Calciphylaxis in Patients with Chronic Kidney Disease Case Presentation and Review

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Abstract

Calciphylaxis is a serious disorder that presents itself as ischemia and necrosis of the skin which occurs more frequently in patients with an end-stage chronic kidney disease, but not exclusively. The pathogenesis is a result of the reduction of arteriolar blood flow, caused by calcification, fibrosis, and thrombus formation that primarily involve the arterioles of the dermis and hypodermis, with a poor prognosis. Case presentation: A 44-year-old patient with a previous diagnosis of chronic kidney disease receiving hemodialysis secondary to polycystic kidney disease, with a history of parathyroidectomy due to primary hyperparathyroidism in 2011. In 2014 the patient presented skin lesions, for which a diagnostic biopsy of calciphylaxis was performed and began treatment with sodium thiosulfate with a poor progression and evolution. New histology compatible with the diagnosis of pyoderma gangrenosum and findings of calciphylaxis were performed. The patient begins treatment with corticosteroids and cyclosporine, with poor clinical evolution and the patient eventually passes away. The objective of this manuscript is to understand this pathology better, which is infrequent but with a high rate of morbidity and mortality.

Keywords

Calciphylaxis, Vascular Calcification Syndrome, Calcific Uremic Arteriolopathy

1. Introduction

Calciphylaxis, also known as Calcific Uremic Arteriolopathy (CUA), is a rare

and a little-known about vascular calcification syndrome with a predilection for patients with an end-stage renal disease [1] [2]. However, it can also present in patients without any chronic renal diseases and is known as non-uremic calciphylaxis [3] [4].

This disorder is characterized by calcification and thrombosis of the microvasculature of the subcutaneous, adipose and dermis tissue. This obstruction generates cutaneous ischemia, producing high morbidity in patients such as severe pain, hard-to-heal wounds, recurrent hospitalizations, ulcerative lesions, and sepsis [5] [6]. The mortality rate per year is estimated at 45% - 80% in patients on dialysis and 30% - 40% in patients not on dialysis [7] [8].

Lesions in patients can be classified as predominantly central which affect subcutaneous cellular tissue, adipose tissue of the abdomen and thighs. This distribution is more frequent in patients with chronic kidney diseases in 70% - 80% of cases compared to 50% of patients without chronic kidney disease.

The peripheral distribution affects the acral regions such as the fingers, in addition, the lesions may not be ulcerated in the early stages of the disease or they're ulcerated in the later stages [8] [9].

Risk factors for the development of calciphylaxis are numerous and predominantly include the female gender, diabetes mellitus, hyperphosphatemia, chronic kidney disease, exposure to warfarin, and liver disease, among others [10] (see Table 1).

2. Case Presentation

44-year-old woman of Latin origin, housewife, married with 2 children, not consuming psychoactive substances with a diagnosis of chronic kidney disease secondary to polycystic kidney and liver disease that occurs at age 20, is currently on hemodialysis three times per week for 8 years through an arteriovenous fistula in the right upper limb adherent to dialysis and pharmacological therapy. Within her personal story, she mainly underwent parathyroidectomy and hyperparathyroidism in 2011, she suffers from hypothyroidism and hypercholesterolemia.

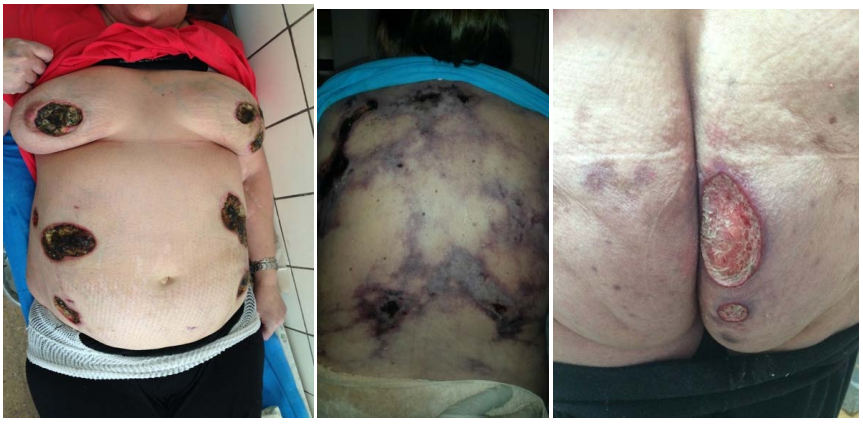
Table 1. Risk factors for calciphylaxis.

