Calciphylaxis: a still unmet challenge

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Abstract

Introduction: Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare disease most frequently occurring in patients with advanced chronic kidney disease (CKD). The clinical picture is typically characterized by very painful skin lesions and ulcerations following calcification and occlusion of small cutaneous arterioles. CUA is life-threatening due to infections and concomitant cardiovascular diseases.

Methods: We performed a literature search for the terms calciphylaxis and calcific uremic arteriolopathy and summarized current state-of-the-art knowledge about pathophysiology, clinical picture, course of the disease, as well as treatment options. We have filled out the literature data with our personal treatment experiences.

Results: A combination of various local and systemic risk factors are necessary to cause the development of calciphylaxis. This pathophysiological cascade is still incompletely understood. Patients with advanced CKD and dialysis patients are especially at risk to develop CUA. Regarding therapy, no randomized prospective trials are available, and treatment is rather based on pathophysiological considerations as well as on evidence derived from case reports or case series. Therapy focuses on optimized dialysis treatment, control of chronic kidney disease–mineral and bone disorder parameters, experimental anticalcification strategies and wound care.

Conclusion: Facing the still deleterious outcome of patients with calciphylaxis, further studies on prophylaxis as well as treatment are urgently needed. Current treatment strategies may help ameliorate the course of the disease in some patients. However, it is still unclear if they are able to decrease mortality.

Key words: Calcific uremic arteriolopathy, Calcification, Calciphylaxis, Chronic kidney disease, Vascular disease

Why should we care about calcific uremic arteriolopathy?

The term calciphylaxis was introduced by Hans Selye based on his early animal experiments in the 1960s (1). Selye induced ectopic calcifications in rodents by the parallel action of sensitization factors (e.g., hyperparathyroidism or hypervitaminosis D) and challenging factors (e.g., trauma). However, strictly speaking, the histopathological picture of Selye’s model is not a good template for what human medicine later called calciphylaxis. Nevertheless, calciphylaxis is nowadays a still widely applied term for a syndrome with rapid subcutaneous tissue calcification. The descriptive term calcific uremic arteriolopathy (CUA) is more appropriate regarding the supposed pathophysiol-
ogy and the predominant pathological findings (2). On the other hand, CUA is also somehow misleading, since “uremic” indicates a unique association with severe or even end-stage kidney disease, but some CUA cases occur in patients with normal renal function. About 30 years ago, the first detailed case series of human CUA were published by Gipstein and coworkers (3). Uncertainties still exist about incidence and prevalence of this overall rare disease. Previously published figures (in 1997) calculating the prevalence in dialysis patients to be about 5% are not supported by more recent publications. Moreover, based on our own experience, we estimate the prevalence to be less than 1% in dialysis patients (4). A prevalence of 1% would equal about 600 German dialysis patients. Although rare, the condition merits both clinical and scientific interest and input for 2 reasons: First, the clinical picture is severe and outcome often devastating (1-year mortality 45% in (5)); second, CUA may serve as a high-speed template for overwhelming extrasosseous calcification and therefore may help – as a kind of natural in vivo model – to elucidate the pathophysiology of vascular calcification in general.

We would like to stress that in most cases, CUA appears not to be another natural fateful sequel of progressive chronic kidney disease (CKD) and should therefore be considered distinct from renal anemia, hypertension, hyperparathyroidism and osteodystrophy. The typical patient presenting with CUA is not a previously unrecognized or “undertreated” renal patient with severe CKD. In contrast, virtually all patients with CUA have been under medical surveillance for quite a long time, and therefore, the development of CUA might actually have iatrogenic components.

In Germany, we initiated an Internet-based registry for all cases of calciphylaxis in late 2006 (V. Brandenburg & M. Ketteler). The registry is supported by a kick-off and ongoing grant from Amgen. The German registry is part of an international initiative (http://www.calciphylaxis.org.uk/) from the International Collaborative Calciphylaxis Network (ICCN). The German registry is accessible via the website at http://www.calciphylaxie.de/. With increasing knowledge of risk factors, response to treatment and outcome, we hope to improve prophylaxis as well as therapy for patients with CUA. During the work with the registry we have thus far collected about 120 cases of CUA with detailed documentation (about 35 cases per year in Germany).

