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# Management of calciphylaxis in a burn center: A case series and review of the literature

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ABSTRACT

Calciphylaxis is a rare, necrotizing skin disorder usually associated with kidney disease, but also caused by many other systemic illnesses. This disease is associated with mortality rates as high as 80% at 1 year. We present the demographic and clinical data of nine patients with calciphylaxis treated at our burn center over a 10 year period. We review the literature on the clinical presentation, pathophysiology, diagnosis and treatment of this rare disease. We propose that these patients be treated similar to patients with thermal burn injury; meaning intensive wound care, surgical management, critical care and physical therapy. Burn centers are uniquely capable of caring for these incredibly complex patients due to their experience in managing patients with extensive skin and soft tissue defects, wounds and diseases.



## 1. Introduction

Calciphylaxis or calcific uremic arteriolopathy (CUA) is a rare and life-threatening necrotizing skin disorder that is typically seen in patients with end stage renal disease (ESRD) on dialysis. Most studies report an incidence between 1 and 4% in patients with ESRD [1–5]. Mortality associated with calciphylaxis is around 30% at 3 months, 50% at 6 months and as high as 80% at one year [6,7]. The cause of death is usually sepsis from wound infection [6,8]. Patients classically present with painful, reddish nodules or plaques that often progress to ulceration with blackened eschar. Such lesions may be complicated by secondary infection, sepsis, and death and benefit from antibiotics, surgical debridement and amputation [1,9,10]. The typical patient is a middle-aged, obese Caucasian woman undergoing dialysis. In many cases, disturbances of mineral metabolism such as secondary hyperparathyroidism, hyperphosphatemia, hypercalcemia, high calcium intake (often from calcium-based phosphate binders), and active vitamin D intake are present [2,3,11]. While there is clearly an association with uremia, CUA has also rarely been reported in non-uremic patients such as those with primary hyperparathyroidism, alcoholic liver disease, malignancy, and connective tissue disorders [12].

We present a single center case series of nine patients with CUA treated at the US Army Institute of Surgical Research's Burn Center in the San Antonio Military Medical Center from 2007 to 2017.

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## 2. Methods

We identified patients admitted to the United States Army Institute of Surgical Research (USAISR) Burn Center who had clinical symptoms of calciphylaxis as a possible diagnosis from January 2007 to June 2017 by searching for the keyword terms "calciphylaxis", "calcific uremic arteriolopathy", and "CUA" in admission diagnoses, discharge diagnoses, history/physical documentation, and discharge summaries. Of the initial nineteen patient encounters discovered by this method, sixteen patients were screened (two of the sixteen patients had multiple hospitalizations accounting for the nineteen total encounters). Of the sixteen patients screened, seven patients were excluded based on comprehensive chart reviews and discussion amongst the authors that concluded the final diagnoses were not consistent with calciphylaxis for these seven patients. The nine remaining patients were included based on the presence of either empiric treatment for clinical presentations suspicious for calciphylaxis and/or histologic confirmation of calciphylaxis. Of these nine cases, specific characteristics including age, gender, race, ethnicity, original diagnosis on admission, presence of obesity, location of lesions, dialysis vintage, dialysis modality, presence or absence of diabetes mellitus, initial parathyroid hormone, calcium, and phosphate levels, number of surgeries undertaken during inpatient stay, presence of warfarin, presence of calcium-containing phosphate binders, presence of protein C deficiency, previous parathyroidectomy, presence of sodium thiosulfate, length of stay in hospital, length of stay in the intensive care unit (ICU), and disposition at discharge were registered into the study. Resolution of calciphylaxis was defined as the patient no longer having new formation of lesions.

This retrospective study was approved as a case series using a research determination approved by the USAISR Regulatory Compliance Department.

