

Calciophylaxis: A Review of Pathogenesis, Diagnosis and Treatment

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Abstract

Calciophylaxis is a rare but devastating complication of end-stage renal disease. The condition involves medial calcification within smaller blood vessels and subsequent intimal fibroelastic proliferation and stenosis. Although first described forty years ago, its etiology and pathogenesis are still incompletely understood. Hyperparathyroidism, hyperphosphatemia, an increased calcium-phosphate product, and exogenous agents including steroids, immunosuppressants, albumin, and blood products may all contribute to the development of calciophylaxis. The disease typically manifests as symmetrical, painful cutaneous nodules on the trunk and extremities progressing to livedo reticularis and eventually skin necrosis and ulceration. Ulceration of the digits, tongue, and penis, and involvement of the heart, nervous system, and gastrointestinal tract have been reported as well. Definitive diagnosis of calciophylaxis requires a skin biopsy. There is no proven treatment for the disorder, which carries a dismal prognosis. Patients frequently progress to infection of their skin ulcers, succumbing to overwhelming sepsis. Local wound care, subtotal parathyroidectomy, systemic antibiotics upon infection, and critical care support are the mainstays of therapy. Low calcium dialysis and hyperbaric oxygen therapy are newer, potential treatments. A recently derived mathematical formula attempts to predict, based on biochemical characteristics, which renal failure patients on dialysis are likely to develop the condition.

Introduction

End stage renal disease of any etiology is associated with significant morbidity and mortality. Frequent complications include: hypertension, anemia, bone loss (as a result of secondary or tertiary hyperparathyroidism), electrolyte abnormalities including hyperkalemia and metabolic acidosis, and accelerated atherosclerosis. A far rarer complication arising in this setting, but one associated with a great deal of patient suffering is calciophylaxis, a disorder with a rapidly deteriorating course and a grave prognosis. This is a syndrome of ischemic tissue necrosis, primarily of the superficial skin, arising secondary to microvascular calcification, fibrosis, and luminal stenosis.^{1,2} It is also known as calcific uremic arteriopathy or uremic small vessel disease.²

Pathology

The characteristic lesion of calciophylaxis is calcification within the media of blood vessels, predominantly those in the range of 0.1 mm in diameter.¹ The calcifications have been described by some as consisting purely of calcium and phosphate crystals² while others have detected the presence of calcium, magnesium, and phosphate in variable stoichiometric relationships.¹ Superimposed upon this are intimal fibroblast deposition, fibroelastic proliferation, and luminal stenosis. Typically an area of perivascular necrosis is seen to accompany these lesions along with acute inflammatory changes. The lesions of calciophylaxis generally involve the skin, and thus manifest as necrosis of the epidermis, dermis, and subcutaneous tissue. These need to be distinguished from other, more common intravascular changes in uremic patients including atherosclerotic intravascular calcification, in which medial smooth muscle cell proliferation, macrophage invasion, and foam cells are present as well.¹

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Another uremic condition, Monckeberg's disease, also involves intravascular calcification although patients with this condition rarely develop clinical manifestations of tissue necrosis.^{3,7}

Pathogenesis

The etiology and pathogenesis of calciphylaxis are incompletely understood. The term was coined in 1961 by Hans Selye, who described experimental soft tissue calcification in rats.⁸ Selye exposed rats to various agents (vitamin D, phosphate, calcium salts, and parathyroid hormone [PTH]) in a process he termed "sensitization." A day later the rats were injected with iron salts, egg albumin, polymyxin, or 5-hydroxytryptamine in a process termed "challenging." The rats developed soft tissue calcification, although importantly, no intravascular calcification was noted.^{1,2,7} Equating the two-step sensitization and challenging process to anaphylaxis, Selye coined the term "calciphylaxis." Selye's concept differs from the modern view of calciphylaxis, which refers to intravascular calcification, endovascular fibro-elastic proliferation, and tissue necrosis, but not to extravascular soft tissue calcification. Current theories regarding the pathogenesis of this disorder postulate a mechanism whereby hyperparathyroidism, a high phosphate level, and a high calcium:phosphate ratio in the setting of uremia predispose patients to the development of intravascular calcification.¹ Although not proven, exposure to various agents including steroids, immunosuppressants, albumin, blood products, and exogenous vitamin D and calcium carbonate has been implicated in the precipitation of these deposits.⁹⁻¹¹ However, this proposed mechanism cannot completely account for the pathogenesis of calciphylaxis since elevated calcium, phosphate, calcium phosphate, or PTH levels is neither necessary nor sufficient to develop or diagnose the condition.^{1,2,6} Furthermore, evidence supporting a correlation between these biochemical parameters and the development of calciphylaxis remains inconclusive.¹² Complicating the picture further is the finding that calciphylaxis does not develop solely in the uremic state, nor does it arise strictly in dialysis patients.^{1,13} The disorder has been reported in patients without end-stage renal disease whose underlying illness was primary hyperparathyroidism or hypercalcemia of malignancy.^{1,13}

