vessel walls, whereas Seyle's model in nonuremic rats primarily resulted in interstitial calcification within the subcutaneous tissue.

Another question is whether there is unanimity in the literature about the meaning of calciphylaxis. Undoubtedly not. The classical definition of calciphylaxis includes the presence of painful violaceous reticulate lesions that progress to necrosis, which typically involves the lower extremities, the association with renal failure, particularly in patients who are undergoing dialysis, an elevated PTH level with dysregulation of calcium and phosphorus metabolism, and a frequently fatal outcome.[5] Patients described under the term "calciphylaxis" have clinical findings and locations different to those previously described, absence of renal insufficiency, absence of elevated PTH, a normal calcium/phosphate product, and good prognosis. This is the reason why cases with characteristics of the so-called calciphylaxis have received multiple denominations, including vascular calcification-cutaneous syndrome, uremic small-artery disease, calcifying panniculitis, uremic gangrene syndrome, uremic small-artery disease with medial calcification and intimal hyperplasia, calcific azotemic arteriopathy, or calcific uremic arteriolopathy. All of them are mostly descriptive, but with a common finding—the calcification of the vessel wall. This is the reason why

[a] Department of Dermatology, Servicio de Dermatología, Hospital Universitario de la Princesa, Diego de León, 62, 28006 Madrid, Spain
[b] Dermatology Unit, Centro de Especialidades de Fuencarral, Madrid, Spain
* Corresponding author.
E-mail address: estebandauden@medynet.com (E. Daudén).

Dermatol Clin 26 (2008) 557–568
doi:10.1016/j.det.2008.05.006

there is a changing concept of what calciphylaxis means, and many authors suggest that the term calciphylaxis be abandoned. Others suggest that although the concept of calciphylaxis is not yet clearly defined, the term "vascular cutaneous calcification" should be used.[6] It is obvious that "calciphylaxis" is an attractive word that has achieved a high implantation on the medical community, but it is equally necessary to reach an agreement on its meaning and limits.

Associated Disorders

Renal disease and hyperparathyroidism

Calciphylaxis, in its classical concept, occurs most commonly—but not invariably— in patients with end-stage renal disease, particularly patients who are undergoing hemodialysis or peritoneal dialysis (**Box 1**).[7] It develops in approximately 1% of patients with terminal renal disease.[8] One percent to 4% of patients with renal failure who are on dialysis are estimated to be affected by calciphylaxis annually.[1,9,10] To be more accurate, most patients who have undergone long-term hemodialysis develop intravascular microcalcification of the type described in calciphylaxis, but only a few eventually manifest the characteristic clinicopathologic syndrome. Renal failure seems to be of varying causes and severity. Chronic renal insufficiency predominates on the acute and transitory forms.[6,11] Calciphylaxis has been described in patients in the setting of moderate renal insufficiency, although other predisposing factors, such as obesity and diabetes mellitus, were present.[12] Calciphylaxis is also frequent in patients who underwent renal transplantation, including patients with functioning grafts.[13] The association between nephrogenic fibrosing dermopathy and calciphylaxis has been described.[14]

As we pointed out previously, calciphylaxis has been reported in the absence of renal disease.[15–19] Some authors consider that the absence of severe renal insufficiency or end-stage renal disease should not dissuade physicians from pursuing the diagnosis of calciphylaxis, because severe renal dysfunction does not seem to be a necessary component for the development of the disease.[12]

Frequently, patients have secondary or tertiary hyperparathyroidism.[9,20,21] In a review of 104 patients with calciphylaxis, Hafner and colleagues[22] found elevated PTH levels in 75 of 79 patients who had levels drawn. Budisavljevic and colleagues[8] reviewed 40 patients with calciphylaxis and showed that PTH levels were elevated in 82%. Recent reports suggested that the presumed association of elevated PTH levels with development of calciphylaxis may not be as convincing as expected based on previous data.[12]In a series of 16 patients with calciphylaxis, Coates and colleagues[23] found that only 6 had increased PTH levels at disease onset, although the other 10 had a history of elevated values. Bleyer and colleagues[24] showed that only two out of nine patients had abnormal PTH levels. Probably many of these patients who presented with normal or near-normal PTH levels reflect the increased usage of medications, such as calcitriol or calcium-containing phosphate binders, in an attempt to lower PTH levels.

Box 1
Cutaneous vascular calcification: associated disorders

Renal failure and hyperparathyroidism

Other disorders

- Liver disease (eg, alcoholic cirrhosis)[25–27]
- Crohn's disease[16]
- Malignancies (eg, metastatic breast carcinoma,[28] cholangiocarcinoma,[29] malignant melanoma,[30] osteosclerotic myeloma,[31] chronic myelomonocytic leukemia[32])
- Rheumatoid arthritis on long-term steroid and methotrexate use[33,34]
- Protein S deficiency[26,33]
- AIDS[35]
- Antiphospholipid antibody syndrome[36]
- POEMS syndrome[37]

Cutaneous vascular calcification as an epiphenomenon[6]

- Calcinosis cutis secondary to injections
- Sclerosing panniculitis in venous insufficiency
- Nodular vasculitis
- Leukocytoclastic vasculitis
- Traumatic ulcer
- Epidermoid carcinoma
- Scars

Other Disorders

Other disorders have been described in association with calciphylaxis.[1,25–37] Most of them do not present with renal failure, and their causal relationship is unclear (**Box 1**). There is controversy regarding whether to consider these cases as true calciphylaxis. Some of them have a clinical and histopathologic picture as described for typical calciphylaxis, but others lack these findings.

Cutaneous Vascular Calcification as an Epiphenomenon

Deposits of calcium at the intimal and medial layer of small- and medium-sized vessels have been

described in cutaneous lesions of diseases with a well-defined diagnosis, such as vasculitis, sclerosing panniculitis, and cutaneous tumors (**Box 1**).[6] They are frequently associated with renal failure or hypertension or diabetes mellitus or signs or symptoms of atherosclerosis. The clinical findings are those of the associated disease, and they predominate on the lower extremities (**Fig. 1**). Their consideration as calciphylaxis is a matter of controversy. The associated disease probably acts as a triggering factor in a predisposed patient.

