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