**THE CLINICAL PICTURE OF CUA**

CUA is characterized by progressive cutaneous lesions finally ending in deep tissue ulcerations in many cases (6). The typical picture is a mixture of large retiform ulceration with thick eschar surrounded by violaceous, indurated, tender, retiform plaques. However, the degree of cutaneous and subcutaneous tissue involvement is highly variable and may also be rather limited to livedo reticularis or to single indurated plaque formation (7). It remains speculative if these different degrees of cutaneous and deep tissue affection represent various stages of the same disease or if they represent closely related, although distinct entities (8, 9). Superficial pain is virtually always part of the initial clinical picture, with zoster neuralgia being a typical differential diagnosis. On palpation, skin and soft tissue surrounding necrotic areas often show a characteristic plaque-like hardening. Most often, it takes only days to a couple of weeks before the full picture of CUA has developed. With increasing awareness of the disease, the interval before the appropriate diagnosis is made gets shorter, at least within our experience. The list of potential differential diagnoses is long and includes a heterogenic group of primary skin diseases or internal diseases with secondary skin manifestations. A detailed list of differential diagnoses has been published (10). Some severe and also potentially fatal differential diagnoses need to be considered: e.g., systemic vasculitis and pyoderma gangrenosum need to be ruled out in a timely and appropriate manner (Fig. 1). Gangrene due to macrovascular obstruction (peripheral arterial disease) is another important differential diagnosis, and many patients have underlying large vessel arteriosclerotic lesions at the time of CUA diagnosis. However, in CUA, distal limb necrosis of toes and fingertips are not a typical finding.

Fig. 1 - A 57-year-old dialysis patient with painful skin lesions on the lower leg. Calciphylaxis was among the differential diagnoses. However, biopsy revealed leukocytoclastic vasculitis.
A crucial question is if skin biopsy should be performed. We do not recommend routine biopsy since many cases of secondary aggravation have been documented after biopsy, and oftentimes the diagnosis can be clinically made without doubt (8). The same is true for, e.g., subcutaneous heparin application, which may induce novel and progressive lesions. Other forms of blunt trauma may also induce calciphylaxis. However, if surgical wound management is indicated we strongly recommend histological tissue analysis with particular emphasis on the presence of calcification. Therefore, the pathologist should perform a calcification-sensitive staining (e.g., van Kossa). Awareness of calciphylaxis wins half the battle. In cases of doubt, biopsy results are definitely helpful. Some authors suggest performing a bone scan that may reveal widespread tracer accumulation in soft tissue as a clear hint for CUA, but this is probably only true for deep and widespread lesions (8).

**Pathology**

The histological picture of CUA is characterized by a triad: medial calcification of cutaneous arterioles (diameter 100-600 µm (9)), intimal hyperplasia and panniculitis (adipose tissue necrosis) (2, 11). Some authors have speculated that calcification is the initial lesion (12) finally ending up in the full picture of luminal obstruction. Janigan and coworkers elaborated the concept of primary lesions (calcification) and secondary lesions (tissue infarction due to luminal obstruction) (13). This concept consists of a “2-hit model” with calcification as the basic lesions, which, however, needs to be followed by thrombus formation (Fig. 2).

