Calcific Uremic Arteriolopathy in End Stage Renal Disease: Pathophysiology and Management

Preethi Yerram, MD, MS,1 Kunal Chaudhary, MD1,2

1Division of Nephrology, Department of Internal Medicine, University of Missouri School of Medicine, Columbia, MO
2Nephrology Section, Harry S. Truman Memorial Veterans Hospital, Columbia, MO

ABSTRACT

Background: Calcific uremic arteriolopathy (CUA), a debilitating condition with high morbidity and mortality, is most commonly seen in patients with kidney disease. The pathophysiology of CUA is multifactorial, leading to a disruption in the balance between factors that promote and those that inhibit calcification, although the exact pathophysiological mechanisms of CUA remain to be elucidated.

Methods: This review provides an overview of the pathophysiology, clinical presentation and diagnosis, and treatment of CUA.

Results: Diagnosis of CUA requires a high degree of suspicion; skin biopsy with histological examination remains the gold standard to confirm the diagnosis. Treatment of CUA requires a multidisciplinary approach.

Conclusion: With a high degree of clinical suspicion and early diagnosis, an aggressive multifactorial treatment approach involving optimal wound management, minimization/avoidance of risk factors and precipitating causes, and correction of calcium-phosphorus abnormalities can significantly improve patient outcomes.

INTRODUCTION

Calcific uremic arteriolopathy (CUA), often referred to as calciphylaxis, is a condition with high morbidity and mortality seen in patients with kidney disease, especially in those with end stage renal disease (ESRD). When this condition is seen in patients without kidney disease, most notably those with primary hyperparathyroidism, malignancy, alcoholic liver disease, or connective tissue disease, it is known as nonuremic CUA. This review focuses on the pathophysiology and management of CUA in the ESRD population.

Although previous small studies have reported a CUA prevalence of 4% in patients on hemodialysis, and 1.3-4.5 per 100 patient years in patients with ESRD, the exact prevalence remains unknown. The number of reported CUA cases has increased in recent years, probably because of the increased recognition of this condition.

In 1962, Hans Selye coined the term calciphylaxis to describe skin necrosis in animals triggered by exposure to certain substances during experiments, such as parathyroid hormone and vitamin D, and associated with cutaneous calcification. However, these lesions are different from the CUA lesions now described in humans. Histopathological examination of human CUA lesions shows small-vessel medial calcification and intimal hypertrophy in association with panniculitis and small-vessel thrombosis that were not described in Selye’s animals. Coates et al suggested that the term calcific uremic arteriolopathy would be more apt to describe these lesions, however, the term calciphylaxis is still frequently used to refer to this condition in humans.

PATHOPHYSIOLOGY

CUA is thought to develop secondary to a disruption of balance between factors that favor calcification and those that normally prevent pathologic calcification. Previously, an increase in the calcium-phosphorus product was thought to cause calcification leading to CUA, but recent research suggests that this calcification involves active cellular processes, not just passive mineralization, because of an increase in calcium-phosphorus concentrations.

Extensive vascular medial calcification is a hallmark of the vasculopathy seen with chronic kidney disease and is associated with increased cardiovas-
cular mortality. CUA involves vascular medial calcification of small arterioles with different clinical manifestations depending on the organ involved, but most commonly skin necrosis.

Multiple risk factors have been associated with the development of CUA (Table). Of these, female sex, diabetes, and obesity have been shown to be independent risk factors. One study showed peritoneal dialysis as a risk factor for CUA, but the exact mechanism is unclear, and this association has not been validated in further studies.

In vitro studies of human smooth muscle cells have shown an increase in the expression of osteogenic markers that predispose patients to calcification on recurrent exposure to high phosphorus levels and other uremic toxins.

Vascular smooth muscle cells in CUA lesions have increased osteopontin expression that is thought to promote vessel lumen occlusion prior to thrombosis by causing cell sloughing into the lumen. In addition, bone morphogenetic protein-4 (BMP-4), which is normally involved in bone repair and development, has appeared in CUA lesions and is thought to promote calcification. The action of BMP-4 is thought to be dependent on the production of reactive oxygen species (ROS) that can activate nuclear factor kappa B (NFκB). In addition, ESRD is a chronic inflammatory state associated with increased generation of NFκB and receptor activator of NFκB ligand (RANKL), suggesting the role of NFκB-osteoprotegerin/receptor activator of NFκB/RANKL axis in bone homeostasis and vascular calcification.

Patients on hemodialysis also have low levels of fetuin-A/z 2-Heremans-Schmid glycoprotein (AHSG), a circulating inhibitor of calcification found in human and animal models. The production of AHSG is also downregulated in systemic inflammation because it is a negative phase reactant.

