Calciphylaxis

Background

Calciphylaxis is a poorly understood and highly morbid syndrome of vascular calcification and skin necrosis. Bryant and White first reported it in association with uremia in 1898. However, the significance of this relationship became uncertain when vascular calcification was subsequently shown to be prevalent in uremia, yet the syndrome of vascular calcification with cutaneous necrosis remained rare.

In 1962, Selye constructed an experimental model and was able to precipitate systemic calcification, somewhat analogous to this syndrome, in nephrectomized rats. He was the first to coin the term calciphylaxis to characterize this enigma. Over the years, many other names have been suggested to characterize the pathogenic process, which has remained elusive. Interestingly, the clinical importance of this syndrome was not recognized until a 1976 report by Gipstein et al. Since then, a multitude of case reports of calciphylaxis have documented data

Using a rat model, Selye demonstrated that a series of events might be necessary for the formation of calciphylaxis. He defined calciphylaxis as a condition of hypersensitivity induced by a set of "sensitizing" agents, in which calcinosis occurred only in those subsequently subjected to a group of "challengers" and only after a critical lag time. Experimental sensitizing events and agents included nephrectomy and exposure to parathyroid hormone (PTH) and vitamin D. Substances used as challengers included egg albumin and metallic salts. Calciphylaxis was the end result.

Although extrapolation of animal data to humans is conjectural, it seems to be true that serial events, most consistently involving renal failure–induced abnormalities in calcium homeostasis, are required to occur over time for calciphylaxis to develop. The cause of calciphylaxis has been elusive, most likely because it is the common endpoint of a heterogeneous group of disorders.

Molecular and cytochemical factors have been identified as crucial in bone metabolism. The receptor activator of nuclear factor-kB (RANK), RANK ligand, and osteoprotegerin appear to regulate skeletal and extraskeletal mineralization.Uremia-induced defects in this system may predispose to calciphylaxis. Corticosteroids, aluminum, hyperparathyroidism, liver disease,

warfarin therapy, and a variety of inflammatory processes all can alter this balance and promote vascular calcification. Chronic inflammatory conditions may predispose to calciphylaxis by reducing serum levels of fetuin-A, an important inhibitor of calcification produced in the liver

Epidemiology

Frequency

International

Calciphylaxis is an uncommon condition that affects 1-4% of the population with ESRD. A concern exists that the incidence has increased during the last decade because of a number of possible factors, including more widespread use of parenteral vitamin D and iron dextran. No good data are available regarding the incidence of calciphylaxis in the general population without ESRD, but it is probably exceedingly rare.

Mortality/Morbidity

The mortality rate of calciphylaxis is reported to be as high as 60-80%. The leading cause of death is sepsis from infected, necrotic skin lesions, although death due to internal organ failure

Age

Calciphylaxis has been reported in individuals ranging in age from 6 months to 83 years. From a large series of patients, a mean patient age of 48 years (±16 y) has been calculated. Individuals seemingly more predisposed are younger patients who have had a longer duration of renal replacement therapy.

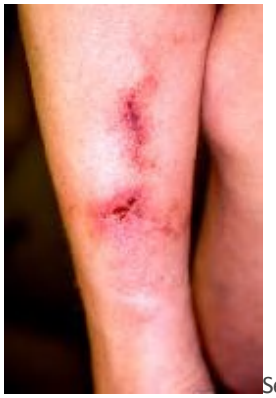
Calciphylaxis Clinical Presentation

History

Most patients with calciphylaxis have a long-standing history of chronic renal failure and renal replacement therapy. On rare occasions, calciphylaxis may occur in a patient with chronic renal failure prior to the initiation of replacement therapy. Very rarely, it may occur in an individual without a history of chronic renal failure.

Many persons who develop calciphylaxis have undergone renal allograft transplantation. The allograft may still be functional when calciphylaxis develops. Frequently, patients have been noncompliant with dietary, medical, and/or dialysis prescriptions prior to the onset of calciphylaxis.

Lesions of calciphylaxis typically develop suddenly and progress rapidly. Lesions may be singular or numerous, and they generally occur on the lower extremities (see image below); however, lesions also may develop on the hands and torso. Intense pain is a constant finding.



Several lesions of calciphylaxis that occurred on the lower extremity of a patient undergoing dialysis. These lesions developed in areas of livedo reticularis and followed the path of the vasculature.

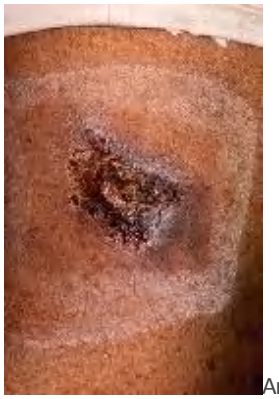
The patient's history may reveal an event that is a suspected trigger or risk factor for the development of calciphylaxis. These triggers include the following

- Long-term obesity
- Recent and sudden weight loss
- Malnutrition
- Infusion of medications such as iron dextran
- Remote and/or recent use of immunosuppressive agents, especially corticosteroids
- Liver disease
- Diabetes mellitus and insulin injections
- Use of vitamin D and calcium-based phosphate binders
- Elevated aluminum levels
- Concomitant vascular disease
- Concurrent use of warfarin anticoagulation: Current data suggest that warfarin therapy may lower protein C concentrations, leading to a procoagulant condition in the calcified vessel. Warfarin may also inhibit carboxylation of matrix Gla protein, an important inhibitor of calcification, thus promoting calcification