Female gender
Diabetes
Chronic Kidney Disease
Exposure To Warfarin
Liver Disease
Obesity
Hypercalcemia
Hyperphosphatemia

In March of 2014, she presented multiple erythematous-violaceous lesions on both breasts, which evolved with ulceration and pain. Additional new lesions at the level of the flanks of the same characteristics. She was moved from another institution specialized in plastic surgery to our institution.

Physical examination upon admission found the following: BP: 90/60 mmHg HR: 100 BPM RR: 22 respirations per minute T˚: 36.5˚C (axillary) O2Sat: 96% (0.21). Obese, lucid, presenting various reticulated, erythematous violet-purple colored lesions on extremities and back. Deep ulcers with irregular borders, erythematous and a necrotic and fibrin in the right breast measuring 10 × 5 cm and 15 × 8 cm on the left breast. 18 × 7 cm on the right flank and 11 × 15 cm on the left flank. And on the right leg measuring 1 × 1 cm presenting punch-type wounds on the posterior part of both thighs measuring around 2.5 × 1 cm. Necrotic ulcers on the back, left armpit and right arm measuring 3 × 4 cm (**Figure 1**). The following laboratory values were found: Hematocrit 28%, Hemoglobin 8.6 mg/dL, MCV 92, WBC 14,000 cells/mm^3, (Neutrophils 70%, Lymphocytes 22%), Platelets 411,000 cells/mm^3, Glycaemia 98 mg/dL, Urea 197 mg/dL, Creatinine 11.37 ng/dL, serum sodium 139 meq/L, serum potassium 6.8 meq/L, chloride 96 mEq/L, Calcium 8.2 meq/L, phosphate 8.5 mEq/L, Mg 2.1 mEq/L, PT 48, KPTT 39, TB 0.2 UI/L, DB 0.4 UI/L, GPT 25 UI/L, GOT 16 UI/L, ALP 145 UI/L, LDH 748 UI/L, CK 64 UI/L, ESR > 140 mm/sec, CRP 23.8 UI/L, Proteins 6.1 g/dl. Albumin is 3 g/dl, pH 7.15, HCO_3 15.6 mmol/L, TSH 1.63 UI/L. The patient's habitual medication consisted of omeprazole, levothyroxine, rosuvastatin, pregabalin, diclofenac + vitamin B12, folic acid, tramadol, tioneurol and sevelamer carbonate.

During her hospital stay a biopsy of these wounds was performed on August of 2014, which showed a superficial epidermal fragment, ulcerated and necrotic covered by a thick fibro-leukocyte scab with the presumptive diagnosis of post-thrombotic necrosis (indirect signs of calciphylaxis). Treatment with sodium



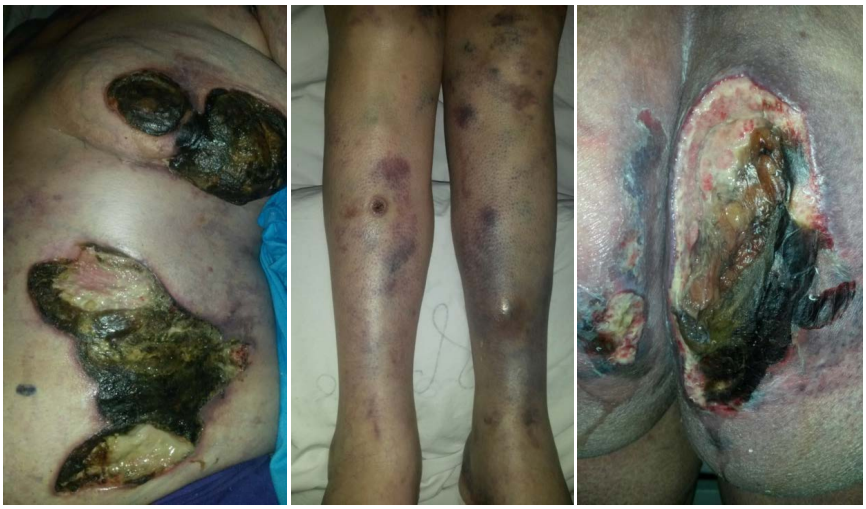
(A) (B) (C)