## 3. Results

Nine CUA patients met the inclusion criteria over the study period. See Table 1 for the clinical data gathered on each patient. The mean patient age was 51 (range of 33–66) years old. A slight majority of patients were female at 55.6%. No trend was apparent in terms of race distribution with a nearly even split between Caucasian and Hispanic patients (4 and 5 respectively), similar to the ethnic distribution of the geographic region. Obese patients represented one third of the group. All patients had chronic kidney disease requiring dialysis. All but one of the patients (89%) had proximal lesions and 78% had distal lesions. Image 1 is an example of a distal lesion and Image 2 is an example of a proximal lesion. Of note, only 2 of the 9 patients had a diagnosis of calciphylaxis at the time of hospital admission. All had biopsies that were eventually resulted as having histopathology consistent with calciphylaxis.

Initial calcium values ranged from 7.8 to 9.9 mg/dl. Initial phosphate levels ranged from 1.2 to 9.7 mg/dl. Parathyroid hormone levels varied; 3 patients had low or normal PTH levels (range 6–41 pg/ml) and 6 patients had elevated PTH levels (range 352–1128 pg/ml).

Seven of 9 patients received intravenous sodium thiosulfate therapy. The one patient who received a parathyroidectomy had the highest recorded PTH level of 1128 pg/ml. The mean number of surgeries performed during the hospitalization for wound debridement, skin grafting or soft tissue flaps was 14 (range 1–57). The wounds were covered with negative pressure wound dressings between surgeries. The decision to graft wounds was made by the attending burn surgeon based on their assessment of the wound bed and their confidence in its ability to accept an autograft. Mean ICU and hospital length of stay were 58 (range 2–265) days and 65 (range 4–265) days respectively. In terms of disposition, three patients died in the hospital, 2 were transferred to a long-term acute care facility, 1 was transferred to home hospice, and 3 were discharged to home.

## 4. Discussion

Calciphylaxis is a feared disease typically occurring in patients with end stage renal disease (Calcific uremic arteriolopathy), but can be seen in patients not undergoing dialysis (Non-uremic calcific arteriolopathy). It is characterized by cutaneous and subcutaneous tissue lesions which progress to ulceration and necrosis. It is associated with extremely high morbidity and mortality. Due to the rarity and variable nature of calciphylaxis, there is not only an incomplete understanding of its pathogenesis, but more significantly an absence of protocol driven studies evaluating therapies and outcomes. In the patients that survive, there is significant morbidity and increased mortality. Given the large open skin wounds and need for frequent debridement, these patients are at risk for nosocomial infections and significant pain [8]. Prolonged hospitalizations are not uncommon. Several of the patients in our case series were transferred to our burn unit with worsening wounds which had not responded to therapy at outside hospitals. Our two shortest admissions (4 and 6 days), died of severe septic shock and multi-organ system failure shortly after transfer. These patients had experienced lengthy hospital courses prior to transfer. Two of our nine patients underwent multiple hospitalizations relating to calciphylaxis.

The clinical presentation can vary, but CUA is generally suspected when patients with ESRD present with painful necrotic skin ulceration. A hallmark feature of CUA is severe pain that is often refractory to standard analgesic therapy. Lesions are typically tender, indurated plaques or nodules most commonly occurring on the abdomen and lower extremities and can progress to ulceration over days to weeks. Once present, necrosis and ulceration tends to progress with spontaneous resolution being uncommon and the risk of death rises significantly [11]. The mortality rate is greater than 80% for patients with ulcerations compared to 30% with non-ulcerative plaques [1]. Early diagnosis and clinically aggressive management is paramount.

CUA can be classified based on location as either proximal with lesions occurring on the trunk, thighs, buttocks, and face or distal, where lesions occurs mainly on the distal extremities. Obese patients are more likely to have proximal lesions,

