

Calciphylaxis: Current Management and Emerging Therapies

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Abstract

Calciphylaxis or calcific uremic arteriopathy is a relatively uncommon condition with poor prognosis. Although it is predominantly observed in patients with end stage renal disease, a few cases of patients without kidney failure have been reported. Calciphylaxis is characterized by calcification of the arteriolar intima media and eventually by vascular thrombosis, tissue ischemia and painful skin necrosis. Septicemia is the main cause of death. According to published literature concerning the pathology of calciphylaxis, prevention and treatment are principally based on interventions in calcium and phosphorus metabolism. Although novel therapies have emerged, due to the rarity of this condition, there is no sufficient data in favor of a certain treatment.

Keywords: Calciphylaxis; Sodium thiosulphate; Bisphosphonates; Treatment

Introduction

Calciphylaxis or calcific uremic arteriopathy is a syndrome of vascular calcification, thrombosis and skin necrosis. It is seen almost exclusively in patients with end stage kidney disease. It is a type of extrasosseous calcification. The exact pathogenetic mechanisms are not well understood and possible factors involved in its pathogenesis are mentioned below. The disease does not only affect patients with kidney failure. Although relatively rare, calciphylaxis results in chronic non-healing wounds and is usually fatal.

Pathogenesis of Calciphylaxis

The main pathologic feature of calciphylaxis, calcification of skin arterioles, has guided research towards factors involved in calcium (Ca) and phosphorus (P) balance.

Factors that Promote Calcification

Parathyroid hormone (PTH)

There are cases of calciphylaxis that have been successfully managed by parathyroidectomy [1-3]. However, not all patients with hyperparathyroidism develop calciphylaxis. Although calciphylaxis is more frequent in the latter, there are also reports of patients with normal, low or undetectable serum PTH that have undergone parathyroidectomy in the past [2,4,5]. On the other hand, there are case reports of calciphylaxis in patients with uncontrolled primary hyperparathyroidism and normal renal function. It is possible that parathyroidectomy may prove beneficial by normalizing Ca and P homeostasis and by rapid declining of the Ca x P product during the postoperative period.

Vitamin D and calcium based phosphate binders

Active vitamin D or vitamin D analogues administration, as well as calcium containing phosphate binders prescribed for the treatment of secondary hyperparathyroidism are potentially involved in the pathogenesis of calciphylaxis by increasing Ca x P product [6-9].

Hypercalcemia and hyperphosphatemia

These disorders seem to be the main factors responsible for arteriolar calcification and the development of calciphylaxis [10-11]. Disturbances in the homeostasis of Ca, P and PTH may depict the initial sensitization part of a two-hit model, where some other stimulus

(systemic or local) is needed in order to initiate the combined process of inflammation and calcification leading to calciphylaxis. On the other hand, Ca deposits may reflect a secondary event, an epiphenomenon following a not yet elucidated triggering primary event. In any case rigorous control of Ca, P and PTH levels is necessary since they have been recognized as precipitating factors in the course of calciphylaxis. [12,13]

Factors that Inhibit Calcification

Matrix-Gla protein (MGP)

MGP is a glycoprotein produced by vascular smooth muscle cells and chondrocytes and it is a local calcification inhibitor. In MGP knockout mice, massive median calcification takes place and death ensues after 6 weeks approximately due to rupture of the aorta [14-15]. MGP activation requires its carboxylation which is vitamin K dependent [16-17]. This fact can partially explain the observation that administration of vitamin K inhibitors like warfarin may be associated with calciphylaxis [4,18].

Fetuin-A

In contrast to MGP which acts locally, fetuin-A is a systemic calcification inhibitor. This glycoprotein is produced in the liver and is found in serum in high concentrations (0.5-1g/L) [19]. Fetuin-A knockout mice develop significant calcifications [20]. Interestingly, fetuin-A levels are reduced in inflammation [19,21]. In the few cases of calciphylaxis in patients without chronic kidney failure, an inflammatory disease was present, like connective tissue disease or Crohn's disease [22,23]. Chronic kidney disease is also an inflammatory state [24] and in the majority of patients undergoing hemodialysis,

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fetuin-A levels are downregulated, a fact which is associated with increased mortality [25,26]. Furthermore, low fetuin-A and high CRP levels are detected in patients with calciphylaxis [20,27].

Epidemiology

The reported rates of calciphylaxis vary among centers. In Germany, until recently, 50 cases per year were reported. However, in a study of 242 dialysis patients, calciphylaxis was present in 4% [28].