Figure 1. (A). Trephine-like wounds of fibronecrotic aspect. (B) Areas with erythematous and violet-purple coloration on the back associated with necrosis of patchy aspect. (C) Ulcers over the right gluteal surface with inflammation peripheral to the wounds borders and a fibrin-rich wound bed.

thiosulfate is started for a duration of 3 months with inadequate progress of clinical manifestations. A new incisional biopsy is performed in October of 2014 for anatomical pathology and microbial analysis, evidencing an ulcerated epidermis with a fibrin-leucocyte pseudomembrane. Coexistence of arterioles without significant alterations and some venules with calcified walls and intimal edema, the histopathological diagnosis is compatible with pyoderma gangrenosum.

The patient evolves to clinical deterioration with the appearance of new reticulated wounds of erythematous and violet-purple color on the back and both upper limbs, new lesions on the lower limbs and an increase in size of preexisting ones (**Figure 2**). Due to presenting fever records of up to 38 degrees in the last 5 days, antimicrobial therapy is started with intravenous amoxicillin/clavulanic acid and meprednisone 40 mg/day. Control of the necrotic wounds is established as well as stabilizing the ulcers, no purulent secretion and less pain. A progressive decrease of corticoid therapy is started due to patient intolerance simultaneously thiosulfate therapy is suspended as decided by the nephrology department. New ulcers start to appear and parts of skin with plaque type violet-purple lesions, of reticulated aspect, concentrating in the torso and extremities, therefore a transfer the institution's internal medicine department is made, where conjunct treatment with high-dose corticoid therapy and cyclosporine 200 mg daily. A new biopsy is taken of the violet-purple plaques which inform *calciphylaxis.*

Despite of treatment with thiosulfate being reinitiated and adequacy of renal support therapy was optimized, the patient progressed with more clinical deterioration and hemodynamic instability and ultimately dies.



(A) (B) (C)

Figure 2. (A) Fibro-necrotic scabs with scarce purulent secretion and fetid smell. (B) Lower limbs with erythematous violet-purple coloration and back associated with patchy aspect. (C) Gluteal right surface presenting ulcers with inflammatory perilesional borders at the start of the clinical presentation.

3. Discussion

In this article we described a case of proximal calciphylaxis presenting in a female of approximately 40 years of age. The following risk factors are found: chronic kidney disease receiving hemodialysis for a duration longer than 2 years, obesity, hyperparathyroidism, hyperphosphatemia with a calcium-phosphate product over 55 and hypoalbuminemia. This pattern of presentation, clinical evolution and characteristics of the ulcerous lesions accompanied by the histological findings documented allow to confirm this diagnosis; however, the rapid progression of these lesions and the appearance of infectious complications, commonly described associated with this disorder, derive in the development of sepsis and septic shock, the patient ultimately passes away as a result from the aforementioned complications.

Calciphylaxis is a disease product of the calcification of vessels of small and medium size within the subcutaneous adipose tissue and the dermis, which results in the development of ischemic infarcts and necrosis of the affected vascular territories and is characterized by the presence of very painful necrotic ulcers in the skin of most advanced cases; Even though it predominantly presents in patients with chronic kidney disease on hemodialysis; it can present in any stage of kidney disease and transplant receptors and even in patients without a clinical background of kidney disease.

4. Epidemiology

Despite its low frequency, it has a global distribution with incidences varying between 0.04% reported in Germany and up to 0.35% in the United States; however, there is an agreement that incidence may be higher due to it being a sub-diagnosed disease [11]. The mean age at the moment of diagnosis oscillates between 50 - 70 years; predominantly in the female gender, obesity and diabetes mellitus are well characterized as independent risk factors; Hypoalbuminemia, presence of autoimmune diseases, drugs like warfarin, cardiovascular disease among other factors constitute additional risk factors. For patients with chronic kidney disease, the most commonly related factors aside from the ones previously described are dialysis treatment for a period longer than 2 years, disorders of bone mineral metabolism such as hypoparathyroidism are associated with the development of this condition. The chronic use of vitamin K antagonists and prolonged corticoid therapy in transplant patients are the drugs with the strongest relation [11] [12].