Matrix Gla protein (MGP) is another calcification inhibitor expressed by in vitro calcification models; MGP knockout mice show extensive vascular calcification but not CUA. The role of MGP in the development of CUA is unclear, but based on the association between CUA and warfarin (a vitamin K antagonist that inhibits γ-carboxylation of MGP), MGP may play a role in the pathogenesis of CUA. A case-control study from Japan indicated warfarin therapy and low albumin level as strong and significant risk factors for the development of CUA in patients on hemodialysis.

A decrease in the levels of circulating inhibitors of calcification in ESRD under the influence of uremic milieu, hyperphosphatemia in particular, is thought to trigger the differentiation of vascular smooth muscle cells into osteoblasts, resulting in vascular calcification. However, vascular calcification alone does not lead to CUA lesions, is thought to precede the development of typical CUA, and can occur either concurrently or be separated by months or years. Wilmer and Magro hypothesized that the vascular lesion develops in the first stage of CUA, which is a period of sensitization induced by parathyroid hormone, vitamin D, or high calcium/phosphorus (similar to Selye’s calciphylaxis). The second stage is a period of challenge such as trauma, surgery, or any other event associated with an increase in inflammatory cytokines. The second stage is marked by end-organ ischemia developments because of expansion of calcific vascular lesions associated with obliterative endovascular fibrosis/vascular thrombosis.

**CLINICAL PRESENTATION AND DIAGNOSIS**

Clinical diagnosis of CUA requires a high degree of suspicion. Other conditions need to be considered and excluded during the diagnosis of CUA, including warfarin-induced skin necrosis, vasculitis, cholesterol embolism syndrome, and nephrogenic systemic fibrosis. CUA lesions initially present as excruciatingly painful subcutaneous nodules with violaceous mottling, similar to livedo reticularis. These lesions can form ulcers and eschars as a result of ischemic necrosis. CUA lesions typically affect areas of the body with higher fat concentrations, such as breasts, abdomen, thighs, hips, and shoulders. Secondary infection is common and can lead to sepsis, which is the main cause of mortality in this patient population. Although the diagnosis of CUA can be made clinically, histopathological examination of a skin biopsy specimen remains the gold standard. The pathognomonic histopathological findings of CUA have been described.
as medial calcification of small arteries and arterioles up to 600 μm with intimal hyperplasia, inflammation, endovascular fibrosis, thrombosis, and tissue necrosis. Panniculitis can also be present.10,23-25

The biopsy method, however, raises concern for initiating a new ulcer that may not heal. Bone scintigraphy, a noninvasive procedure, has been described as useful in the diagnosis of CUA because of its ability to detect soft tissue microcalcifications.26-28 Bone scintigraphy has a sensitivity of 97% in detecting abnormal calcifications and is also thought to reveal the true extent of disease better than clinical examination alone. Bone scintigraphy has also been described as a useful tool for monitoring progress/improvement with treatment.9

**TREATMENT**

Treatment of CUA requires a multidisciplinary approach involving optimal wound management, antibiotic use in the presence of infection, correction of biochemical abnormalities, avoidance of cutaneous/subcutaneous trauma, and use of sodium thiosulfate (Treatment Options sidebar).

**General Measures**

Subcutaneous or intramuscular injections should be avoided to prevent trauma and ulcer formation. The risk factors associated with the development of CUA should be minimized where possible, including discontinuing warfarin if alternate anticoagulants are possible because warfarin has been implicated in the development of CUA by blocking vitamin K-dependent carboxylation of MGP.

Anecdotal data suggest intensifying the hemodialysis regimen (4 hours daily for 7 days followed by 5-6 times a week) as part of a multinterventional approach in the treatment of CUA;29 this treatment may help correct hyperphosphatemia.

**Wound Care**

Optimal wound care with special attention to prevention of superinfection and sepsis is vital in the management of CUA. Wound management aims to remove the necrotic tissue, aid in wound healing, prevent infection, and help with pain control. Gentle debridement to remove the necrotic tissue may be needed to allow proper wound healing, although debridement is not indicated for wounds covered with eschars. Sterile maggot therapy has also been used successfully in the debridement of necrotic CUA ulcers and is an option for wound management in CUA.30,31

CUA lesions are extremely painful, often requiring use of narcotic analgesia for general pain control.

Morphine is thought to cause accumulation of toxic morphine glucuronide by-products that may cause hypotension and further decrease tissue perfusion; therefore, fentanyl may be preferred for pain control.7

Hyperbaric oxygen (HBO) has been described to promote wound healing in CUA lesions.32 HBO therapy is thought to promote angiogenesis, arteriolar vasoconstriction, and bactericidal activity of neutrophils by forming ROS and to stimulate fibroblast function by improving oxygenation of the wound.32,33

Although not a routine practice, according to one report, limb revascularization as a treatment for CUA lesions involving the extremities led to poor outcomes; lesions did not improve and continued to progress in many patients.34
Correction of Biochemical Abnormalities

Once the diagnosis of CUA is made, measures should be taken to lower calcium, phosphorus, and parathyroid hormone levels. Calcium-based phosphorus binders should be replaced with non–calcium-based binders; calcium supplements and vitamin D analogs should be discontinued to prevent or treat hypercalcemia.