Pathogenesis

The pathogenesis of calciphylaxis is still poorly understood and remains speculative. It is thought to be multifactorial. One of the key factors involved in the mechanism of tissue calcification, at least in a wide number of patients, is the dysregulation of the calcium/phosphate metabolism, which leads to an elevated calcium/phosphorus product. It is usually a consequence of renal failure and secondary hyperparathyroidism. Levin and colleagues[38] even published a mathematical formula to predict patients at risk for calciphylaxis. They developed an interesting model for the prediction of the likelihood of calciphylaxis in patients with chronic renal failure. Gipstein and colleagues[39] were among the first investigators to demonstrate these changes (all 11 patients of their with chronic renal failure and calciphylaxis had hyperphosphatemia). Although these alterations in metabolism were considered the sine qua non of calciphylaxis, recent reports have shown growing evidence of cases with normal levels of calcium and phosphorus.[8,12] In a case control study of nine patients with calciphylaxis, Bleyer and colleagues[24] observed that calcium/phosphate products did not significantly differ from those of the control patients. A history of diabetes mellitus (most often with complications of the microcirculation, such as retinopathy or neuropathy), obesity, and atherosclerotic vascular disease is frequently found in these patients,[6,40] which suggests that a predisposed ground helps the deposition of calcium.

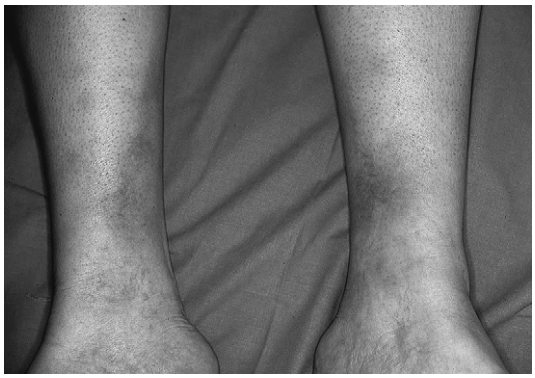

Fig. 1. Lipomembranous panniculitis with cutaneous vascular calcification.

On the other hand, these abnormalities do not explain the thrombosis in calciphylaxis. In 1990, Mehta and colleagues[41] tried to explain this phenomenon, which in turn might result in ischemia and tissue necrosis. Their theory was based on the similarity in the skin lesions of warfarin necrosis and calciphylaxis. They measured antigenic and functional protein C levels in patients with end-stage renal disease and systemic calciphylaxis undergoing hemodialysis, patients without calciphylaxis undergoing dialysis, and normal volunteers. Antigenic levels of protein C were normal in all patients, whereas functional levels were significantly reduced in patients with calciphylaxis compared with patients in the other groups. The hypercoagulable or prothrombotic state might result in thrombosis in vessels already narrowed by calcification. Their findings have been confirmed by some investigators, even demonstrating quantitative reductions of protein C and S.[21,42–44]

On the contrary, other studies have not substantiated the aforementioned hypothesis. Ross and colleagues[45] questioned the relevance of a low protein C level because it persisted even when the lesions were healing, and Rudwaleit and colleagues[46] described a renal transplant patient on long-term oral anticoagulant therapy who developed calciphylaxis, which suggested that hypercoagulability does not seem to have played a significant role. Essary and Wick[47] assessed histologic specimens from 13 cases of calciphylaxis, all with renal insufficiency. They found frank thrombosis infrequently, with venular and arteriolar microthrombi present in 23% of cases. Their results may reflect a sampling bias, but it also may be true that acquired coagulopathies help to define a subset of calciphylaxis cases rather than the entire patient group with this disorder. Endovascular fibrosis also has been thought to be the cause of ischemic tissue damage. Sheila and Crawford[48] performed a three-dimensional analysis of a calciphylaxis plaque and found vascular mural calcification as an early and essential process in the development of the plaque, probably preceding the other pathologic features.

Recently, studies on vascular disease in humans, including calciphylaxis, have revealed the presence of bone glycoproteins, such as matrix Gla protein, osteopontin, and bone morphogenic protein-4, in pathologic calcified arteries.[49,50] These findings support the view that they play a role in the development of vascular fibrosis and calcification.

In predisposed individuals and predisposed tissue, several aggravating or triggering factors for vessel calcification in calciphylaxis have been recognized (eg, systemic corticosteroids, vitamin D exposure, blood transfusions, low serum albumin, oral phosphate binders, metallic salts, calcitriol, local trauma, ultraviolet light treatment, warfarin use, malnutrition and weight loss, and insulin injections).[1,5,40,51–53] Their role is still controversial because some have proved paradoxically to be useful in the treatment of calciphylaxis.[54]

Clinical Manifestations

The mean age of presentation of patients with calciphylaxis is 48 years (range, 6 months to 83 years).[5] It is rarely described in children.[55,56] Although a patient's sex does not seem to predict higher prevalence, some authors suggest a female preponderance.[6,13,40,57]

Skin Manifestations

The clinical manifestations of the skin are heterogeneous. The most common presentation in early lesions may include erythema, tenderness, mottling/violaceous discoloration that resembles livedo reticularis, and—rarely—flaccid or hemorrhagic bullae over the affected region. Lesions appear as painful indurate violaceous plaques or nodules surrounded by a reticulate purpura, which are most commonly located on the medial thighs, buttocks, and lower part of the abdomen (**Fig. 2**). Progression results in the rapid development of central necrosis and deep ulcerations with eschar formation (**Fig. 3**). Ulcers are nonhealing and irregularly shaped and have angulated or stellate borders. Lesions tend to be symmetric, bilateral, and well demarcated. Sometimes the lesions are so painful that patients require frequent narcotic medications.[58] Peripheral gangrene of the toes and fingers (distal digital gangrene) develops occasionally. Peripheral pulses are preserved distal to the areas of necrosis. Some cases present without purpura, livedo reticularis, or ulceration.[59,60] Although lesions tend to localize to the lower extremities and abdomen, they may involve the neck, breast, tongue,[61] vulva,[5] or penis.[7,58,62–64] Some authors suggest that the distribution of the lesions may predict prognosis; cases that involve acral (fingers, toes, penis) and distal (calves, forearms) distribution have a better prognosis than cases that involve proximal distribution (thighs, buttocks, trunk).