5. Physiopathology

The entirety of the physio-pathologic mechanisms implied in the development of this disease currently remains without being completely understood.

Vascular calcification was formerly considered to be a passive phenomenon derived from the accumulation of calcium within the affected tissues and as a response to different stimuli; however, current theoretical models have shown

that its more similar to the process of bone remodeling, which starts with the differentiation of smooth muscle vascular cells into a phenotype equivalent to an osteoblast and chondroblast. This change in phenotype, which preferentially affects the arterioles located in the skin and subcutaneous tissue is mediated by an interaction between multiple factors and local signaling pathways as well as systemic ones that proceeds from stimuli, triggered mainly by elevated serum concentrations of calcium, phosphate and alkaline phosphatase, PTH, reactive oxygen species, uremic toxins, inflammatory cytokines, states of hypercoagulability among others [13].

The main point of focus has centered around bone morphogenic proteins (BMP) which belong to a superfamily of growth factors, such as those mainly involved in the induction of osteoclast differentiation, creation of bone de novo and extra-osseous calcification [13] [14]. Chronic inflammatory stimuli, such as those characterizing advanced chronic kidney disease and disease of autoimmune origin, insulin resistance as well as an increase in the production of tumoral necrosis factor alpha, inflammatory cytokines (IL-1 and IL-6) and the production of oxygen derived free radicals, increase the concentrations of nuclear factor kappa B and overexpression of its ligand (nuclear factor Kappa B receptor), which act as direct inductors of BMP type 2 - 4 synthesis, beginning a cascade of events that lead to a phenotype change in the smooth muscle vascular cell participating directly in the process of vascular calcification and extravascular characteristics of this disease such as endovascular fibrosis, intimal hyperplasia and ultimately thrombosis of affected vascular beds.

In the stages of intimal hyperplasia and endovascular thrombosis, the presence of high concentrations of inflammatory mediators, vasoconstricting substances such as endothelin 1, and protein C and S deficiency have been observed, which suggests the contribution of hypercoagulability phenomena in the progression of calciphylaxis (see **Figure 3**).

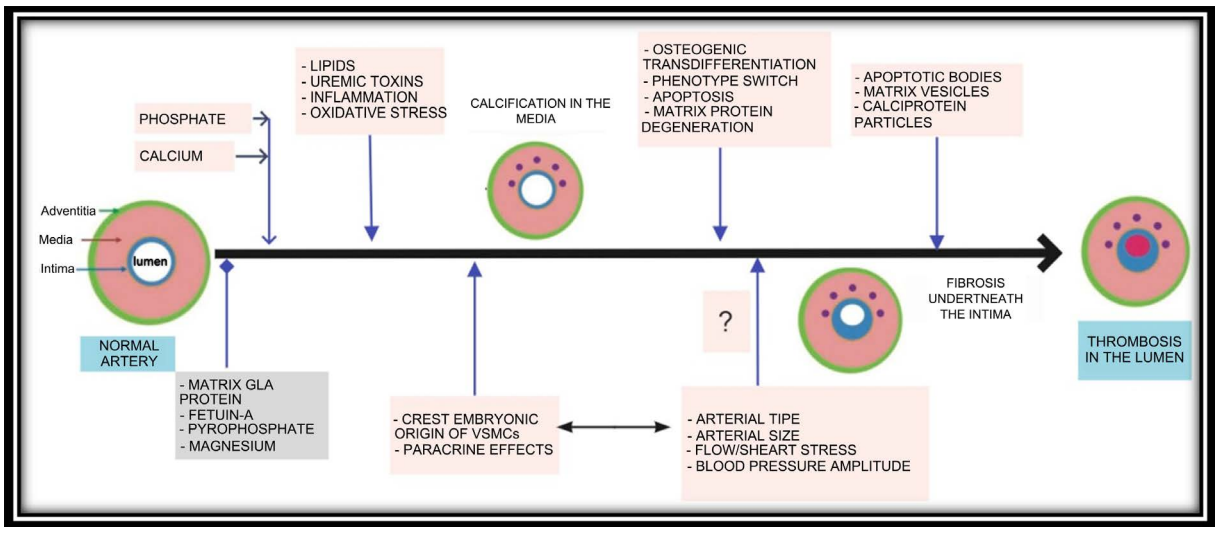


Figure 3. Physiopathology. Several factors can induce vascular calcification and are likely responsible for variable susceptibility to vascular calcification. Systemic circulating and local factors may enhance or prevent vascular calcification.