In our experience, we have used low-calcium dialysate and extended dialysis therapies with citrate-based regional anticoagulation and systemic calcium infusion to maintain serum calcium levels in the normal to low-normal levels for patients with hypercalcemia.

Secondary hyperparathyroidism can be treated medically with a calcimimetic such as cinacalcet, but parathyroidectomy may be required in cases that do not respond to medical treatment. A prospective randomized trial studying the effect of parathyroidectomy on survival from CUA showed that surgical correction afforded superior benefit compared to medical therapy; however, this study was completed prior to the availability of newer non–calcium-based phosphate binders and calcimimetic agents such as cinacalcet.35

Sodium Thiosulfate (STS)

Sodium thiosulfate (STS) is known as an antidote for cyanide poisoning, but it has also been used to prevent cisplatin and carboplatin toxicity. It is now becoming known as a treatment for CUA.

A study by Nigwekar et al evaluated the response of 172 patients with CUA to intravenous (IV) STS treatment and found that the majority of the patients showed improvement with this therapy.36 STS is thought to treat CUA through its antioxidant activity and the chelation of calcium to form calcium thiosulfate complexes.22,37 STS has been shown to prevent vascular calcification in a uremic rat model by forming highly soluble complexes with calcium, thus preventing calcium phosphate precipitation.38 The antioxidant activity of STS may result from the 2 unpaired electrons it has, which it donates to scavenge the unpaired electrons associated with ROS.23 STS has been reported to provide rapid pain relief within a few weeks for patients with CUA, perhaps the result of its antioxidant properties leading to recoupling of the endothelial nitric oxide synthase and, consequently, to a decrease in subdermal ischemia and associated pain.22,23

STS is usually given at a dose of 25 gm IV (at the end of dialysis for patients on hemodialysis) 3 times a week. It is usually well tolerated; the most common side effects are nausea, vomiting, diarrhea, and abdominal cramping. Long-term STS use has been associated with decreased bone strength, and, as a result, bone density should be monitored for patients with long-term use.38 STS use has also been associated with increased anion gap metabolic acidosis that can be managed by adjusting bicarbonate concentration in the dialysate.39,40 Successful intraperitoneal use of STS has also been reported for the treatment of CUA,41 but another case report detailed peritonitis with its use.42

Although the antioxidant effects of STS are seen early in the treatment, the chelating effects that potentially decrease the subcutaneous and vascular calcification with subsequent healing of the CUA lesions may take longer.22,23,38,43,44 In our experience, we have used STS until the wounds are completely healed, about 3 months on average; other anecdotal experiences recommend continuing STS treatment for about 2 months after the CUA lesions are healed.22,23

A report of 4 patients successfully treated with intrallesional STS published in 2013 suggests that this highly targeted therapy has some promise, but this use must be studied further.45 The use of oral STS following IV STS treatment in 4 patients stabilized or improved CUA lesions, suggesting oral STS as maintenance therapy given the high cost of IV STS.46

Other Potential Therapeutic Options

Given the histological findings of arterial thrombosis in CUA, anticoagulants such as low-molecular-weight heparin and thrombolytic therapy have been tried as treatment. One study reported complete healing of CUA lesions with the use of Fraxiparine.47 In another case report, low-dose tissue plasminogen activator was shown to help with wound healing in CUA.48

Bisphosphonates, which reportedly increase osteoprotegerin production and inhibit NFκB/RANKL activity that can decrease osseous mineral loss and extraosseous mineralization, have been used to treat CUA with some success.43,44,49,50 Bisphosphonates can also decrease proinflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-1, and IL-6.51

The use of corticosteroids in the treatment of CUA remains controversial. In one report, the use of prednisone in patients with nonulcerated lesions resulted in stabilization or improvement of the lesions;9 however, prednisone is considered a risk factor for CUA and may predispose the patient to systemic infection.10

CONCLUSION

CUA is a debilitating and potentially fatal disorder, primarily affecting patients with kidney disease. However, with a high degree of clinical suspicion and early diagnosis, an aggressive multifactorial
treatment approach involving optimal wound management, minimization/avoidance of risk factors and precipitating causes, and correction of calcium-phosphorus abnormalities can significantly improve patient outcomes, especially with the recent promise of STS use.

**CALCIFPHYLAXIS REGISTRY**

The Kansas University Medical Center has established a global registry of calciphylaxis cases, and practitioners managing patients with CUA can provide medical information at the following website: www2.kumc.edu/calciphylaxisregistry/. This registry may provide valuable information on the progression and treatment of this debilitating condition.

**REFERENCES**


This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.