**Table 1 – Patient demographic data, clinical characteristics, laboratory data and outcomes.**

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Age | 52 | 33 | 35 | 66 | 58 | 56 | 58 | 36 | 61 |
| Gender | Female | Female | Female | Male | Male | Female | Male | Female | Male |
| Race/ethinicity | Hispanic | Caucasian | Hispanic | Caucasian | Caucasian | Caucasian | Hispanic | Hispanic | Hispanic |
| Original diagnosis | Necrotizing fascitis | SSTI | Calciphylaxis | Calciphylaxis* | Diffuse desquamating skin rash | Warfarin-induced skin necrosis | warfarin-induced skin necrosis | Bullous pemphigoid vs vasculitis | Peripheral vascular disease |
| Obesity | Yes | Yes | No | No | No | No | No | Yes | No |
| Proximal lesions | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| Distal lesions | Yes | Yes | Yes | Yes | Yes | No | Yes | No | Yes |
| Type of dialysis | Hemodialysis | Hemodialysis | Hemodialysis | Hemodialysis | Hemodialysis | Peritoneal | Hemodialysis | Hemodialysis | Hemodialysis |
| Dialysis vintage (years) | 0 | 0 | 5 | 3 | 0 | 0.2 | 5 | 0 | 5 |
| Diabetes | Yes | No | No | Yes | No | Yes | No | Yes | Yes |
| PTH (pg/ml) | 41 | 563 | 1128 | 352 | 38 | 1246 | 673 | 6 | 840 |
| Calcium (mg/dl) | 8.2 | 8.3 | 9.9 | 9.4 | 7.8 | 9.2 | 9.2 | 8.9 | 8.6 |
| Phosphate (mg/dl) | 1.2 | 5.4 | 4 | 9.7 | 5.7 | 2.7 | 2.7 | 1.8 | 6.5 |
| Protein C Deficiency | No | No | No | No | No | Yes | No | No | No |
| Warfarin | No | No | No | No | No | Yes | Yes | No | No |
| Calcium-based phosphate binders | No | No | No | No | No | No | No | No | No |
| Sodium thiosulfate (25 g IV thrice weekly) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No |
| Cinacalcet | No | Yes | Yes | Yes | No | Yes | Yes | Yes | No |
| Dialysis modality | CRRT/IHD | CRRT/IHD | IHD | IHD | CRRT | CRRT | CRRT | CRRT | IHD |
| Parathyroidectomy | No | No | Yes | No | No | No | No | No | No |
| Number of surgeries | 57 | 8 | 6 | 9 | 1 | 4 | 1 | 36 | 3 |
| ICU LOS | 168 | 63 | 2 | 7a | 6 | 14 | 4 | 265 | 13b |
| Hospital LOS | 168 | 103 | 29 | 45a | 6 | 14 | 4 | 265 | 17b |
| Disposition | LTAC | Home | Home | Home | Deceased | Deceased | Deceased | LTAC | Home Hospice |

[a]Multiple admissions; known diagnosis of CUA.
[b]Multiple admissions.

while malnourished patients with CUA often present with distal lesions. Furthermore, those with proximal lesions tend to have more severe course with prominent deep ulcerations and fat necrosis and higher mortality, while those with disease limited to superficial skin of distal extremities have higher survival rates [1,13]. Necrotic lesions involving the tongue, penis, lungs, and bowel have been reported but are very atypical [11]. Of our nine patients, five were female, four were Caucasian, three were obese, four had a dialysis vintage of at least 3 years, and two were on warfarin at the time of diagnosis.

Other skin conditions with similar clinical presentations are necrotizing fasciitis, pyoderma gangrenosum, antiphospholipid antibody syndrome, purpura fulminans, cryoglobulinemia, cholesterol emboli, systemic vasculitis, and gangrene from atherosclerotic peripheral vascular disease [14]. Due to the large number of disease mimics, misdiagnosis and delayed treatment are relatively common [7]. Only two of our nine patients were diagnosed with calciphylaxis initially, having been misdiagnosed with warfarin induced skin necrosis, vasculitis, bullous pemphigoid, skin and soft tissue infection, necrotizing fasciitis, and desquamating rash prior to having the correct diagnosis made. The correct diagnosis was made when histopathologic changes consistent with calciphylaxis were seen on patient biopsies.

Calcific uremic arteriopathy or calciphylaxis is typically a clinical diagnosis, but skin biopsy for confirmation remains the gold standard for diagnosis. Skin biopsy is often not performed due to the risk of initiating new ulcer formation or proliferating existing lesions, but is recommended if the diagnosis remains uncertain. The classic histologic findings on skin biopsy are medial calcification of the small cutaneous arterioles, panniculitis, and tissue necrosis [15]. Alternative methods for diagnosis such as plain radiography, bone scan, mammography and circulating fetuin A levels are gaining popularity but have not been systematically evaluated and are not recommended at this time [7].