Risk Factors

1. End stage renal disease patients. This population accounts for most cases and this is why the term “calcific uremic arteriolopathy” has been used as a synonym for calciphylaxis [4,6].
2. Female sex [4,10].
3. Obesity [29].
4. Hyperphosphatemia [10,11]
5. Vitamin D or its analogs and calcium based phosphate binders [6-9]. Possibly however, selective Vitamin D receptor activators could play a beneficial role through their non-classical effects [18]. However, any vitamin D therapy would need to be used very cautiously and with close monitoring because of the risk of increasing the Ca x P product.
6. Warfarin [4,18]
7. Corticosteroids [30] There is a study however which demonstrates a beneficial effect of corticosteroids when timely administered [6].
8. Hypercoagulability states like protein C or S deficiency or the antiphospholipid syndrome [31-33].

Non-uremic Causes of Calciphylaxis

Primary hyperparathyroidism, malignancy (e.g. cholangiocarcinoma, malignant melanoma, multiple myeloma, chronic myelocytic leukemia and metastatic breast cancer), alcoholic liver disease, connective tissue diseases (giant cell arteritis and rheumatoid arthritis), diabetes and weight loss have been reported among others as causes of non-uremic calciphylaxis. The proposed pathogenetic mechanisms include deficiency of vascular calcification inhibitors (e.g. Fetuin-A and MGP), disturbances of NF- κ B receptor activator (RANK), RANK ligand and osteoprotegerin leading to extraskeletal calcification, decrease in the activity of MGP (due to inhibition of its vitamin K dependent carboxylation), increased levels of matrix metalloproteinases etc. However, the reported causes cannot always be clearly differentiated from simple associations and the exact underlying mechanisms are far from being understood. Interestingly, systemic use of corticosteroids had detrimental effects in most cases of non-uremic calciphylaxis [22,23].

Clinical Features-diagnosis

Calciphylaxis lesions are usually found in areas rich in adipose tissue like the thighs, abdomen and buttocks [4,6,29]. It can however affect the fingers, with a better prognosis or other unusual places like the breast or genital area [34,35]. Hard painful subcutaneous violaceous nodules or plaques are the initial lesions followed by dysesthesia, the development of livedo reticularis and eschars. The subcutaneous calcified nodules and/or plaques are often palpable and pruritus may

develop in adjacent areas. These lesions can be ulcerated or infected [4,6]. Differential diagnosis of skin lesions includes lesions due to peripheral vascular disease with distal extremity lesions, cholesterol emboli, cryoprecipitate disorders, vasculitic lesions (autoimmune disease associated, hepatitis-C associated or other necrotizing vasculitides), oxalate vasculopathy, calcinosis cutis and other rare skin disorders [12,36,37].

Medial calcification and intimal hyperplasia of small subcutaneous arterioles and vascular thrombosis are common histological features. Subcutaneous tissue calcification with cellulitis and lipid necrosis, as well as inflammatory cell infiltration is not uncommon [38,39]. Although skin biopsy is required for a definite diagnosis, three points warrant further attention. Firstly, a biopsy must be performed with special caution since it can produce a non-healing ulceration that can accelerate the lesions and dramatically increase mortality. Secondly, needle biopsy does not provide enough tissue and a small skin incision around the main lesion is required. Furthermore, special stains should be used like AgNO₃-Kossa method or Alizarin Red in order to demonstrate the calcifications [6,40]. Serum PTH, Ca and P levels are often but not always elevated.

Conventional x-rays, high resolution computed tomography or even better x ray mammography demonstrate the calcifications. In the latter method, arteriolar calcification is depicted as a plexus in the affected area. Mammography is used for imaging of lesions of the extremities and requires compression between two plaques which could be extremely painful in case of calciphylaxis [41].

Alternatively, ^{99m}Tc bone scintigraphy might offer a noninvasive modality that could be used in diagnosis and disease monitoring since the tracer is accumulated in lesions where osteopontin, a bone protein is present [42,43]. However, its findings could be misinterpreted in the presence of severe hyperparathyroidism.

Prognosis

Calciphylaxis carries a poor prognosis. One and five year survival rates are 45% and 35% respectively [44]. Intensive wound care, treatment of infections, aggressive management of calcium and phosphorus balance and novel therapies seem to be quite promising in improving survival [30,44].

Management of Calciphylaxis

Due to the fact that cases of calciphylaxis are sporadic and relatively uncommon, large prospective studies are lacking. Current management is mostly based on small retrospective studies. However, emerging therapies are promising for the future. Creation of registries and data bases for calciphylaxis will prove beneficial in the better evaluation of these therapies.

Current Therapies

Intensive wound care for prevention of local or systemic infection is mandatory. It encompasses the use of special enzymes for dead tissue removal, wound dressings and antibiotics administration if necessary [45]. Surgical debridement is usually extremely painful and increases the risk of sepsis.

