CONTACT HOUR: 2.0 HRS

Calciphylaxis in patients with end-stage kidney disease

By Nashita Tabassum and Marisa Battistella

LEARNING OBJECTIVES

1. Describe the pathophysiology of calciphylaxis
2. List the risk factors and medications associated with development of calciphylaxis
3. Compare the therapeutic alternatives for treatment of calciphylaxis
4. Outline common complications/sequelae associated with calciphylaxis and their management

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy, is a syndrome of vascular calcification and thrombosis of arterioles and capillaries of the subcutaneous adipose tissue and dermis, resulting in painful, ischemic, and necrotic skin lesions (Nigwekar et al., 2018). Though rare, the disease is under-recognized and is primarily seen in patients with end-stage kidney disease (ESKD) on dialysis (this is called uremic calciphylaxis). However, it may occur in those without ESKD (non-uremic calciphylaxis). The purpose of this article is to review the diagnosis, pathophysiology, and current management of calciphylaxis.

AUTHOR NOTE

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CLINICAL PRESENTATION AND DIAGNOSIS

Calciphylaxis presents most commonly as painful ischemic necrotic skin lesions that may cover a varying surface area of the body. Some patients experience pain prior to the development of skin lesions. This pain is somatic (caused by infarction) and is generally severe throughout the course of the disease. Initial skin manifestations may include induration, plaques, nodules, livedo, or purpura, which rapidly progress to stellate, malodorous ulcers with black eschars. The lesions are typically bilateral, and the surrounding skin may have a "leather-like" structure. The lesions may have a central distribution (focused in areas with abundant adipose tissue, such as the abdomen or thighs) or a peripheral distribution (focused in areas with minimal adipose tissue, such as the digits). Central distribution is more common in those with ESKD (70%–80% of patients) compared to those without ESKD (50% of patients). These lesions may also be non-ulcerated or ulcerated depending on the stage of disease (Nigwekar et al., 2018). The most common sites of skin lesions include distal lower extremities (55%), proximal lower extremities (39%), trunk (31%), distal upper extremities (7%), and proximal upper extremities (3%; Udomkarnjananun et al., 2018). Penile lesions may also occur (occurring in approximately 6% of patients) and are associated with a higher risk of mortality (Gabel et al., 2021). Extraskeletal calcification is a less common presentation that requires imaging studies for detection. These extraskeletal calcifications rarely may lead to skeletal myopathy, intestinal bleeding, or visual impairment (Nigwekar et al., 2018).

Differential diagnoses should be excluded (see Table 1), using careful assessment of lab findings, imaging, and histopathologic features. Skin biopsy is the gold standard for diagnosis of calciphylaxis. However, biopsy itself can produce new, non-healing ulcers, infection, and induction of necrosis. As a result, if a patient has ESKD and has the classic presentation of a painful necrotic ulcer covered with a black eschar, a biopsy is not necessary and can be reserved for patients with atypical presentation. Furthermore, in the case of an acral, penile, or infected lesion, biopsy is contraindicated (Nigwekar et al., 2018).

Table 1

Differential Diagnoses for Calciphylaxis

Warfarin-induced skin necrosis
Atherosclerotic vascular disease
Venous stasis ulcer
Endarteritis obliterans
Cellulitis
Cholesterol embolization
Dystrophic calcinosis cutis
Livedoid vasculopathy
Nephrogenic systemic fibrosis
Oxalosis
Antiphospholipid antibody syndrome
Cardiac myxoma
Pyoderma gangrenosum
Purpura fulminans
Necrotizing vasculitis
Radiation arteritis
Martorell's ulcer

PATHOPHYSIOLOGY

Histologic analysis reveals that calcification, fibrosis, and thrombus formation result in reduced blood flow and ischemia, which manifest as cutaneous lesions (Nigwekar & Thadani, 2023). Abnormalities caused by chronic kidney disease-bone mineral disease (CKD-BMD) likely have a role in this. Retrospective studies have shown an association between calciphylaxis and primary hyperparathyroidism, active vitamin D administration, and elevated plasma calcium and phosphate. The benefits of parathyroidectomy have also been seen; this is thought to reduce calciphylaxis risk by correcting the hypercalcemia and hyperphosphatemia associated with hyperparathyroidism (Nigwekar & Thadani, 2023). However, analysis of a German calciphylaxis registry revealed that less than 6% of patients had parathyroid hormone (PTH) levels above the range recommended by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (Brandenburg et al., 2017; Ketteler et al., 2017). Elevated serum calcium and phosphorus levels also are not universally seen in patients with calciphylaxis (Brandenburg et al., 2017). It is hypothesized that the development of calciphylaxis, despite this lack of elevation, may paradoxically be attributed to overuse of calcium and vitamin D supplementation, leading to oversuppression of hyperparathyroidism, and resultant low bone turnover (adynamic bone disease; Brandenburg et al., 2017). Adynamic bone has an impaired ability to regulate circulating minerals, and it is thought that these circulating minerals are involved in the formation of extraskeletal calcium depositions. The mixed evidence suggests that CKD-BMD is only one of many factors involved in the development of calciphylaxis (Nigwekar & Thadani, 2013).