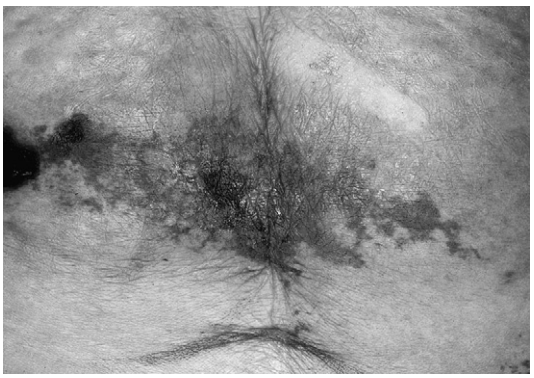

Fig. 2. Erythematous plaque surrounded by reticulate purpura. End-stage renal disease under peritoneal dialysis.

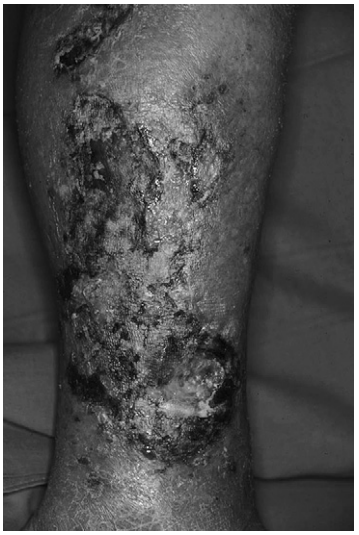

Fig. 3. Deep, nonhealing, irregularly shaped ulcers in the lower limb. Renal failure.

Systemic Manifestations

In addition to the cutaneous syndrome, other systemic manifestations,[20,65] caused by vascular and extravascular calcification of soft tissues and internal organs, may be present. Because patients with calciphylaxis usually have multiple pathologies (renal failure, diabetes mellitus), sometimes the origin of the systemic involvement is not clear. Manifestations include skeletal muscle signs or symptoms that appear as muscle weakness, tenderness, or severe myositis[15] with rhabdomyolysis,[19] calcific cerebral embolism,[66] dementia and infarction of the central nervous system, pulmonary involvement[67] with fulminant pulmonary calciphylaxis and metastatic calcification causing acute respiratory failure,[68] heart disease (myocardium infarction, cardiac valvular dysfunction, atrioventricular block, and calcification of the cardiac conduction system, called by some as the syndrome of "bony" heart).[69] Cardiac valve

involvement has been attributed to nanobacteria,[70] gastrointestinal involvement (bowel infarction with massive gastrointestinal hemorrhage),[71] calcification of the stomach, and occasionally calcification of the pancreas and adrenals.

Laboratory and Image Findings

Typical cases of calciphylaxis associated with renal failure present with elevated PTH levels, high calcium, an elevated phosphate level, an elevated calcium phosphorus product, elevated alkaline phosphatase, a high urea and creatinine value, and anemia. Normal values of these parameters do not exclude diagnosis of calciphylaxis in patients.

Within radiologic grounds, small vessel involvement, defined by some as a diameter less than 0.5 mm, may be considered the most specific radiographic finding in calciphylaxis.[5] Radiography may miss many of the smaller calcifications. Intraparietal calcification is recognizable as a fine double-lined network (**Fig. 4**); however, it should be noted that vascular calcifications, but not calciphylaxis, may be present in 10% of all patients undergoing hemodialysis, 58% with secondary hyperparathyroidism, and 75% with tertiary hyperparathyroidism.[65] Bleibel and colleagues[72] demonstrated that simple, safe, and inexpensive radiographic imaging using the mammography technique was superior to plain soft-tissue radiography and three-dimensional CT scanning in showing the hallmark arteriolar calcifications of patients with calciphylaxis. They proposed a possible role for this technique in diagnosing calciphylaxis.

Xeroradiography also has been shown to be a useful technique in determining the involvement of subcutaneous arterioles in calciphylaxis. The appearance of arteriolar calcification differs from that of atherosclerosis, allowing a differential diagnosis.[73] High-resolution, high-frequency ultrasound may aid in the diagnosis of lesions before the occurrence of the typical skin lesions.[74] Finally, scintigraphic findings were reported in a patient with calciphylaxis and renal failure showing increased tracer accumulation in subcutaneous tissue of the trunk and lower extremities.[75]

Histopathologic Features

Many histopathologic features have been described in the cutaneous lesions of patients with calciphylaxis (**Box 2**). The finding that defines calciphylaxis is the presence of small and medium vessel calcifications (**Fig. 5**). Small arteries, arterioles, and venules may be involved. Robinson and di Giovanna[5] reported that the size of affected vessels ranged from 0.02 to 0.60 mm and averaged 0.1 mm. Calcium deposits are usually extensive within the walls of vessels and frequently show a concentric, circumferential, ring-like pattern. It seems that there is no apparent relationship between the size and density of calcium deposits and the clinical status of the lesions.[47] Calcification is found chiefly within the media and intima. The number of calcified vessels varies. They are found within the dermis and subcutaneous fat (**Fig. 6**), particularly in the upper portion of the

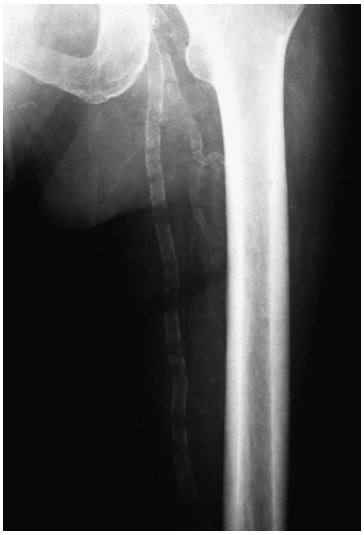

Fig. 4. Thigh radiology. Vascular calcification in soft tissues.

Box 2
Histopathologic features in calciphylaxis

- Small and medium vessel calcifications (small arteries, arterioles, and venules)
- Intimal hyperplasia (endovascular endothelial proliferation and intimal fibrosis)
- Fibrin thrombi in the dermal and subcutaneous vessels
- Epidermal ulceration
- Dermal or subcutaneous necrosis
- Degeneration and necrosis of dermal collagen
- Erythrocyte extravasation
- Acute and chronic septal and lobular panniculitis
- Mixed inflammatory infiltrate around superficial and deep vessels
- Interstitial deposition of calcium
- Epidermal, hair follicle, and perineurial calcification
- Pseudoxanthoma elasticum-like features

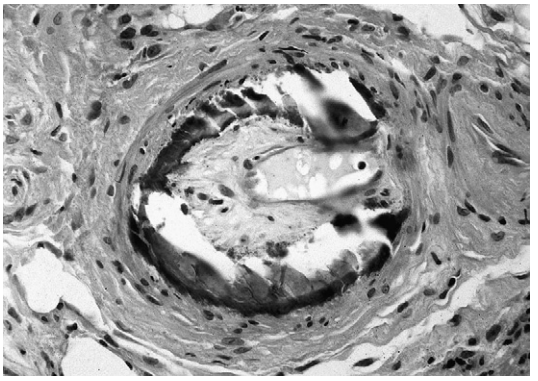

Fig. 5. Concentric calcium deposits within the vessel wall. Intimal hyperplasia with partial obliteration of the lumen.

subcutaneous tissue. Usually hematoxylin/eosin examination is wholly sufficient, but in certain cases, a Von Kossa stain may highlight calcium deposits and yield a black reaction product. Sometimes the calcification is associated with luminal thrombosis.