The deficit in the activation of calcification inhibitory proteins is no less important within the physiopathology of this entity. The MGP protein (Matrix Gla Protein), was the first identified calcification inhibitor, it is a vitamin K-dependent protein constitutively produced in the endothelium and in the vascular smooth muscle cell, which in its carboxylated form directly inhibits type 2 bone morphogenic protein [11] [12] [13] [14]. Conditions that are associated with vitamin K deficiency, such as that produced in patients receiving warfarin, are associated with a high risk of calciphylaxis. In fact, the development of calciphylaxis in up to 40% to 50% of patients with advanced chronic kidney disease receiving warfarin therapy is well documented [12] [13] [14].

The mechanism by which this elevated risk is explained relates to the fact that vitamin K is an essential enzymatic cofactor that allows the carboxylation of MGP; The absence of carboxylation of MPG is associated with a reduction in the activation of this protein with the subsequent activation of the RANK-RANKL-BPM 2 axis and the subsequent change in the phenotype of the vascular smooth muscle cell towards an osteoblast lineage.

Another calcification inhibitor, fetuin-A (*a*2-Heremans-Schmid glycoprotein), is a glycoprotein serum produced by the liver, considered an important inhibitor of hydroxyapatite formation that has been shown to reduce crystal formation in solutions containing calcium and *in vitro* phosphorus; It is considered the main circulating inhibitor of vascular calcification. Fetuin A is synthesized as an acute-phase negative reactant; chronic inflammatory states are associated with low serum levels of this protein. Serum levels of fetuin A are reduced in patients with chronic kidney disease on hemodialysis, which is associated with accelerated vascular calcification and increased cardiovascular mortality [13] [14].

6. Clinical Presentation

The clinical presentation differs depending on the evolutionary stage of the disease. Cutaneous involvement in calciphylaxis varies from hyperpigmented or erythematous macular lesions, reticular papules, nodules that progress to necrotizing ulcers of various sizes that without treatment evolve to areas of gangrene. It is noteworthy that, especially in the initial lesions, the pain is neuropathic in nature and is often described as strikingly disproportionate to the type of skin lesion.

Two patterns of distribution of the lesions are distinguished on physical examination; A central one that affects the trunk predominantly in the abdomen and more proximal segments of the lower extremities such as thighs and gluteal region; This type of distribution has been seen more in female, obese and chronic kidney disease patients. A second acral distribution pattern, in which the lesions predominate in the lower extremities, can present in the initial stages with lesions indistinguishable from those that occur in arterial occlusive disease; this form is the one that predominates in patients without chronic kidney disease, and it seems to have a more benign course [9].

7. Diagnosis

The diagnosis of calciphylaxis is clinical; the findings on physical examination, the presence of risk factors, chronic kidney disease, the pattern and distribution of the skin lesions, allow for a high clinical suspicion and guide the tests to be performed.

Because a wide variety of skin alterations can present in patients with chronic kidney disease, the possible differential diagnoses to consider covers a large range of possibilities, particularly in the early stages of calciphylaxis in which the lesions are nonspecific. The entities to consider include: follicular hyperkeratosis, calcinosis cutis, peripheral arterial disease, pyoderma gangrenosum, vasculitis, warfarin-induced necrosis, non-uremic calcifying vasculopathy [15].

Radiographies with a mammography technique are useful low-cost test that can contribute to the diagnosis, it allows to demonstrate the presence of calcifications in the soft tissues in a reticular pattern with a reported sensitivity of 90% when clinical suspicion is high.

Bone scintigraphy, which shows accumulation of radio tracer diffusely in the affected areas, has also proven useful in selected cases. Other imaging tests that have been evaluated include ultrasound and high-resolution tomography in which calcifications of subcutaneous vessels can be observed, however they lack sufficient sensitivity and specificity to be recommended as methods for routine use [16].