Additionally, patients with calciphylaxis have reduced levels of inhibitors of vascular calcifications, such as fetuin-A (2-Heremens-Schmid glycoprotein) and matrix Gla protein (MGP). Carboxylated MGP (CGMP) – the active form of MGP – is a potent inhibitor of calcification, and its carboxylation requires vitamin K. CGMP inhibits the pro-calcifying factors: bone morphogenetic protein 2 (BMP-2) and bone morphogenetic protein 4 (BMP-4). In the absence of vitamin K (as would be seen in patients receiving warfarin) and this inhibition, expression of BMP-2 and BMP-4 is increased, leading to vascular smooth muscle with more osteogenic physiology. Additionally, fetuin-A is a serum glycoprotein that binds calcium and phosphate in the circulation; it is notably deficient in CKD, leading to soft-tissue calcification and vascular calcium deposition (Nigwekar et al., 2018; Rick et al., 2022).

EPIDEMIOLOGY AND RISK FACTORS

Although rare, calciphylaxis has been reported worldwide. In the United States, its prevalence ranges from one to four percent for patients with ESKD receiving dialysis (Rogers et al., 2008). These rates are much lower in other countries, such as Japan, with a reported prevalence rate of less than three cases per 10,000 hemodialysis patients per year (Hayashi et al., 2012). There are no Canadian data available. In the United States, the prevalence is increasing, although this may be related to greater awareness of the disease. The mean age of disease onset is between 50 to 70 years, and patients receiving peritoneal dialysis (PD) are known to have a higher incidence than those receiving hemodialysis (HD; Nigwekar et al., 2018). Table 2 lists risk factors for the development of calciphylaxis. Among them are hypercalcemia, hyperphosphatemia, and hyperparathyroidism—as discussed above, these likely play some role in the pathophysiology of calciphylaxis. Some more general risk factors include obesity, diabetes mellitus, female sex, and dependence on dialysis for more than two years. Medications that have been associated with the development of calciphylaxis include warfarin, calcium, vitamin D, iron, recombinant PTH and systemic corticosteroids (Weenig et al., 2007). The role of iron and its mechanism is not well understood, but several studies have reported its association

Table 2

Risk Factors for Calciphylaxis

End-stage renal disease
Female sex
Obesity
Diabetes mellitus
Hypercalcemia
Hyperphosphatemia
Hyperparathyroidism (primary and secondary)
Over-suppressed PTH with adynamic bone disease (low bone turnover)
Elevated alkaline phosphatase
Vitamin K deficiency
Hepatobiliary disease
Thrombophilia (e.g., antithrombin deficiency, protein C deficiency, or lupus anticoagulant)
Autoimmune disorders (e.g., systemic lupus erythematosus)
Hypoalbuminemia
Metastatic cancers
POEMS syndrome
Genetic polymorphisms (e.g., rs4431401 and rs9444348)
Skin trauma (e.g., from subcutaneous injections)
Recurrent hypotension
Rapid weight loss
Exposure to ultraviolet light
Exposure to aluminum
Medications (e.g., warfarin, calcium, vitamin D, iron, recombinant PTH, systemic corticosteroids)

Note. PTH = parathyroid hormone; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes.

with calciphylaxis (Wickens et al., 2022). Warfarin, a vitamin K antagonist, increases risk by inhibiting vitamin K, which plays an important role in the conversion of MGP to its active form of CMGP. Of note, calciphylaxis associated with skin trauma from subcutaneous insulin or heparin administration has also been reported. This may be of particular importance in selecting therapy for these patients. If an injectable agent is needed, rotating injection sites and avoiding trauma at lesion sites is recommended (Nigwekar et al., 2015).

TREATMENT

Management of calciphylaxis should be multifactorial and interdisciplinary. Generally, treatment can involve multiple services including, but not limited to, dermatology, wound care, nephrology, urology, infectious diseases, pain and palliative medicine, plastic surgery, and hyperbaric medicine. There are no approved treatments for calciphylaxis. Furthermore, the majority of evidence comes from retrospective and observational studies.