Intimal hyperplasia with endovascular endothelial proliferation and intimal fibrosis in cutaneous blood vessels is another characteristic finding. It is more common in advanced lesions.[47] The intimal layer has a fibroedematous appearance that leads to variable degrees of obliteration, rarely complete. No relationship to the presence or degree of vascular microcalcification in the same blood vessels has been found.[34] Endovascular fibrosis seems be an active cause of ischemia.[76] Fibrin thrombi in the dermal and subcutaneous vessels are usually found.[41,44] They may be associated with parietal calcification, but in our experience, calcified vessels are usually free of thrombi.[6] They are mainly present close to areas of epidermal/dermal necrosis. Essary and colleagues[47] considered vascular thrombotic occlusion an infrequent event, with venular and arteriolar microthrombi present in 23% of cases.

Other findings include epidermal ulceration secondary to epidermal ischemia and necrosis, dermal or subcutaneous necrosis under the epidermal damage, preceded in early lesions by degeneration and necrosis of dermal collagen. Erythrocyte extravasation within the dermis and subcutis is also an early event.[47] Acute or chronic panniculitis is a frequent feature. Calciphylaxis is included in panniculitis classifications within the group of mostly lobular panniculitides without vasculitis and few or no inflammatory cells.[77] Essary and colleagues[47] considered that in addition to microvascular calcification, the most consistent feature of calciphylaxis was that of acute or chronic panniculitis (85% of cases), but with a predominant septal pattern. In our series of patients, involvement of septal and lobular (with fat necrosis) areas was easily identified (**Fig. 7**).[6] On the other hand, in early lesions there are scant or absent inflammatory infiltrates, but in well-formed lesions a slightly to moderately mixed inflammatory infiltrate composed of neutrophils, lymphocytes, and histiocytes is observed around superficial and deep vessels of the dermis and subcutaneous fat.

Less commonly, interstitial deposition of calcium is observed in the dermis and subcutaneous adipose tissue, sometimes as delicate groups surrounding adipocytes (**Fig. 8**).[6] Other findings exceptionally described include epidermal and hair follicle calcification,[78] perineurial calcium

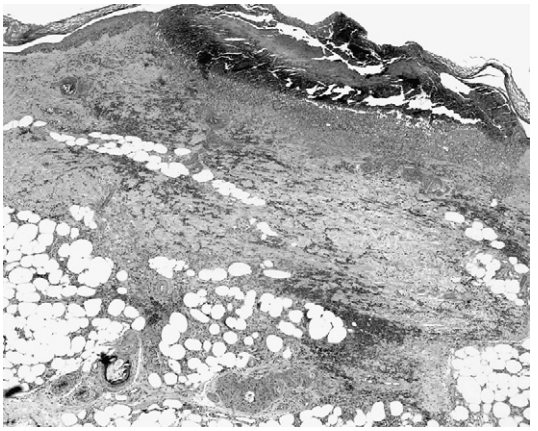

Fig. 6. Vessel wall calcification. Septal and lobular panniculitis. Epidermal necrosis. Marked erythrocyte extravasation.

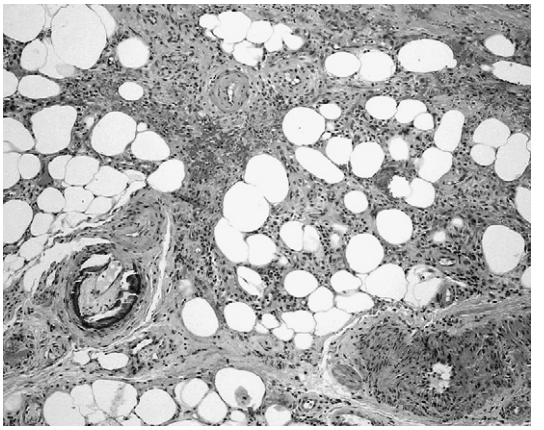

Fig. 7. Lobular involvement of the subcutaneous tissue around a calcified vessel. Mixed inflammatory infiltrate.

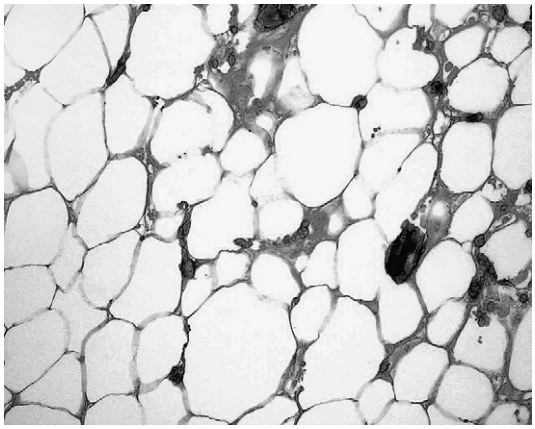

Fig. 8. Extravascular calcification. Calcium deposits between adipocytes. Fat necrosis.

deposits,[79] and pseudoxanthoma elasticum-like features.[80]

Prognosis

Prognosis of calciphylaxis is generally poor and is considered a devastating and life-threatening condition. Patients often die, most commonly from sepsis, with the bacterial port of entry being skin ulcerations. Mortality rates have been estimated to range from 60% to 80%. Fine and Zacharias[40] reported on 36 patients with calciphylaxis (although only 4 had cases confirmed by skin biopsy). They found that their patients deteriorated rapidly; 89% of patients who had ulcers at presentation or developed ulcers were dead at the 6-month follow up. The overall mortality rate of patients who presented with calciphylaxis was 45% at 1 year, 41% for patients who presented with plaque only, and 67% for patients who presented with ulceration. All deaths resulted from sepsis, weight loss/malnutrition, or discontinuation of dialysis. Unfortunately, high morbidity and prolonged hospitalization define the course of patients who survive, and a significant number of them remain either severely disabled or completely incapacitated by limb amputation. Several studies have found that proximal locations of necrosis carry an unfavorable prognosis compared with distal involvement.[13,22] On the contrary, a relationship among distal location of the lesions, normal serum albumin, and early diagnosis was related to survival rather than the type of treatment received.[81] Although the general view based on the reported publications is devastating, we believe that with current management and control of cutaneous lesions and associated diseases, the prognosis is much better. Statistics of future prospective controlled studies probably will be more favorable in terms of survival.