**Is it time to define CUA subgroups?**

We suggest classifying CUA into different subgroups. This classification takes into account the clinical picture and basic patient characteristics. In our experience, we need to classify CUA due to variable prognoses and responses to therapy. Regarding localization (anatomic distribution), some CUA patients develop cutaneous lesions merely at the distal extremities: forearm and lower leg (Fig. 3). This distribution pattern is in contrast to those CUA patients in whom proximal lesions (trunk, thighs and/or buttocks) predominate. The proximal lesion pattern is often associated with deep ulcerations and fat tissue necrosis (Fig. 4), while the distal pattern is often limited to the superficial skin layers. However, intermediate forms are possible; especially development of necrosis with deep ulcerations at the distal extremities may occur (Fig. 5). While the proximal, ulcerative CUA often develops in obese patients, the distal, more superficial CUA often develops in slim and malnourished patients. Robust data regarding whether these 2 forms have significant impact upon outcome still need to be established. However, in accordance with the literature we feel that mortality is higher in the ulcerative forms than in the nonulcerative forms (8). Another very interesting aspect for classification of CUA is the question of whether CKD is present (renal form of CUA) or not. Only very limited data are available for the so-called nonrenal form of CUA (14). There are no comparative data available regarding mortality and morbidity between these 2 forms.
We would like to clearly emphasize that many aspects of CUA pathogenesis are only incompletely understood. Vascular calcification including atherosclerosis and arteriosclerosis is a wide-spread phenomenon in patients with advanced renal failure and can be considered as a generalized, multilocular disease (15). However, the unique clinical picture, the distribution of affected vessels and also the rarity of the disease make clear that CUA is a unique phenomenon. Many factors have come into play as potential risk factors for the development of CUA. Up to now, there is an ongoing debate as to which of these factors are only associated and which are truly causative. This distinction may actually be decisive, because only the establishment of causality may direct treatment. Because the vast majority of cases with calciphylaxis occur in patients with severe or end-stage renal disease, many publications discuss chronic kidney disease–mineral bone disorders (CKD-MBDs) such as hyperparathyroidism or hyperphosphatemia as pathogenetic factors (16). However, such associative conclusions cannot explain why thousands of dialysis patients with comparable degrees of CKD-MBD never develop CUA. Moreover, most often CUA patients do not show uncontrolled hyperparathyroidism, hyperphosphatemia and/or overt hypercalcemia at the time of CUA diagnosis (5, 17). Compared with those in the majority of dialysis patients, these parameters are rather unremarkable in recently diagnosed CUA cases. In that respect, longitudinal and regular data collection during the months before CUA diagnosis would be a great help for progress in terms of risk factor analysis. Therefore at present, an overview of risk factors / associated factors for the development of CUA is not more than just a descriptive list of a statistical phenomenon. CUA outside the nephrology world is a rarity, so uremia seems to play a very important pathogenetic role as underlying predisposing condition (5, 8, 18, 19). A predominance of females has been found, so hormonal influences regarding CUA are likely (5, 8, 18, 19). Other risk factors / associated factors include diabetes (8, 19), heavy body weight (18), liver disease (18), calcium supplementation (8), vitamin D treatment (8), use of corticosteroids (18), low albumin serum levels (5) and elevated alkaline phosphatase (AP) levels (5). The link between AP and CUA is another nice example for how difficult interpretation of causality may be: high AP levels have been associated with CUA; however, no data are available as to whether high AP levels reflect renal osteodystrophy (in that case AP is a biomarker), or whether high AP levels cause calcification (AP induces pyrophosphate hydrolysis, so AP could be the “hen”), or whether AP levels reflect vascular smooth muscle cell transformation to bone-like cells (the vascular calcification process induces increase of circulating AP, so AP could be an “egg”). The fact that only a small minority of patients with such particular diseases such as CKD-MBD or diabetes finally develop CUA makes a multifactorial pathogenesis most likely. It appears that many factors (already defined, as well as yet to be discovered) need to be present in parallel (or to occur sequentially).
Evident, though also disturbing, support for the theory that CUA is at least in part a “home-made” phenomenon derives from the association between CUA and vitamin K antagonist (Coumadin) treatment. Vitamin K antagonists such as warfarin interfere with the function of matrix Gla protein (MGP). MGP is a locally active calcification inhibitor (20) whose function is suppressed with warfarin (20). Based on our German registry data, about 50% of incident patients with CUA have been treated with vitamin K antagonists. Another prototypic calcification inhibitor is serum fetuin-A (21). We know that dialysis patients have lower levels of fetuin-A compared with healthy controls and that there is a correlation between low levels of fetuin-A and high calcification burden. The serum levels of both calcification inhibitors are especially low in patients with CUA, and the ability to inhibit basic calcium phosphate precipitation of CUA serum is much lower than in healthy controls (22, 23). The association of low calcification inhibitor levels in the circulation of patients with CUA allows 2 interpretations: either the inhibitors are consumed and trapped at places of overwhelming calcification, or some other triggers reduce their levels and secondarily induce calcification. We again end up with the question of what is cause and effect. Figure 6 shows an instructive example of how disease progression (expressed with C-reactive protein levels) in CUA takes an anti-parallel course to changes in fetuin-A serum levels.