Additional models have suggested a relationship between calciphylaxis and the use of warfarin anticoagulation, while others have proposed that a high dose of calcium carbonate used as a gastrointestinal phosphate binding agent promotes the condition.^{2,14} Obesity, hypoalbuminemia, and a longer duration of hemodialysis have also been shown to be independently associated with the development of calciphylaxis.^{12,15} Finally, there have been several reports of mild to severe deficiency in the intrinsic anticoagulation factors protein C and S among patients developing calciphylaxis, suggesting that fluctuations in these factors, or an inherited thrombogenic predisposition, may render patients susceptible to the condition.^{2,7}

Epidemiology

Among hemodialysis patients, calciphylaxis is estimated to occur

at an incidence of 1% per year. Unfortunately, the incidence in the entire chronic renal failure population is unknown.^{3,16} The prevalence of the disease has been reported at 4.1%.¹² However, calciphylaxis is highly underreported in the literature with fewer than two hundred cases published since the concept was introduced. The disease has been reported predominantly in adult patients between the ages of 18 and 83.^{1,7} There is no clear increased prevalence in any particular ethnic group.^{12,15} The disease appears to occur more commonly in females, with female to male ratios between 1.5 to 1 and 4 to 1 having been reported in various studies.^{2,12,15,17}

Etiology

End stage renal disease is responsible for 90% of reported cases of calciphylaxis.¹ The underlying etiology of the renal disease in these patients is varied and includes diabetes mellitus, hypertensive nephrosclerosis, chronic interstitial nephritis, polycystic kidney disease, and various glomerulonephritides. Eight percent of reported patients developed the condition due to primary hyperparathyroidism and 2% in the setting of hypercalcemia of malignancy.^{1,13}

Clinical Presentation and Disease Manifestations

Patients developing calciphylaxis undergo a rather typical progression of events.^{1,2,12,17} During onset, extremely painful cutaneous nodules develop, which may be intensely pruritic. These most commonly involve the skin of the trunk and proximal lower extremities symmetrically although distal lower extremity and upper extremity disease are frequent as well; involvement of the head is rare. The lesions progress to a diffuse, violaceous, lace-like and mottled pattern termed livedo reticularis. Involved areas undergo superficial skin necrosis to form large ulcerations, which may become infected and gangrenous. These ulcers resemble burn wounds and are highly prone to infection. Infrequently the ulcers will invade deeper than the superficial skin to involve underlying skeletal muscle.¹ Subsequently, patients often develop wound infection and sepsis, which are usually refractory to antibiotics and intensive care unit support. A second common manifestation of calciphylaxis is acral ulceration and gangrene progressing to autoamputation.²

The superficial lesions of calciphylaxis have also been described on the prepuce and glans penis, with progress on to painful ulceration, infection, and gangrene necessitating debridement and at times penectomy.^{2,14,18,19} Involvement of the tongue requiring a hemiglossectomy has been reported.⁶ Cardiovascular complications include a rapid onset of aortic valve and ascending aorta calcification,²⁰ mitral valve calcification and thickening with calcific plaque embolization to the cerebral circulation causing a stroke,²¹ and myocardial dysfunction secondary to intramyocardial calcification in patients with systemic lupus erythematosus and end-stage renal disease.²² Colonic ischemic necrosis resulting in gastrointestinal hemorrhage,^{2,5} ischemic myopathy mimicking dermatomyositis,³ polyneuropathy,¹³ ischemic optic nerve atrophy,¹ and corneal and conjunctival

ulceration⁷ have all been described as well. In many of these reports, surgical resection and autopsy revealed calciphylaxis in the diseased organs and tissues, suggesting that calciphylitic lesions were responsible for organ dysfunction.

Diagnosis

The presence of calciphylaxis is not accurately predicted by biochemical laboratory parameters.¹ Several case reports and retrospective case studies suggest a correlation of calciphylaxis with serum calcium, phosphate, calcium phosphate product, PTH, or alkaline phosphatase (ALP) levels.^{12,15,17} However, there are several reports of patients developing calciphylaxis without an abnormality in these values.^{2,7,15} Furthermore, although in most cases PTH and phosphate levels tend to be elevated, both these markers are highly non-specific in the setting of chronic renal failure and end-stage renal disease.