Treatment

The treatment of calciphylaxis is generally unsatisfactory and largely supportive. Patients are often refractory to different therapies. To improve the prognosis, early recognition of diseased patients is important to choose the therapy on an individual basis and perform a multidisciplinary approach.[82]

Calcium/Phosphate Metabolism Control

Adjusting serum calcium and phosphate levels and controlling secondary hyperparathyroidism are important issues. In some cases, however, the lesions have progressed despite effective control of such abnormalities, which suggests that other factors are important in determining healing. Although currently there is no unanimity in the way to approach the condition, varied measures have been shown to be effective including

- Diet with low phosphate intake
- Phosphate binders (eg, sevelamer hydrochloride)
- Biphosphonates. Pamidronate inhibits arterial calcification in animal models and proved to be useful in a patient with calciphylaxis.[83] Oral etidronate disodium is also effective.[84]
- Cinacalcet is a new calcimimetic that has been used successfully for the treatment of primary and secondary hyperparathyroidism normalizing serum calcium. Its efficacy in patients with calciphylaxis has been demonstrated by different investigators, presenting as an alternative to parathyroidectomy.[85,86]
- Sodium thiosulfate is a potent antioxidant and chelator of calcium. Used intravenously, it is useful in reversing the signs and symptoms of calciphylaxis.[87–91] Sodium thiosulfate was used intraperitoneally in a patient intolerant to the intravenous administration. The drug was well tolerated and led to removal of extra calcium with peritoneal dialysis.[92]
- Parathyroidectomy is a matter of controversy in the treatment of calciphylaxis.[22] For some, it is the treatment of choice when hyperparathyroidism is determined. Success varies, however, with some patients being cured and others continuing to progress. The definite value of parathyroidectomy is not yet established because the outcome of patients is unpredictable. Total, subtotal, ''near total'' parathyroidectomy (a vascularized parathyroid remnant is left in situ),[93] and autotransplantation of tissue to the forearm[22] have

been tried. Patients who respond favorably to parathyroidectomy have shown a rapid resolution of the cutaneous lesions leading to decrease in necrosis and wound healing, rapid relief of pain, and longer survival.[94–97] Hafner and colleagues[22] reported survival of 38 of 58 patients who underwent parathyroidectomy compared with 13 of 37 patients who did not undergo surgery. Duffy and colleagues reported on 15 patients with calciphylaxis: 9 were treated with medical therapy (bisphosphonates and phosphate binders) and 6 underwent parathyroidectomy. They concluded that subtotal or total parathyroidectomy was associated with long-term survival and was more likely to promote healing if performed earlier in the course of diseas.[96,97] Finally, Arch-Ferrer and colleagues[98] presented data about 23 of 35 patients who underwent parathyroidectomy. Patients with calciphylaxis and secondary hyperparathyroidism who underwent surgery had better clinical outcomes and longer survival times than patients who did not ($P < .04$). On the contrary, other investigators have not reported beneficial effects of parathyroidectomy in the progression of necrosis, lesion ulceration, and survival.[8]

Avoidance, Control, or Minimizing Associated and Triggering Factors

Factors known to be associated with calciphylaxis or factors capable of aggravating or triggering the disease should be controlled. This is the case in renal failure, obesity, diabetes mellitus, hypertension, use of albumin or exogenous vitamin D supplements, local trauma, and administration of immunosuppressant drugs and corticosteroids. Although steroids have been attributed to playing an aggravating role in calciphylaxis, it is also true that is some cases it has beneficial effects on ulcer healing.[54] Fine and colleagues[40] showed how 80% of 14 patients with nonulcerating lesions who were treated with steroids presented a significant clinical improvement.

Wound Care and Prevention of Sepsis

Wound care to promote healing and prevention of sepsis is an essential feature because it is the most frequent cause of death in these patients. Under certain conditions, the following measures may be necessary:

- Surgical debridement. The role of debridement is controversial.[99] Some authors consider debridement to be contraindicated. On the contrary, Weenig and colleagues[100] reported an estimated 1-year survival rate of 61.6% for 17 patients who underwent surgical debridement compared with 27.4% for the 46 patients who did not ($P = .008$). In general, we consider debridement of ulcers a weighty measure to practice.
- Hydrocolloid and biologic dressings
- Skin grafts and autologous keratinocyte grafts, which allow pain relief and subsequent parathyroidectomy under optimal conditions[101]
- Systemic antibiotics
- Oral pentoxifillin combined with maggot therapy[102]
- Nutritional support
- Hyperbaric oxygen therapy, which has been shown to be useful in some patients with calciphylaxis,[103,104] promotes wound healing by elevating the partial pressure of oxygen within diseased tissue, improving angiogenesis and phagocytosis, inhibiting bacterial growth, and decreasing local tissue edema
- Revascularization and amputation in cases in which all other interventions have failed

Other Measures

Other measures that might complement the previously mentioned features include

- Control of pain through analgesics. Pollizotto and colleagues[105] reported symptomatic treatment of pain with multimodal analgesia with high-dose opioids, ketamine, and benzodiazepines. Neurolytic lumbar sympathetic blockade also has been demonstrated to be useful for alleviating pain associated with calciphylaxis.[106]
- Correction of thrombosis at the cutaneous vascular system. Anticoagulation has been proposed, based on the theory of Mehta et al,[41] to avoid thrombosis. Rudwaleit and colleagues[46] described a renal transplant patient on long-term oral anticoagulant therapy who developed calciphylaxis. Finally, treatment to increase the level of functional protein C (eg, purified protein concentrates, fresh frozen plasma) has been suggested in cases in which deficiency has been demonstrated.

REFERENCES

1. Arseculeratne G, Evans AT, Morley SM. Calciphylaxis: a topical overview. J Eur Acad Dermatol Venereol 2006;20:493–502.

