Calciphylaxis.

Leaning Objectives:

1. **To be able to describe the clinical presentation of calciphylaxis;**
2. **To understand the contributing factors to it's development;**
3. **To appreciate the role of co-morbid factors in it's development;**
4. **To understand the general management strategies involved in treating calciphylaxis.**

Calciphylaxis is a poorly understood and highly morbid syndrome of vascular calcification and skin necrosis, first reported it in 1898. The term 'calciphylaxis' was introduced in 1962 to characterize the syndrome of vascular calcification with cutaneous. The clinical importance of this syndrome was not recognized until a 1976 report by Gipstein et al, but since then, a multitude of case reports of calciphylaxis have documented data outlining its morbidity and therapeutic dilemmas, as well as attempting to gain a better understanding of its aetiology and pathogenesis.

The pathogenesis of calciphylaxis remains unclear, but is likely to be the result of a multiplicity of comorbid factors or events. Disorders that are most often implicated in the pathogenesis of calciphylaxis include chronic renal failure, obesity, diabetes mellitus, hypercalcemia, hyperphosphatemia, an elevated calcium-phosphate product, and secondary hyperparathyroidism. However, although these abnormalities are extremely common in patients with end-stage renal disease (ESRD), calciphylaxis itself remains relatively rare, affecting 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. Currently, reliable data

is not available regarding the incidence of calciphylaxis in the general population without ESRD, but it is probably exceedingly rare.

The mortality rate of calciphylaxis is reported to be as high as 60-80%, with the leading cause of death being sepsis from infected, necrotic skin lesions, although death due to internal organ failure has been reported. The mortality rate is higher in patients with proximal disease than in those with only distal or acral disease. A 2-fold increase in mortality is seen in those with ulcerative disease. The overall 1- and 5-year survival rates have recently been reported to be 45% and 35%, respectively.

The disease appears to be more prevalent in whites, with females affected more often than males, with a female-to-male ratio of approximately 3:1. Females also appear to be more commonly affected with non-uremic calciphylaxis.

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

Clinical features.

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 patients 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. They may be singular or numerous, and they generally occur on the lower extremities; however, lesions also may develop on the hands and torso. These lesions tends to be intensely painful.

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
- 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.

Early lesions of calciphylaxis appear 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 (fig 1). Multiple lesions of variable age may be present, following the path of the vasculature (fig 2). Less commonly, lesions may manifest as either bullae (fig 3), or distinct subcutaneous, erythematous nodules suggestive of erythema nodosum. The lesions are very painful, and extremely firm.

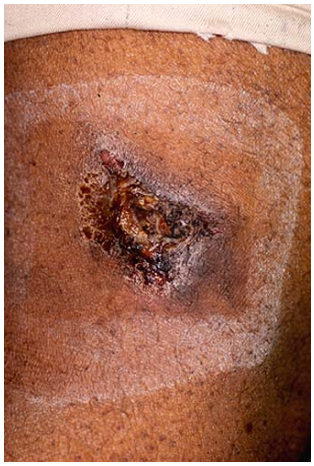

Figure 1

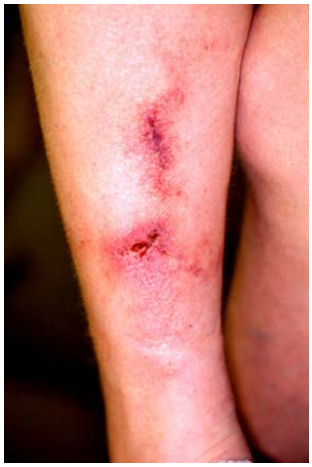

Figure 2

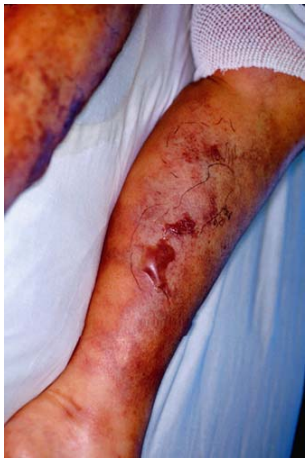

Figure 3

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 (Figs 4 & 5); proximal lesions occur on the thighs or the trunk (Fig 6).
- 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.