Correction of the underlying plasma calcium and phosphorus abnormalities is required in order to lower the Ca x P product below 55mg²/dl² and keep serum P levels between 3.5 and 5.5 mg/dl [46]. Diet

restriction and non calcium based phosphate binders like sevelamer or lanthanum are necessary to achieve these goals [8,9,47]. Intensive dialysis (HD or PD) with a lower calcium bath can be very helpful [8,9,48].

Management of hyperparathyroidism should be aggressive. Calcimimetics (cinacalcet) which, besides PTH suppression, lower Ca X P product may be used instead of vitamin D and analogs which tend to elevate Ca x P product [49,50]. In refractory cases, parathyroidectomy seems to be the only solution and could be beneficial [1-5].

Vitamin K inhibitors like Coumadin or warfarin must be immediately discontinued. Low molecular weight heparin can be used instead.

Novel Therapies

Sodium thiosulphate

This agent has been used for over one hundred years for the management of conditions like cyanide poisoning and nephrocalcinosis. Sodium thiosulphate has been lately involved in the treatment of calciphylaxis [51-55]. Although dosing (5-25g IV, 3-4/wk) and duration of treatment (6 months -2 years) vary among studies, significant relief from pain, improvement of inflammation and wound healing are reported. Sodium thiosulphate is believed to dissolve precipitated calcium from tissues to soluble calcium thiosulphate, which can be more effectively removed by hemodialysis. Furthermore, STS may promote vasodilation via the vasodilatory properties of its metabolite hydrogen sulfide and its antioxidative action (as it enhances glutathione generation). STS may also restore endothelial dysfunction due to decreased smooth muscle cell proliferation (through nitric oxide synthesis induction), its antithrombotic properties and its action on matrix metalloproteinases. STS is a rather safe agent. High anion gap metabolic acidosis due to sulphate retention in ESRD patients can be managed by raising bicarbonate concentration during the dialysis session [12,36].

Bisphosphonates

They inhibit bone catabolism, macrophage activity and inflammation. In one study, six doses of intravenous pamidronate resolved the lesions in a CKD patient [56]. In another study, oral etidronate administration showed favorable results [57]. The possible underlying mechanisms may include reduction of high bone absorption and Ca control, anti-inflammatory properties, or direct effects on tissue calcification (increase in osteoprotegerin and inhibition of RANKL, lowering of bone alkaline phosphatase activity and inhibition of calcium-phosphate crystal formation). [12] These drugs have not been adequately tested in dialysis patients, they may increase the risk of lowering bone turnover and their use is contraindicated in cases of adynamic bone disease.

Hyperbaric oxygen

In general, wound healing is impaired if tissue oxygen partial pressure falls below 20mmHg. Also, hypoxemia inhibits the antibacterial activity of neutrophils. Hyperbaric oxygen therapy is a way to restore adequate tissue oxygenation by delivering 100% of oxygen under high pressure with the patient in a sealed chamber [58,59]. Only one retrospective study in which, 9 patients with calciphylaxis were treated with an average of 40 90-minute sessions at 2.5 atmospheres with good

results in 8 of them has been reported [59]. More studies are needed in order to justify the use of this expensive and not widely available therapy in the treatment of calciphylaxis.

Corticosteroids

There is a study in which prednisone administration in 14 hemodialysis patients with non ulcerated lesions of calciphylaxis resulted in improvement or stabilization of 11 of them [6]. However, the use of all immunosuppressants in patients at high risk of sepsis could be very dangerous and further studies are required to establish the role of corticosteroids in calciphylaxis. Under the current knowledge they should be used with great caution only in cases where other measures have proved ineffective and should be completely avoided in non-uremic calciphylaxis.

Lower extremities revascularization procedure

There are few reports of patients, however with disappointing results [60].

Lucilia sericata larvae (common green bottle fly)

They have been tested with success [61]. These larvae can debride wounds. They enhance fibroblast migration and secrete antibacterial substances mainly against Gram positive bacteria including methicillin and vancomycin resistant staphylococci.

To summarize, calciphylaxis is characterized by systemic medial calcification of the arterioles, i.e. calcification of intima media, vascular thrombosis leading to tissue ischemia including skin ischemia and, hence, skin necrosis. The lesions are usually located in thighs, abdomen and buttocks. It is seen almost exclusively in patients with stage 5 CKD, however the disease is not limited to patients with kidney failure. Disturbed calcium and phosphorus homeostasis (increased Ca x P product), decreased calcification inhibitors and inflammation seem to be the principal factors involved in the pathogenesis of calciphylaxis. Calciphylaxis carries a poor prognosis and most patients die from sepsis. Current therapeutic management requires wound care and aggressive control of calcium and phosphorus control. Novel therapies are under testing, among which sodium thiosulphate seems to be most promising.

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