Although there is still no consensus, the diagnosis of calciphylaxis is confirmed with histopathological findings through skin biopsy; however, if clinical suspicion is high, it may not be necessary in patients with advanced chronic kidney disease and clearly documented risk factors. The skin biopsy is related to the appearance of infectious complications, tissue necrosis or the presence of false negatives as it is not possible to obtain samples of adequate quality and depth due to the severity of the disease. Originally described histological findings include calcification of the tunica media of the cutaneous arterioles and subcutaneous fat, endovascular fibrosis, fibro-intimal hyperplasia that reduces the lumen of the vessel until thrombosis. Calcification of the tunica media is demonstrated in immunohistochemistry staining by Von Kossa and with hematoxylin eosin a purplish staining pattern is observed. Other no less important histopathological findings are the presence of panniculitis, diffuse inflammatory response, extra cellular calcium deposits and extravascular necrosis of variable intensity and distribution [16].

8. Treatment

To this date no curative treatment exists for this disorder, and therapeutic measures used are based on understanding of physio-pathologic mechanisms. Multiple retrospective studies have been performed, case series, case reports, more so than large randomized studies [3]. However, there is a general consensus that a more active multidisciplinary approach is required in order to provide

more comprehensive care for a rare and disabling disease, as there is no specific treatment, with these preventive measures we lower the incidence even more and hence mortality.

Identifying and controlling all modifiable risk factors form part of the central concept of treatment as to control the disease's progression and to allow specific therapeutic interventions; therefore, control of hyperphosphatemia with a non-calcium-containing phosphate binder, stimulate decrease of dietary phosphate intake, increase of dialysis sessions in frequency or duration, and are recommended measures in all cases. For the treatment of hypercalcemia, besides the previous recommendations the use cinacalcet is described for the control of phosphate levels, achieving a decrease in calcium levels, as well as the use low-calcium dialysate (2.5 mEq/L). The use of vitamin D analogues must be avoided, due to its known effects on the increase of calcium and phosphate levels. The objective of these interventions is to maintain a Ca/P product of less than 55 and calcium and phosphate levels close to its inferior limit of reference. Regarding hyperparathyroidism, it's recommendable to maintain parathyroid hormone values within the established limits by clinical practice guidelines; for the pharmacological management the use of cinacalcet is described in literature, however if necessary, surgical removal of parathyroid hormones should be performed; likewise, prevention of hypoparathyroidism should be treated for. Vitamin K antagonists must be avoided and suspended in patients receiving treatment with this class of drugs given its association with the development of this disease [17] [18] (see **Table 2**).

For treatment focusing on removing vascular calcification, sodium thiosulfate is available as treatment of choice for calciphylaxis, its main effects seem to involve its capacity to form hydrosoluble complexes of calcium which facilitates its elimination from tissues, additionally antioxidant and vasodilating properties have been attributed to its use furthermore this direct vascular anti-inflammatory effect seems to improve vascular reactivity translating in an enhanced recovery of cutaneous lesions. Several studies have documented a decrease in 1-year mortality related to the use of sodium thiosulfate. Recommended dose is 25 grams for patients with a body weight larger than 60 kg and 12.5 mg for patients weighing less than 60 kg, its administration is performed within the last hour of a dialysis session, during each dialytic treatment. Generally, sodium thiosulfate is well tolerated, nauseas, vomiting and metabolic acidosis are the most common secondary effects, but rarely require suspension of treatment. Its use in local injections has been described with satisfactory results in the wounds of patients without a vascular access. To this date the best duration of treatment remains unknown, however its prolonged administration (up to 6 months) is described as presenting better wound healing and general recovery of skin rates.

The use of bisphosphonates is known for its inhibitor effect on osteoclast activity and bone remodeling. In several small prospective studies, it improved skin lesions after 2 to 4 weeks of intravenous administration, it is used as an adjuvant drug in combination with sodium thiosulfate [19] (see **Table 2**).

Table 2. Strategies for the treatment of calciphylaxis.