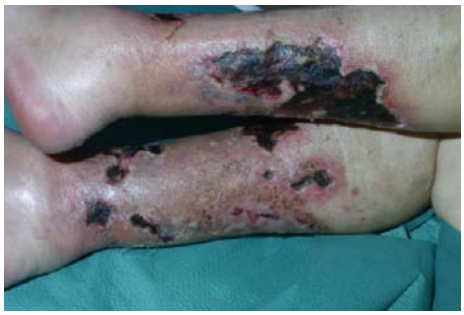

Figure 4

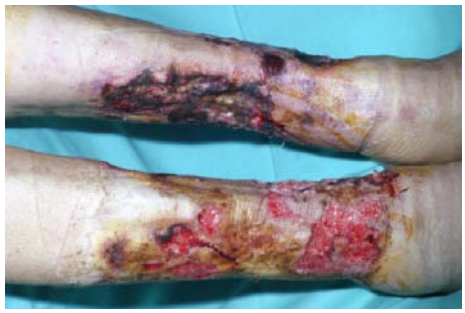

Figure 5

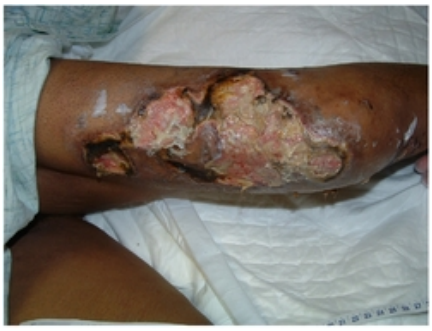

Figure 6

An intact peripheral pulse (as was the case in Fig 6) helps to distinguish acral calciphylaxis from atherosclerotic peripheral vascular disease. Ulceration is considered a late finding and is associated with a higher mortality rate.

Aetiology

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.

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. However, calciphylaxis may occur in the setting of normal, or minimally elevated, calcium and phosphate 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.

Patients 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, and microthrombi are found in most cases. 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.

Management

Due to the nature of the disease medical care is mainly supportive. Aggravating conditions should be addressed, and trigger factors need to be identified and eliminated. This may mean the discontinuation of parenteral iron therapy, calcium supplementation, and vitamin D supplementation. Although implicated as a trigger in the past, recent studies suggest that some patients may benefit early on from systemic glucocorticoids, unless ulcerated lesions are present.

Serum calcium and phosphate concentrations must be brought to low-normal levels as quickly and safely as possible. This can be with conservative therapy, such as changes to diet, the use of non-calcium, non-aluminum phosphate binders

and low-calcium bath dialysis. Some benefit may be achieved with increasing the frequency or duration of dialysis sessions. Calcimimetics such as cinacalcet hydrochloride may be beneficial in cases of hyperparathyroidism. These agents increase the sensitivity of the calcium receptors to available calcium, thereby decreasing PTH secretion. Studies have shown efficacy in decreasing PTH, calcium, and phosphate levels. Increasing evidence of successful outcomes with these agents as adjunctive therapy for calciphylaxis are emerging.

Bisphosphonates (eg, pamidronate,etridronate) increase osteoprotegerin production and inhibit arterial calcification. Case reports suggest these may be helpful in some cases of calciphylaxis, even without changing calcium or phosphate levels.

Significant improvement of calciphylaxis has also been reported with the use of intravenous sodium thiosulfate. Sodium thiosulfate is a potent antioxidant, and it also increases the solubility of calcium deposits. Success has been reported in uremic and nonuremic calciphylaxis. Calciphylaxis therapy with sodium thiosulfate is off-label usage, but reports of success are mounting. It has been administered both intravenously and intraperitoneally, and it has been used in both adults and children.

Careful use of antibiotics has been beneficial, and in some cases, hyperbaric oxygen may be beneficial to promote wound healing.

Conditions of hypercoagulability should be sought and addressed. Patients with documented conditions of hypercoagulability may benefit from proper and adequate anticoagulation. Successful treatment of calciphylaxis with low-dose tissue plasminogen activator has been reported. However, the role of anticoagulation in all cases of calciphylaxis is controversial. Random prophylactic use of warfarin or heparin is probably not indicated because precipitation of calciphylaxis has occurred with indiscriminate use. In addition, most patients with ESRD have a prolonged bleeding time due to the uremic condition, and anticoagulation or tissue plasmogen activator therapy should be approached cautiously.

Because of the high levels of pain experienced by patients, pain management is also crucially important. Consultation with pain-management specialists may be necessary.

There is still much debate regarding aggressive wound care and debridement, with some feeling that it may be necessary to avoid wound infection and sepsis. The decision to debride, and to what extent, depends on the patient's overall health and the clinical picture. Use of a vacuum-assisted closure device has been successful in several cases of calciphylaxis after extensive debridement and prior to skin grafting. Total or subtotal parathyroidectomy with autotransplantation has been shown to be of therapeutic benefit to many, but not all, individuals. Some investigators believe it is the single most effective treatment option, but this remains controversial. Only a few studies have been able to demonstrate a decrease in the mortality rate in patients who undergo parathyroidectomy. Hyperparathyroidism may recur after surgery.

Complications

Complications of calciphylaxis range from moderate interference with activity to death. Lesions of calciphylaxis frequently result in nonhealing ulcers and cutaneous gangrene. Acral lesions may fail to heal with conservative therapy and lead to amputation. Sepsis may result from the nonhealing wounds. Patients with internal involvement may develop gastrointestinal hemorrhage, infarction, or organ failure. Patients treated with calcimimetics, sodium thiosulfate, and parathyroidectomy must be monitored for hypocalcemia.

Prognosis

The prognosis is generally not good, with mortality rates as high as 60-80% in patients with ulcerative disease. Patients who do not die of sepsis or organ failure frequently undergo amputation of an involved limb. Vascular calcification is

theoretically reversible with aggressive management, but many patients have numerous comorbid diseases. Currently, the 1- and 5-year survival rates are estimated to be 45% and 35%, respectively.

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