2. Bryant JH, White WH. A case of calcification of the arteries and obliterative endarteritis associated with hydronephrosis in a child aged six months. Guys Hosp Rep 1898;55:17–28.
3. Selye H, Gobbiani G, Strebel R. Sensitization to calciphylaxis by endogenous parathyroid hormones. Endocrinology 1962;71:554–8.
4. Abdelbaqi-Salhab M, Shalhub S, Morgan MB. A current review of the cutaneous manifestations of renal disease. J Cutan Pathol 2003;30:527–38.
5. Robinson-Bostom L, Di Giovanna JJ. Cutaneous manifestations of end-stage renal disease. J Am Acad Dermatol 2000;43:975–86.
6. Dauden E, Ruiz-Genao D, Fraga J. Calcificación vascular cutánea: correlación clínico-patológica y proposición de una nueva clasificación de las calcinosis cutáneas. Actas Dermosifiliogr 2002;93:22–34.
7. Ivker RA, Woosley J, Brigaman RA. Calciphylaxis in three patients with end-stage renal disease. Arch Dermatol 1995;131:63–8.
8. Budisavljevic MN, Cheek D, Poth DW. Calciphylaxis in chronic renal failure. J Am Soc Nephrol 1996;7: 978–82.
9. Angelis M, Wong LL, Myers SA, et al. Calciphylaxis in patients on hemodialysis: a prevalence study. Surgery 1997;122:1083–90.
10. Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in prevention, diagnosis and treatment. Semin Dial 2002;15:172–86.
11. Aragües M, Suárez C, Sánchez J, et al. Necrosis cutáneas, calcificaciones vasculares e insuficiencia renal aguda. Actas Dermosifiliogr 1989;80: 339–42.
12. Smiley CM, Hanlon SU, Michel DM. Calciphylaxis in moderate insufficiency: changing disease concepts. Am J Nephrol 2000;20:324–8.
13. Oh DH, Eulau D, Tokugawa DA, et al. Five cases of calciphylaxis and a review of the literature. J Am Acad Dermatol 1999;40:979–87.
14. Lewis KG, Lester BW, Pan TD, et al. Nephrogenic fibrosing dermopathy and calciphylaxis with pseudoxanthoma elasticum changes. J Cutan Pathol 2006;33:695–700.
15. Edelstein CC, Wickham MK, Kirby PA. Systemic calciphylaxis presenting as a painful systemic myopathy. Postgrad Med J 1992;68:209–11.
16. Barri YM, Graves GS, Knochel JP. Calciphylaxis in a patient with Crohn's disease in the absence of end-stage renal disease. Am J Kidney Dis 1997; 29:773–6.
17. Pollock B, Cunliffe WJ, Merchant WJ. Calciphylaxis in the absence of renal failure. Clin Exp Dermatol 2000;25:389–92.
18. Goyal S, Huhn KM, Provost TT. Calciphylaxis in a patient without renal failure or elevated parathyroid hormone: possible aetiological role of chemotherapy. Br J Dermatol 2000;143:1087–90.
19. Randall DP, Fisher MA, Thomas C. Rhabdomyolysis as the presenting manifestation of calciphylaxis. Muscle Nerve 2000;23:289–93.
20. Adrogue HJ, Frazier MR, Zeluff B, et al. Systemic calciphylaxis is revisited. Am J Nephrol 1981;1: 177–83.
21. Goldsmith DJ. Calciphylaxis, thrombotic diathesis, and defects in coagulation regulation. Nephrol Dial Transplant 1977;12:1082–3.
22. Hafner J, Keusch G, Wahl C, et al. Uraemic small-artery disease with medial calcification and intimal hyperplasia (so-called calciphylaxis): a complication of chronic renal failure and benefit from parathyroidectomy. J Am Acad Dermatol 1995;33: 954–62.
23. Coates T, Kirkland GS, Dymock RB, et al. Cutaneous necrosis from calcific uremic arteriolopathy. Am J Kidney Dis 1998;32:384–91.
24. Bleyer AJ, Choi M, Igwemezie B, et al. A case study of proximal calciphylaxis. Am J Kidney Dis 1998;32:376–83.
25. Lim SP, Batta K, Tan BB. Calciphylaxis in a patient with alcoholic liver disease in the absence of renal failure. Clin Exp Dermatol 2003;28:34–6.
26. Goli AK, Goli SA, Shah LS, et al. Calciphylaxis: a rare association with alcoholic cirrhosis. Are deficiencies in protein C and S the cause? South Med J 2005;98:736–9.
27. Ferreres JR, Marcoval J, Bordas X, et al. Calciphylaxis associated with alcoholic cirrhosis. J Eur Acad Dermatol Venereol 2006;20:599–601.
28. Mastruserio DN, Nguyen EQ, Neilsen T, et al. Calciphylaxis associated with metastatic breast carcinoma. J Am Acad Dermatol 1999;41:295–8.
29. Reigert-Johnson DL, Kaur JS, Pfiefer EA. Calciphylaxis associated with cholangiocarcinoma treated with low-molecular heparin and vitamin K. Mayo Clin Proc 2001;76:749–52.
30. Kutlu NO, Aydin NE, Aslan M, et al. Malignant melanoma of the soft parts showing calciphylaxis. Pediatr Hematol Oncol 2003;20:141–6.
31. Raper RF, Ibels LS. Osteosclerotic myeloma complicated by diffuse arteritis, vascular calcification and extensive cutaneous necrosis. Nephron 1985; 39:389–92.
32. Goff HW, Grimwood RE. A case of calciphylaxis and chronic myelomonocytic leukaemia. Cutis 2005;75:325–8.
33. Korkmaz C, Dunbar E, Zubaroglu I. Calciphylaxis in a patient with rheumatoid arthritis without renal failure and hyperparathyroidism: the possible role of long-term steroid use and protein S deficiency. Clin Rheumatol 2002;21:66–9.
34. Ozbalkan Z, Calguneri M, Onat AM. Development of calciphylaxis after long-term steroid and methotrexate use in a patient with rheumatoid arthritis. Intern Med 2005;44:1178–81.