While useful biochemical parameters remain elusive, radiological investigations may suggest the presence of calciphylaxis. Frequently a non-specific, stippled pattern of vascular calcification is observed on plain film radiographs along with metastatic soft tissue calcification.¹ The presence of calcifications less than 0.5 mm in width on these radiographs may be more specific for the presence of calciphylaxis.¹ Nonetheless, a tissue biopsy from a site of cutaneous involvement demonstrating the pathology described above is necessary to confirm the diagnosis.

Differential Diagnosis

The differential diagnosis of calciphylaxis may be broad and depends in part on the stage of the disease at presentation.^{1,23,24} Important considerations are vasculitides, warfarin-induced skin necrosis with recently initiated warfarin therapy, cellulitis or necrotizing fasciitis, atheroembolic diseases including peripheral vascular disease and cholesterol emboli, endocarditis, cryofibrinogenemia, pyoderma gangrenosum, and superficial thrombophlebitis.

Treatment

There is no clinically proven, completely effective treatment for calciphylaxis. Most suggested therapies have been tried on only a small number of patients and therefore their efficacies are not fully established. The treatment approach consists of supportive, symptomatic care of the severely painful and disfiguring lesions and an attempt at cure. Supportive care involves stepwise increase in analgesic medication, aggressive skin wound management through cleaning, debridement and split-thickness skin grafting, and the administration of antibiotics upon infection.^{11,12,17,25} The use of prophylactic antibiotics has not been reported. Supportive care through resuscitation and aggressive life support for the cardiac, gastrointestinal, and systemic complications may also be required as the disease progresses. Amputation of an extremity, and in rare cases resection of the bowel, tongue, penis, or other involved organ may be necessary.^{2,5,6,11,18,19}

Subtotal parathyroidectomy is often attempted as a therapeutic procedure. Its usefulness is questionable given that assessments of the effectiveness of this procedure is limited to case series and retrospective chart reviews.¹ The value of parathyroidectomy is particularly unclear when PTH levels are not elevated and performing this procedure in this setting may lead to deleterious induction of low turnover bone disease.^{17,26,27}

Kane *et al.* described three patients with calciphylaxis who developed the typical severe superficial skin ulcers and underwent parathyroidectomy.¹⁷ All demonstrated complete or near-complete healing of the wounds within several months, with no recurrence. Similarly, 8 of 10 patients in the series reported by Angelis *et al.* underwent parathyroidectomy for calciphylaxis related lesions with subsequent resolution of pain and ulcers over the next several months.¹² Chan *et al.* found no survival benefit with parathyroidectomy in a series of 47 patients.²⁸ Unfortunately, it is difficult to comprehensively evaluate the effectiveness of parathyroidectomy on the basis of such limited case series. In the only available large, retrospective review of parathyroidectomy in the setting of calciphylaxis, Hafner *et al.* analyzed the literature to find reports of hemodialysis patients with calciphylaxis who did or did not undergo parathyroidectomy.⁷ Sixty six percent of the 58 patients who underwent parathyroidectomy survived, as opposed to a 35% survival among the 37 patients those who did not receive surgery. The range of survival among parathyroidectomy patients was 2 weeks to 21 months (no mean survival was established) while those not undergoing the procedure had a survival range of several days to 2 years. Unfortunately, this study had many limitations including its retrospective nature, reliance upon a literature replete with small series and case reports spanning decades, lack of clarity regarding the actual mean and median survival benefits conferred by parathyroidectomy, and a heterogeneous population. Therefore, the benefits conferred by parathyroidectomy in these patients remain uncertain, particularly when PTH levels are not elevated. Performing the procedure in this setting may lead to deleterious induction of low turnover bone disease. Nevertheless, one author has proposed prophylactic parathyroidectomy in patients with elevated PTH and radiographic evidence of vascular calcification.²⁹

Several authors also suggest the discontinuation of sensitizing and precipitating agents if clinically possible. These include steroids, immunosuppressant and immunotoxic agents, albumin, blood products, iron injections, and high doses of calcium carbonate and vitamin D derivatives.⁹⁻¹¹ It must, however, be remembered that none of these agents has definitively been shown to cause onset or progression of calciphylaxis. These medications may be essential in controlling the underlying systemic illness causing the renal disease or a secondary unrelated condition. Therefore, a cost-benefit analysis considering the impact of withdrawing such medications as immunosuppressants and immunotoxic

agents (in patients with autoimmune disorders, for example) must be performed before such treatment is withheld in the hope of improving the course of calciphylaxis.