Review of the patient's medical record usually reveals a history of hyperphosphatemia with hyperparathyroidism and hypoalbuminemia. Patients with nonuremic calciphylaxis frequently have a history of primary hyperparathyroidism, malignancy, alcoholic liver disease, or underlying connective-tissue disease or pro-inflammatory condition

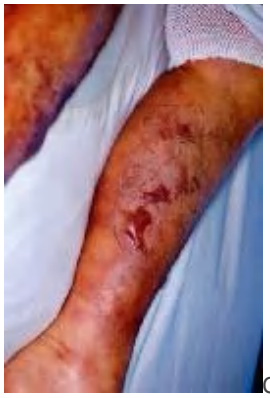
Physical

Early lesions of calciphylaxis manifest as nonspecific violaceous mottling; as livedo reticularis; or as erythematous papules, plaques, or nodules. More developed lesions have a stellate purpuric configuration with central cutaneous necrosis (see the image below).



An isolated lesion of calciphylaxis manifesting as an enlarging necrotic plaque on the lower extremity of a patient undergoing dialysis. The stellate purpuric morphology can be appreciated surrounding the area of necrosis.

Multiple lesions of variable age may be present, following the path of the vasculature. Less commonly, lesions may manifest as either bullae (see the image below) or distinct subcutaneous, erythematous nodules suggestive of erythema nodosum. Lesions are excruciatingly tender and extremely firm.



Calciphylaxis may manifest as rapidly progressive, diffuse and extensive, cutaneous necrosis, as is seen in this patient with chronic renal failure. Bullae may also be seen as a rare manifestation of calciphylaxis.

The distribution of the lesions may be characterized as proximal or distal. Ninety percent of lesions of calciphylaxis occur on the lower extremities. Distal lesions are those that occur below the knee; proximal lesions occur on the thighs or the trunk. Proximally distributed lesions occur in 44-68% of patients, with lesions developing predominantly on the thighs, the buttocks, and the lower part of the abdomen. Distal and visceral involvement are not uncommon.

An intact peripheral pulse helps to distinguish acral calciphylaxis from atherosclerotic peripheral vascular disease. Ulceration is considered a late finding and is associated with a higher mortality rate.

Causes

Disorders associated with the development of calciphylaxis include the following

- Common associations include chronic renal failure, hypercalcemia, hyperphosphatemia, elevated calcium-phosphate product, hyperparathyroidism, and vascular calcification.
- Speculative associations include aluminum toxicity, coagulation abnormalities, and iron dextran infusion.
- Associations suggested from clinical observations include renal transplantation, immunosuppressive agents, corticosteroid use, and obesity.
- Systemic inflammation appears to be a predisposing factor.

The cause of calciphylaxis remains obscure. Most cases occur in the setting of chronic renal failure, abnormal calcium-phosphate homeostasis, and hyperparathyroidism. Both hypercalcemia and hyperphosphatemia may be present, and the calcium-phosphate product frequently exceeds 60-70 mg^2/dL^2. However, calciphylaxis may occur in the setting of normal, or minimally elevated, calcium and phosphate levels.

Case reports exist of calciphylaxis occurring in primary hyperparathyroidism, cirrhosis, Crohn disease, malignancy, and rheumatoid arthritis, without renal disease. The pathogenesis of calciphylaxis in these cases is uncertain. The exact role of PTH is uncertain because calciphylaxis may occur after total parathyroidectomy, in the absence of measurable PTH levels.

Patients at an increased risk appear to be those who are obese and those who have been exposed to immunosuppressive agents, including glucocorticoids. Calciphylaxis occurs more frequently in areas where body fat is most abundant, such as the thighs, the buttocks, and the lower part of the abdomen. Fatty areas may be at higher risk for thrombosis, owing to lower blood flow or the increased potential for vascular kinking.

Persons with diabetes mellitus may also be at an increased risk; insulin injections may be an independent risk due to trauma to the subcutis.

The clinical appearance of the lesions of calciphylaxis (livedo reticularis and stellate purpura) suggests that the common endpoint of the process is small vessel occlusion. Indeed, microthrombi are found in most cases. Note the following:

- Hypercoagulable conditions, including protein C and protein S deficiencies, and the presence of a circulating anticoagulant have been described in a number of patients. However, conditions of hypercoagulability are not found uniformly. If they do exist, they could possibly precipitate or exacerbate calciphylaxis in a predisposed patient.
- Vascular calcification is a constant finding in cases of calciphylaxis. Theoretically, various pathologic roles may be attributed to this vascular calcification. First, calcification of the vascular endothelium may alter the local interaction of procoagulant and anticoagulant factors, predisposing to a microenvironment of hypercoagulability. Alternatively, extensive

endothelial calcification and intimal hyperplasia, which are known to compromise the luminal size of vessels in calciphylaxis, may result in vascular occlusion. Finally, data suggest that the uremic milieu may promote calcification through inhibition of various endogenous inhibitors of calcification such as alpha2-Heremans-Schmid glycoprotein/fetuin A (AHSG), osteopontin, and matrix Gla protein. These theories remain speculative.

Reference:
http://emedicine.medscape.com