35. Cockerell CJ, Dolan ET. Widespread cutaneous and systemic calcification (calciphylaxis) in patients with the acquired immunodeficiency syndrome and renal disease. J Am Acad Dermatol 1992;26:559–62.
36. Wong JJ, Laumann A, Martinez M, et al. Calciphylaxis and antiphospholipid antibody syndrome. J Am Acad Dermatol 2000;42:849.
37. De Roma I, Filotico R, Cea M, et al. Calciphylaxis in a patient with POEMS syndrome without renal failure and/or hyperparathyroidism: a case report. Ann Ital Med Int 2004;19:283–7.
38. Levin A, Mehta RL, Goldstein MB. Mathematical formulation to help identify the patient at risk of ischemic tissue necrosis: a potentially lethal complication of chronic renal failure. Am J Nephrol 1993; 13:448–53.
39. Gipstein RM, Coburn JW, Adams DA, et al. Calciphylaxis in man: a syndrome of tissue necrosis and vascular calcification in 11 patients with chronic renal failure. Arch Intern Med 1976;136: 1273–80.
40. Fine A, Zacharias J. Calciphylaxis is usually nonulcerating: risk factors, outcome and therapy. Kidney Int 2002;61:2210–7.
41. Mehta RL, Scott G, Sloand JA, et al. Skin necrosis associated with acquired protein C deficiency in patients with renal failure and calciphylaxis. Am J Med 1990;88:252–7.
42. Rostaing L, Feki S, Delisle MB, et al. Calciphylaxis in a chronic hemodialysis patient with protein S deficiency. Am J Nephrol 1995;15:524–7.
43. Whittam LR, McGibbon DH, MacDonald DM. Proximal cutaneous necrosis in association with chronic renal failure. Br J Dermatol 1996;135:780–1.
44. Pérez-Mijares R, Guzmán-Zamudio JL, Payán-López J, et al. Calciphylaxis in a haemodialysis patient: functional protein S deficiency? Nephrol Dial Transplant 1996;11:1856–9.
45. Ross CN, Cassidy MJ, Thompson M, et al. Proximal cutaneous necrosis associated with small vessel calcification in renal failure. Q J Med 1991;289: 443–50.
46. Rudwaleit M, Schwarz A, Trautmann C, et al. Severe calciphylaxis in a renal patient on long-term anticoagulant therapy. Am J Nephrol 1996; 16:344–8.
47. Essary LR, Wick MR. Cutaneous calciphylaxis: an underrecognized clinicopathologic entity. Am J Clin Pathol 2000;113:280–7.
48. Sheila A, Crawford RI. Three-dimensional analysis of a calciphylaxis plaque: clues to pathogenesis. J Am Acad Dermatol 2002;47:53–7.
49. Canfield AE, Farrington C, Dziobon MD, et al. The involvement of matrix glycoproteins in vascular calcification and fibrosis: an immunohistochemical study. J Pathol 2002;196:228–34.
50. Griethe W, Schmitt R, Jurgensen JS, et al. Bone morphogenic protein-4 expression in vascular lesions of calciphylaxis. J Nephrol 2003;16:728–32.
51. Dahl PR, Winkelmann RK, Connoly SM. The vascular-calcification-cutaneous necrosis syndrome. J Am Acad Dermatol 1995;33:53–8.
52. Ruggian JC, Maesaka JA, Fishbane S. Proximal calciphylaxis in four insulin-requiring diabetic haemodialysis patients. Am J Kidney Dis 1996;28: 409–14.
53. James LR, Lajoie G, Prajapati D, et al. Calciphylaxis precipitated by ultraviolet light in a patient with end-stage renal disease secondary to systemic lupus erythematosus. Am J Kidney Dis 1999;34:932–6.
54. Elamin EM, McDonald AB. Calcifying panniculitis with renal failure: a new management approach. Dermatology 1996;192:156–9.
55. Imam AA, Mattoo TK, Kapur G, et al. Calciphylaxis in pediatric end-stage renal disease. Pediatr Nephrol 2005;20:1776–80.
56. Feng J, Gohara M, Lazova R, et al. Fatal childhood calciphylaxis in a 10-year-old and literature review. Pediatr Dermatol 2006;23:266–72.
57. Gómez E, Vicente FJ, Álvarez JG, et al. Calcifilaxis en pacientes dializados. Actas Dermosifiliogr 2004; 95:178–82.
58. Bocaletti VP, Ricci R, Sebastio N, et al. Penile calciphylaxis. Arch Dermatol 2000;136:259–64.
59. Nahm WK, Badiavas E, Toumas DJ, et al. Calciphylaxis with peau d'orange induration and absence of classical features of purpura, livedo reticularis and ulcers. J Dermatol 2002;29:209–13.
60. Somorin AO, Al Harbi A, Subaity Y, et al. Calciphylaxis: case report and literature review. Afr J Med Sci 2002;31:175–8.
61. Bedoya RM, Gutierrez JL, Mayorga F. Calciphylaxis causing localised tongue necrosis: a case report. J Oral Maxillofac Surg 1997;55:193–6.
62. Fariña MC, De Sequera P, Soriano ML, et al. Calcifilaxis. Actas Dermosifiliogr 1997;88:333–6.
63. Jacobsohn HA, Jenkins PG, Jacobsohn KM. Penile calciphylaxis. Urology 2002;60:344.
64. Woods M, Pattee SF, Levine N. Penile calciphylaxis. J Am Acad Dermatol 2006;54:736–7.
65. Khafif RA, De Lima C, Silverberg A, et al. Calciphylaxis and systemic calcinosis: collective review. Arch Intern Med 1990;150:956–9.
66. Katsamakis G, Lukovits TG, Gorelick PB. Calcific cerebral embolism in systemic calciphylaxis. Neurology 1998;51:295–7.
67. Matsuo T, Tsukamoto Y, Tamura M. Acute respiratory failure due to "pulmonary calciphylaxis" in a maintenance haemodialysis patient. Nephron 2001;87:75–9.
68. Li YJ, Tian YC, Chen YC, et al. Fulminant pulmonary calciphylaxis and metastatic calcification causing