The pathogenesis of CUA is not completely understood. Classically, disturbances in bone and mineral metabolism were considered promoters of metastatic vascular calcification and thus involved in the pathogenesis of CUA. As such, an elevated PTH level was thought to be a likely culprit and thus parathyroidectomy became a therapeutic option. However, other evidence suggests that hyperparathyroidism is not essential for development of CUA [16]. High serum phosphorus levels have been associated with increased risk of CUA and high phosphorus levels have been associated with increased osteoblastic differentiation of vascular smooth muscle cells and directly enhance extracellular calcification by these cells [17]. A risk factor for development of the disease is a high calcium/phosphorus product [7]. This increases the likelihood for precipitation and tissue calcification. Many ESRD patients have a high calcium/phosphorus product; however, only a small percentage of these patients develop this devastating disease. Mechanisms to inhibit calcification must be present to prevent widespread extra-osseous calcification as even under normal physiologic conditions serum concentrations of

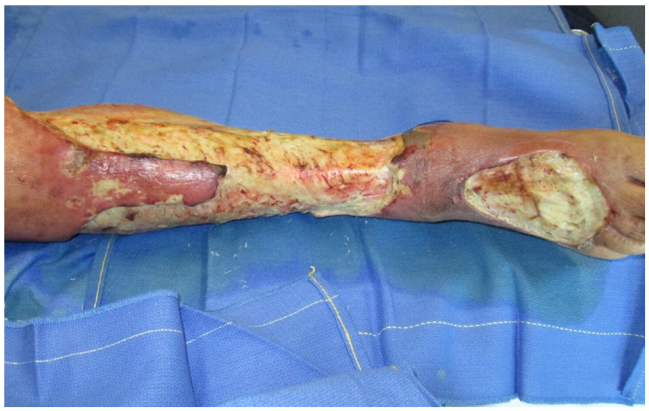

**Image 1 – Distal calciphylaxis wound.**

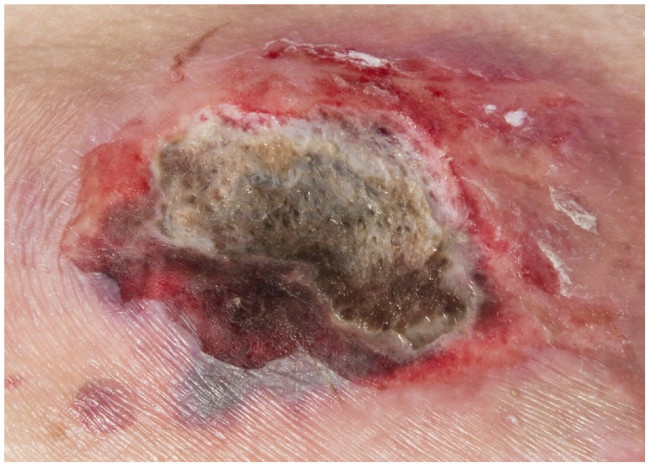

**Image 2 – Proximal calciphylaxis wound.**

calcium and phosphate greatly exceed their solubility product [18]. Among our patients there was significant variability among calcium, phosphate, and parathyroid levels. On admission to our burn center, our patients all had normal serum calcium levels, four out of nine had hyperphosphatemia, and six out of nine had elevated PTH levels.

Vascular calcification is not passive, but rather a very active and highly regulated process. Two of the most prominent calcification inhibitors, fetuitin-A and Matrix G1a (MGP) are significantly reduced in CUA, which is indicative of either consumption at sites of intense calcification or that their levels were reduced by other factors such as inflammation or oxidative stress [2,19]. MGP activation is dependent on vitamin K-mediated carboxylation, so one potential mechanism for decreased activity is warfarin administration, which is fairly common in CUA patients [20].