Strategies to stop calcification of blood vessels	
Correct Hyperphosphatemia	- More and longer dialysis sessions (4 - 5 times/wk) - Dietary phosphate restriction: avoid colas and processed food; seek nutrition consult - Non Ca++ phosphate binder
Correct Hypercalcemia	- Reduce Ca++ concentration in dialysis bath to 1.5 or 2 mEq/l; ovoid 2.5 mEq/l - Stop Ca++ based phosphate binder (Ca++ acetate)
Correct Hyperparathyroidism	- Cinacalcet (medical parathyroidectomy) - Surgical parathyroidectomy in medically refractory cases
Stop Vitamin D	- E.g. calcitriol
Stop Warfarin	- Evaluate need for alternate anticoagulant - No data to justify anticoagulation for stroke prevention in atrial fibrillation in dialysis patients - Apixaban 2.5 mg bid in pulmonary embolism, deep vein thrombosis, mechanical valve (limited safety data)
Convert to Hemodialysis from Peritoneal Dialysis	
Strategies to promote decalcification of blood vessels	
Sodium Thiosulfate	- Route and dose - Intravenous (standard): 25 gm if weight > 60 kg; 12.5 gm if weight < 60 kg: infusion in the last hour of dialysis - Subcutaneous (non standard) 0.25 to 0.75 gm (1 to 3 ml of 250 mg/ml); at the periphery and center of the lesion - Duration of iv infusion: minimum of 2 - 3 mos.; typical total duration of 6 mos. or until lesions completely heal
Vitamin K	- Route and dose: 10 mg per so three times a week (normal daily vitamin k intake: 0.10 - 0.15 mg)
Wound care and pain control	
Debridement	- Surgical debridement for infected and wounds with exudates - Nonsurgical debridement for noninfected and dry wounds
Hyperbaric Oxygen Therapy	- Delivery of 100% oxygen at 2.5 times the atmospheric pressure in a sealed chamber for 90 min - Aim for 20 - 30 sessions (optimal number unknown) - Reserved for refractory wounds
Pain Control	- Fentanyl and methadone preferred in renal failure. Avoid morphine and hydromorphone because accumulating active metabolite can cause respiratory depression.

Regarding wound care, as mentioned earlier, this process usually requires the participation of a plastic surgeon, dermatologist and experts in wound care, the main objectives in treating these wounds are the removal of most if not all non-viable tissue, ease the process of wound healing and prevent infection; the decision of performing surgical or medical treatment whether through enzymatic or autolytic treatment tends to be a difficult one and can be a challenge for the medical team, the factors that determine a good clinical evolution or deterioration are: extension, severity and compromise of the lesions; as general guideline

for surgical debridement of ulcers, this procedure is usually reserved for severe cases with large wound extension with necrotic tissue or infection having no means of possibly controlling said complications with other methods. Non-surgical management of these wounds include guaranteeing an adequate nutritional status, pain management, local wound care with hydrocolloid patches and prevention of infection; antibiotic treatment should be guides by culture reports and corresponding sensibilities, prophylactic use of antibiotics in this context is not recommended. The use of hyperbaric oxygen and Lucilla sericata larvae have been described as management for complex wounds as secondary treatment options [17] [18] [19] [20].

9. Conclusion

Calciphylaxis is a rare complication associated with advanced CKD; from its initial description of this disease by Seley in 1962, our knowledge pertaining to the physiopathological mechanisms involved in the genesis of calcific uremic vasculopathy remain incomplete; certain known and previously described risk factors exist, requiring a high index of suspicion and an early and multidisciplinary approach with the purpose of reducing the impact this disease continues to present in its morbidity and mortality rates. It produces a great amount of physical disability for these patients and a sensation of medical frustration, due to no curative treatment being available and an ominous prognosis.

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Availability of Data and Materials

The data and materials were all included in the manuscript.

Authors' Contributions

Jose Lucas Daza (JLD) and Yaroslad de la Cruz (YDLC) are responsible for the writing of the manuscript. JLD and YDLC performed the acquisition and interpretation of data and drafted and revised the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient for publication of this case report, and the accompanying images were additioned at the bibliographic references. This study/report was approved by the Ethical Committee of the

Hospital de Clínicas José de San Martín (approval number: HCJSM12/16) and was conducted in accordance with the National Law on the protection of personal data No 25.326 and the Declaration of Helsinki (Last version, Fortaleza 2013).

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report, and the accompanying images were additioned at the bibliographic references.

Conflicts of Interest

The authors declare that they have no competing interests.

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List of Abbreviations

CUA: calcific uremic arteriolopathy; BMP: bone morphogenic proteins; CKD: chronic kidney disease.