**TREATMENT FOR CUA**

There is no evidence-based medicine treatment option available for patients with CUA. Moreover, no medication has official approval for this disease. Any treatment options offered in the following section are derived from case reports or case series from the literature, or from pathophysiological considerations or are based on personal experiences. The heterogeneity of patients and disease manifestations on the one hand, and the rarity of the disease on the other, have prevented the accomplishment of any prospective trial so far.

Appropriate to the presumably complex etiology of CUA, treatment is multimodal. Experts in wound care management and infection therapy, dermatologists, surgeons and nephrologists need to work hand-in-hand. We will focus upon systemic treatment modalities. The mainstay of therapy in patients with CUA is the normalization of calcium, phosphorous and parathyroid hormone metabolism. After diminishing the amount of calcium salts administered to dialysis patients (mostly peritoneal dialysis patients), the incidence of CUA dropped significantly at 1 center over several years (24). Some case series report rapid improvement of CUA after parathyroidectomy (25). However, we recommend careful evaluation of the indication for parathyroidectomy since in our experience many patients with CUA do not have uncontrolled hyperparathyroidism. In contrast we are afraid of low bone turnover being associated with CUA development in a large proportion of affected patients (26). If high parathyroid hormone levels are suspected as a trigger for CUA, cinacalcet administration is an alternative to operative parathyroidectomy. We administer calcium-free phosphate binders to patients with CUA, and we reduce dialysate calcium to levels of ≤1.25 mmol/L. Although the final decision on beneficial effects of calcium avoidance has not been made (27, 28), reduction of external calcium supply is a basic approach in our treatment strategy. We decrease the dosage of active vitamin D, but give native vitamin D in cases of severe deficiency as indicated by low levels of calcidiol (25OH vitamin D). Optimization of dialysis regimen is our aim. We intensify frequency and/or duration of dialysis sessions in affected patients to increase calcium and phosphate removal. A change from peritoneal to haemodialysis may help. In severe cases, hospital admission for daily wound care is necessary. As far as possible, we stop vitamin K antagonist treatment (e.g., in most cases with atrial fibrillation) and administer vitamin K instead. Thereby, we hope to stimulate the MGP-based anticalcification protection system (29). Future stud-
ies are needed to determine if the administration of heparin or other anticoagulants instead improves blood supply to affected tissue by increasing flow through areas of widespread microthromboses (30). As pointed out by Janigan et al, acute luminal obstruction potentially triggered by thrombus formation (the “secondary lesion” – see above) is necessary before tissue infarction can develop (13). Hyperbaric oxygen therapy (HBO) has been shown to improve CUA; however, positive effects were largely limited to patients with distal forms of CUA (31).

Sodium thiosulfate (STS), which sequesters calcium ions to form highly soluble calcium thiosulfate complexes, can prevent calcium phosphate precipitation. Several case reports and case series show that pain relief and more rapid wound granulation may occur with STS administration (32). Pain relief, i.e., symptomatic treatment, is actually of great importance in patients with CUA, so we start STS in all patients with (suspected) CUA, because side effects are low if the infusion rate is low (100 mL STS 25% solution over 2 hours).

We are very cautious about using 2 therapeutic measurements cited in the literature: application of bisphosphonates and steroids. Although bisphosphonates might have some anticalcification properties (33), we are afraid of negative effects on bone metabolism in preexisting low-turnover renal osteodystrophy. Steroids might improve nonulcerative forms of CUA (8). However, other studies report deleterious effects on outcome (14) or accuse steroid usage of triggering the development of CUA (18).

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REFERENCES