acute respiratory failure in a uremic patient. Am J Kidney Dis 2006;47:47–53.
69. Kloeppel R, Luebke P, Mittag M, et al. Acute hypercalcaemia of the heart ("bony heart"). J Comput Assist Tomogr 2001;25:407–11.
70. Jelic TM, Malas AM, Groves SS, et al. Nano-bacteria caused mitral valve calciphylaxis in a man with diabetic renal failure. South Med J 2004;97:194–8.
71. Brown DF, Denney CF, Burns DK. Systemic calciphylaxis associated with massive gastrointestinal haemorrhage. Arch Pathol Lab Med 1998;122:656–9.
72. Bleibel W, Hazar B, Herman R. A case report comparing various radiological tests in the diagnosis of calcific uremic arteriolopathy. Am J Kidney Dis 2006;48:659–61.
73. Lazorik FC, Friedman AK, Leyden JJ. Xeroradiographic observations in four patients with chronic renal disease and cutaneous gangrene. Arch Dermatol 1981;117:325–8.
74. Tierfenthaler M, Riedl-Huter C, Roth T, et al. Ultrasonic diagnosis of calciphylactic lesions. Ultraschall Med 2002;23:403–6.
75. Norris B, Vaysman V, Line BR. Bone scintigraphy of calciphylaxis: a syndrome of vascular calcification and skin necrosis. Clin Nucl Med 2005;30:725–7.
76. Requena L, Sánchez-Yus E. Panniculitis. Part II. Mostly lobular panniculitis. J Am Acad Dermatol 2001;45:325–61.
77. Requena L, Sánchez-Yus E. Panniculitis. Part I. Mostly septal panniculitis. J Am Acad Dermatol 2001;45:163–83.
78. Solomon AR, Comite SL, Headington JT. Epidermal and follicular calciphylaxis. J Cutan Pathol 1988;15:282–5.
79. Ruiz-Genao D, García-F-Villalta M, Fraga J, et al. Perineurial and vascular calcification in a patient with chronic renal failure. Acta Derm Venereol 2005;85:72–3.
80. Nikko AP, Dunnigan M, Cockerell CJ. Calciphylaxis with changes of pseudoxanthoma elasticum. Am J Dermatopathol 1996;18:396–9.
81. Galimberti RL, Farias R, Parra IH, et al. Cutaneous necrosis by calcific uremic arteriolopathy. Int J Dermatol 2005;44:101–6.
82. Roe SM, Graham LD, Brock MB, et al. Calciphylaxis: early recognition and management. Am Surg 1994;60:81–6.
83. Monney P, Nguyen QV, Perroud H, et al. Rapid improvement of calciphylaxis after intravenous pamidronate therapy in a patient with chronic renal failure. Nephrol Dial Transplant 2004;19:2130–2.
84. Shiraishi N, Kitamura K, Miyoshi T, et al. Successful treatment of a patient with severe calcific uremic arteriolopathy (calciphylaxis) by etidronate disodium. Am J Kidney Dis 2006;48:151–4.
85. Sharma A, Burkitt-Wright E, Rustom R. Cinacalcet as an adjunct in the successful treatment of calciphylaxis. Br J Dermatol 2006;155:1295–7.
86. Velasco N, MacGregor MS, Innes A, et al. Successful treatment of calciphylaxis with cinacalcet: an alternative to parathyroidectomy? Nephrol Dial Transplant 2006;21:1999–2004.
87. Cicone JS, Petronis JB, Embert CD, et al. Successful treatment of calciphylaxis with intravenous sodium thiosulphate. Am J Kidney Dis 2004;43:1104–8.
88. Brucculeri M, Cheigh J, Bauer G, et al. Long-term intravenous sodium thiosulphate in the treatment of a patient with calciphylaxis. Semin Dial 2005;18:431–4.
89. Hayden MR, Tyagi SC, Kolb L, et al. Vascular ossification-calcification in metabolic syndrome, type-2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. Cardiovasc Diabetol 2005;4:4.
90. Guerra G, Shah RC, Ross EA. Rapid resolution of calciphylaxis with intravenous sodium thiosulphate and continuous veno-venous haemofiltration using low calcium replacement fluid: case report. Nephrol Dial Transplant 2005;20:1260–2.
91. Meissner M, Bauer R, Beier C, et al. Sodium thiosulphate as a promising therapeutic option to treat calciphylaxis. Dermatology 2006;212:373–6.
92. Mataic D, Bastani B. Intraperitoneal sodium thiosulfate for the treatment of calciphylaxis. Ren Fail 2006;28:361–3.
93. Milas M, Weber CJ. Near-total parathyroidectomy is beneficial for patients with secondary and tertiary hyperparathyroidism. Surgery 2004;136:1252–60.
94. Girotto JA, Harmon JW, Ratner LE, et al. Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism. Surgery 2001;130:645–50.
95. Younis N, Sells RA, Desmond A, et al. Painful cutaneous lesions, renal failure and urgent parathyroidectomy. J Nephrol 2002;15:324–9.
96. Duffy A, Schurr M, Warner T, et al. Long-term outcomes in patients with calciphylaxis from hyperparathyroidism. Ann Surg Oncol 2006;13:96–102.
97. Couto FM, Chen H, Blank RD, et al. Calciphylaxis in the absence of end-stage renal disease. Endocr Pract 2006;12:406–10.
98. Arch-Ferrer JE, Beenken SW, Rue LW, et al. Therapy for calciphylaxis: an outcome analysis. Surgery 2003;124:941–5.
99. Martin R. Mysterious calciphylaxis: wounds with eschar: to debride or not to debride. Ostomy Wound Manage 2004;50:64–6.

100. Weenig RH, Sewell LD, Davis MD. Calciphylaxis: natural history, risk factor analysis and outcome. J Am Acad Dermatol 2007;56:569–79.
101. Acher-Chenebaux A, Maillard H, Potier A, et al. Necrose cutanee par calciphylaxie traitee par greffe de keratinocytes autologues et parathyroidectomie partielle. Ann Dermatol Venereol 2006;133:260–3.
102. Tittlebach J, Graefe T, Wollina U. Painful ulcers in calciphylaxis: combined therapy with maggot therapy and oral pentoxyfillin. J Dermatol Treat 2001; 12:211–4.
103. Podymow T, Wherrett TC, Burns KD. Hyperbaric oxygen in the treatment of calciphylaxis: a case series. Nephrol Dial Transplant 2001;16: 2176–80.
104. Basile C, Montanaro A, Masi M, et al. Hyperbaric oxygen therapy in the treatment of calciphylaxis: a case series. J Nephrol 2002;15:676–80.
105. Polizzotto MN, Bryan T, Ashby MA, et al. Symptomatic management of calciphylaxis: a case series and review of the literature. J Pain Symptom Manage 2006;32:186–90.
106. Green JA, Green CR, Minott SD. Calciphylaxis treated with neurolytic lumbar sympathetic block: case report and review of the literature. Reg Anesth Pain Med 2000;25:310–2.