Evidence of thrombosis in CUA lesions suggests that abnormalities in the coagulation system may lead to a thrombotic state and play a key role in the development of the disease. Tissue biopsy in confirmed cases reveals microvascular calcification and vascular thrombosis which helps to explain the disease on a gross level, but the cellular/molecular etiology is not fully characterized [7,8,21,22]. Given that CUA most frequently develops in dialysis patients also suggests some role of the uremic milieu in its pathogenesis. Uremia is associated with increased inflammation and oxidative stress, which could potentially worsen endothelial dysfunction and further promote thrombosis [2,19,23]. Only a very small percentage of dialysis patients ever develop CUA, which suggests a multifactorial process with sequential or parallel presence of many factors. Of note, all of our patients with CUA had ESRD.

The current general treatment approach to CUA is designed to promote wound healing and reduce the burden of vascular calcification. The most important aspect of management is largely supportive care including wound management, antibiotics for infection, and pain control. There is no accepted standard of therapy for the treatment of calciphylaxis. Several therapies have shown promise, and novel agents are being developed with randomized controlled trials underway [8]. At this time however, no prospective trials have been published and the majority of case reports and series which ascribe benefit to various therapies have done so with multiple treatments being used [7]. Sodium thiosulfate (STS) use in CUA

was first reported in 2004 by Cicone and has since emerged as widely used therapeutic option [24]. The mechanism of action is thought to be antioxidation, vasodilation, and chelation of calcium salts [18,25,26]. STS presumably decreases soft tissue calcium deposition via formation of calcium thiosulfate complexes, which are much more soluble than calcium oxalate or calcium phosphate [25]. No standard dosage has been identified, but most centers treat with 5–25 g three times per week [26]. After a test dose of 12.5 g, STS is typically administered at 25 g thrice weekly during the last hour of hemodialysis and continued treatment for 2 months following skin healing [22]. An alternate regimen is 12.5 or 25 g four to five times per week with or without intralesional STS [7]. The optimal duration is not known, though typically continued until successful ulcer healing has occurred. The majority of our patients received 25 mg STS three times per week. We did not observe a rapid resolution of calciphylaxis with the use of STS, even when dosed daily, in conjunction with renal replacement therapy.

Other commonly reported therapies include bisphosphonates and cinacalcet, a calcimimetic. These therapies aim to alter calcium, phosphorus and PTH levels, ultimately to reduce the calcium-phophorus product. Cinacalcet may be beneficial in those with hyperparathyroidism [26]. For patients with refractory hyperparathyroidism, parathyroidectomy remains an option. The role of parathyroidectomy remains controversial, but could be considered in patients with persistently elevated PTH, calcium, and phosphorus levels.

Additional measures include discontinuing warfarin, vitamin D therapy, and calcium-based phosphate binders, and reducing dialysate calcium concentration to 2.0–2.5 mEq/l. Furthermore, it is recommended to ensure dialysis adequacy by increasing duration or frequency of dialysis and considering switching from peritoneal dialysis to hemodialysis in patients with newly diagnosed CUA.

A recent large case series showed the only treatment to have statistically significant improvement on mortality was surgical debridement [6]. Wound debridement is necessary, but wound closure strategy varies amongst providers and institutions [6,26]. All patients in our study underwent at least one surgical debridement. Our patients received an average of 14 procedures including debridement and grafting. To best manage these patients and achieve the desired goals of therapy benefits from a multidisciplinary approach with the involvement of nephrologists, surgeons, nutritionists, pharmacists, dermatologists, and wound care specialists.

## 5. Conclusion

In summary, we have described a series of nine patients with calciphylaxis undergoing care in a burn intensive care unit. We believe a burn center is the ideal setting for management of a patient with calciphylaxis as wound infection and sepsis are leading causes of death in these patients and burn centers have vast experience with wound management and infection prevention. Additionally, burn centers usually have plastic surgeons available to assist with the complex surgical management of these patients. There is a great need for a multi-center, protocol driven study of this disease. Unfortunately, due to the rarity and variable severity of presentations, this has proven difficult. In the meantime, providers with experience treating calciphylaxis are encouraged to publish case reports and case series as this constitutes the bulk of the literature on this topic. Additionally, we encourage providers managing patients with calciphylaxis to refer those patients to burn centers with experience in caring for these patients.

## Conflict of interest

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army, Air Force or the Department of Defense.

The authors have no financial disclosures or conflicts of interest.

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