Supportive Management

Patients with calciphylaxis require analgesia for symptomatic management of severe pain associated with skin lesions. A multimodal pain management strategy should be used. These patients often require very high doses of opioids such as hydromorphone or fentanyl. In addition to opioids, pain management with gabapentin, ketamine, intravenous ketorolac, or spinal anesthetic agents, is an option, especially if the patient is showing signs of pain refractory to opioids or of opioid toxicity (Polizzotto et al., 2006). Ketorolac is generally reserved for patients in whom preservation of renal function is not a priority. The role of wound care involves selection of appropriate dressings, debridement of necrotic tissue, and prevention of infection. However, collaboration with a pain specialist and plastic surgery is often required as the severity of pain makes debridement difficult. If surgical debridement is done appropriately, retrospective studies have shown that this can result in significantly better overall survival (McCarthy et al, 2016; Weenig et al., 2017).

Risk Factor Modulation

For treatment of calciphylaxis beyond supportive care, first-line therapy is modification of risk factors, including treatment of calcium, phosphorus, and parathyroid hormone abnormalities. If abnormalities in serum calcium and phosphorus levels are present in a patient, these should be corrected to be within the normal range. Vitamin D and its analogues should be avoided as these may increase serum calcium and phosphorus. Calcimimetic agents such as cinacalcet should be used in patients with secondary hyperparathyroidism with PTH greater than KDIGO target levels. Finally, if PTH is refractory to other therapies, surgical parathyroidectomy should be explored as an option for correction of PTH levels (Nigwekar et al., 2015).

In terms of other modifiable risk factors, medications that can increase risk of calciphylaxis such as warfarin, systemic corticosteroids, calcium, vitamin D, and iron supplementation, should be discontinued. Although vitamin K theoretically may be used to treat calciphylaxis, this has not been well-studied and is not routinely done (Nigwekar & Thadani, 2023).

Dialysis

Most patients will also require intensification of their dialysis regimen. If the patient is receiving PD, this may mean increased frequency of dialysis or transition to HD. In a patient already undergoing HD, this will mean increased frequency or duration of treatment, for example, going from thrice weekly to daily dialysis (Brandenburg et al., 2017).

Sodium Thiosulfate

In terms of pharmacotherapeutic agents, sodium thiosulfate (STS) is trialed in all patients unless contraindicated. STS is an inorganic salt that is theorized to have antioxidant and vasodilatory properties, as well as the ability to chelate calcium to form calcium thiosulfate, a far more soluble salt (Baker et al., 2007) The majority of evidence comes from retrospective studies and case series, and at least three recent attempts at conducting randomized clinical trials (RCTs) have been terminated due to failure of patients to meet the inclusion criteria or lack of patient enrolment (Sinha et al., 2021). In fact, two meta-analyses of retrospective studies did not find any improvement in skin lesions or mortality. For example, Wen et al. (2023) looked at 422 patients across 19 retrospective cohort studies and found no difference in skin lesion improvement (RR, 1.23; 95% CI, 0.70–1.10) or survival (HR, 0.82; 95% CI, 0.57–1.18). Despite the lack of conclusive evidence, anecdotal evidence has shown efficacy of this agent, and many clinicians will use it as a first-line agent. STS is given at a dose of 25 g intravenously over 30 to 60 minutes during the last hour of each HD session or over 60 minutes, three times weekly for patients receiving PD. Adverse effects include transient mild rhinorrhea, sinus congestion, nausea, vomiting, as well as high anion gap metabolic acidosis (Baker et al., 2007). Of note, the optimal duration of STS therapy is not known; on average, patients will receive 12 weeks of therapy, but this ranges between 8 to 24 weeks (Udomkarnjananun et al., 2018).