New innovative treatments include the use of low calcium dialysis. In one case report by Lipsker *et al.*, a 46 year old male with renal failure secondary to amyloidosis developed the cutaneous manifestations of calciphylaxis (proven with biopsy).³⁰ Use of low calcium dialysis was followed by cessation of wound progression in 1 week, wound regression in 6 weeks, and recovery in 3 months. Two authors have reported the use of hyperbaric oxygen therapy in patients with calciphylaxis refractory to medical and surgical therapy.^{31,32} In both reports, patients' wounds healed completely following 7 to 8 weeks of hyperbaric oxygen therapy. The high oxygen tension may function to promote angiogenesis in the region of skin necrosis, thereby increasing the number of patent blood vessels and promoting regeneration of the destroyed tissue. Low molecular weight heparin and bisphosphonates are other treatment modalities that have been considered although neither has been extensively tested or tried clinically.^{33,11}

There is one report of a 60 year old female with chronic renal failure and cutaneous manifestations of calciphylaxis which were refractory to phosphate binders, low phosphate diet, low calcium dialysis, and parathyroidectomy, but resolved with a course of 10 days of oral prednisone (40 mg twice daily) followed by 3 months of oral cimetidine (300 mg twice daily).³⁴ It is uncertain what role cimetidine or prednisone had in improving the manifestations of calciphylaxis in this patient. Furthermore, although cimetidine is believed to have some immunomodulatory properties, it is entirely unclear by what mechanism the medication may exert a beneficial effect in calciphylaxis.³⁴ The only rationale for this intervention was a previous report of successfully treating a different condition involving inflammation of subcutaneous blood vessels, termed fasciitis-panniculitis syndrome, using oral prednisone and cimetidine.^{34,35}

Prognosis

Patients developing calciphylaxis have a poor prognosis regardless of the treatment modalities used. Overall mortality is estimated at 60 to 90%, the usual etiology being sepsis from wound infections.^{1,2} Even with parathyroidectomy and aggressive life support, patients on average do not survive longer than several months.⁷ It is also difficult to predict who will improve with medical or surgical therapy, as outcome does not correlate well with pretreatment biochemical parameters.⁷ In general, the prognosis is considered poorer if there is trunk or proximal limb involvement as opposed to distal extremity involvement alone.^{1,2,7,28} Patients who are discovered to have the disease earlier may receive medical and surgical intervention prior to the development of severe ulceration and tissue destruction. In theory, this should decrease the likelihood of developing large infection-prone ulcerations and cutaneous and visceral ischemia, but the benefit of early intervention in decreasing morbidity and mortality is not established.

Levin *et al.* attempted to derive a mathematical model to identify patients at risk of developing calciphylaxis.¹⁶ A multivariate regression analysis was not possible due to the rarity of the condition. Instead the authors derived an arithmetic model based on physiological reasoning, clinical observations, and a literature review of chronic dialysis patients (excluding those with diabetes, systemic lupus erythematosus, and renal transplant). The derived model is an expression: $2 \times [(\text{Calcium} \times \text{Phosphate}) - 5] \times \text{ALP} \times \text{PTH}$ ratio. The calcium and phosphate units are in millimoles per litre, ALP is in international units (IU) and the PTH ratio is the measured PTH value divided by the upper limit of normal for PTH at the reporting laboratory. Values greater than 1000 were considered high risk for developing calciphylaxis. The model attempts to incorporate several commonly abnormal biochemical parameters in calciphylaxis in order to increase specificity (given that individual parameters can be abnormal in many patients with renal disease). At the same time it emphasizes the importance of the calcium phosphate product (if the product is less than 5 the result will be negative, immediately rendering the patient low risk).

When the model was tested on a separate group of patients, sensitivity was found to be 80% and specificity 92%. The positive predictive value was 66% and negative predictive value 96% (as can be expected in a disease with low prevalence). Clearly, this model contains several limitations. Patients with common diseases (diabetes, systemic lupus erythematosus) were excluded, derivation and testing samples were small, and testing of the model used retrospective data. Nevertheless, it does offer a starting point for trying to identify and potentially treat patients at risk for developing this devastating disease.

Conclusion

Calciphylaxis is a relatively rare complication of end stage renal disease. However, when the disease does develop it imposes a tremendous burden and suffering on patients and almost invariably carries a dismal prognosis. Depending on its presentation, the disease may also pose a diagnostic or therapeutic challenge to various medical and surgical specialties. Given the underreporting of calciphylaxis, the incomplete understanding of its pathogenesis, and the fact that current treatment options do not prolong life significantly, increasing awareness of the disease is necessary to promote future basic science research and prospective clinical trials in medical and surgical management.

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