Hyperbaric Oxygen Therapy

In recent years, evidence from case reports, case series, and a narrative review have suggested that hyperbaric oxygen therapy (HBOT) can improve survival and the proportion of patients with complete wound healing, and lead to greater response even in those who only experience partial wound healing (An et al., 2015; Charaghvandi et al., 2020; Lipinski & Sahu, 2020). HBOT involves breathing 100% oxygen at pressures higher than ambient pressure (one atmosphere absolute [ATA]) while the patient is situated inside a sealed treatment chamber. Exposure to greater amounts of oxygen in the air allows improved oxygenation to hypoxic tissues, resulting in greater wound healing through fibroblast proliferation and angiogenesis, as well as improved oxygen-dependent neutrophil bactericidal activity (Lipinski & Sahu, 2020). As a result, HBOT is often used as a second-line or as an add-on therapy to STS. Potential complications of HBOT include middle ear barotrauma, claustrophobia, and pulmonary/central nervous system oxygen toxicity; in general, these are quite uncommon in practice (Kranke et al, 2015). Untreated pneumothorax is considered an absolute contraindication, while relative contraindications include concurrent chemotherapy (if the agent impedes wound healing),

the presence of an implantable device such as a pacemaker, pregnancy, as well as underlying respiratory diseases, such as chronic obstructive pulmonary disease (COPD) or asthma (Ortega et al., 2021).

Other Therapies

Bisphosphonates, such as IV pamidronate and oral alendronate, have been used to treat calciphylaxis patients who have hypercalcemia. However, a meta-analysis showed that bisphosphonate treatment did not lead to improved clinical outcomes (Udomkarnjananun et al., 2018). Newer therapies are also being explored in this area. Myo-inositol hexaphosphate, also known as phytate, is an antinutrient (referring to its ability to decrease the bioavailability of important minerals such as calcium) found in seeds, legumes, nuts, and whole cereals (Grases & Costa-Bauza, 2019). It inhibits the formation and growth of hydroxyapatite crystals, the final common pathway in the pathophysiology of vascular calcification (Brandenburg et al., 2019).

A recent open-label, single-arm, repeat-dose phase two clinical study of SNF472 (an intravenous formulation of myo-inositol hexaphosphate) assessed the efficacy of intravenous administration of 7 mg/kg SNF472 three times per week for 12 weeks in 14 patients with calciphylaxis (undergoing thrice-weekly hemodialysis and standard care). Results showed a statistically significant improvement in wound healing (mean score reduction 8.1±8.5, measured using Bates-Jensen Wound Assessment Tool), non-significant improvement in pain (mean 33% score reduction, measured using Visual Analogue Scale) and non- significant improvement in wound-related quality of life (Brandenburg et al., 2019). Currently, the CALCIPHYX study—a randomized, double-blind, placebo-controlled, phase three clinical trial of SNF472 for the treatment of calciphylaxis—is undergoing patient recruitment. Its eventual results will add important information to the body of evidence regarding myo-inositol hexaphosphate and its usability for calciphylaxis (Sinha et al., 2021). Other experimental therapies that are not routinely used to treat calciphylaxis include tissue plasminogen activator, LDL-apheresis, sterile maggot therapy, and recombinant platelet-derived growth factor (Nigwekar et al., 2018).

COMPLICATIONS AND PROGNOSIS

Mortality is very common. One study reported an estimated mortality of 40% at six months, whereas another reported 44% at one year (Gabel et al., 2021; McCarthy et al., 2016). Patients with kidney failure have a worse prognosis than those without (one-year mortality of 45%–80% versus 25%–45%), likely caused by the differences in comorbidities and the distribution of lesions (Nigwekar et al., 2018). Patients with a central distribution of lesions tend to be women with higher body mass index (BMI) and have a higher risk of death.

Infection is an extremely common complication of wounds caused by calciphylaxis. Infected wounds may present with additional pain and swelling with or without purulent discharge. These wounds should be debrided, and antimicrobial therapy should be administered. In terms of antimicrobial coverage, wound swabs are not reliable for identifying a specific organism. As such, empiric antibiotics should cover against streptococci, methicillin-resistant Staphylococcus aureus, aerobic gram-negative bacilli, and anaerobes (Nigwekar & Thadhani, 2023). The wounds caused by cutaneous calciphylaxis also often lead to recurrent sepsis in patients, making sepsis the most common cause of death among this population (Nigwekar et al., 2018).

SUMMARY

Calciphylaxis is a rare, debilitating disease that manifests commonly as painful, necrotic skin lesions. Theorized to be caused by CKD-BMD abnormalities and deficiencies in inhibitors of vascular calcification, many medications, such as warfarin, calcium, vitamin D, iron, recombinant PTH, and systemic corticosteroids, can also increase the risk of a patient developing calciphylaxis. Although evidence is sparse, patients are treated with pain management, wound care, modification of risk factors, and sodium thiosulfate with or without hyperbaric oxygen therapy. Other potential therapeutic options include bisphosphonates and vitamin K, as well as myo-inositol hexaphosphate, which is currently being studied in a phase three RCT. Future research in this area should be a priority to improve outcomes in this patient population.

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