Calciphylaxis: Controversies in Pathogenesis, Diagnosis and Treatment

Haneol S. Jeong, BA, BBA and Arturo R. Dominguez, MD

ABSTRACT

Calcific uremic arteriolopathy, otherwise known as calciphylaxis, is a rare disease characterized by skin ulceration and tissue necrosis, likely the result of vascular calcification with accompanying intimal hypertrophy and small vessel thrombosis. Although most often associated with end-stage renal disease, it has also been seen in a number of other disorders (collectively referred to as nonuremic calciphylaxis). The purpose of this review is to summarize and analyze the currently available literature regarding the pathophysiology, risk factors, clinical presentation, diagnostic features and treatment modalities for this exceptionally uncommon illness. A series of recommended treatments is proposed for optimal treatment of calciphylaxis lesions.

Key Indexing Terms: Calciphylaxis; Calcific uremic arteriolopathy; Pathogenesis; Diagnosis; Treatment. **[Am J Med Sci 2016;351(2):217–227.]**

INTRODUCTION

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare, oftentimes fatal complication usually associated with end-stage renal disease (ESRD).[1] It is characterized by skin ulceration and necrosis leading to significant pain. Histopathologic examination in these patients is often significant for medial calcification and intimal proliferation of small arterioles and subcutaneous capillaries, leading to thrombosis and ischemic necrosis, although recent work has suggested far greater variability in histopathologic presentation.[2,3] Wounds are often secondarily infected, leading to death in up to 60% of patients within 1 year.[4]

Cutaneous findings include tender, indurated subcutaneous plaques with overlying livedo racemosa that progress to nonhealing stellate-shaped ulcers covered by black eschar.[5] Areas of involvement include adipose-rich areas on the trunk and extremities, particularly the legs; however, acral involvement, including penile[6,7] and digital[8] necrosis is well described. Rarer complications include gastrointestinal, cardiac,[9] pulmonary[10] and ocular[11] involvement.

The incidence of CUA has risen in the last decade, with recent estimates as high as 5% of dialysis-dependent patients,[12] but the true prevalence is likely unknown.[13] The most comprehensive analysis, conducted by the Partners Research Patient Data Registry, noted 567 cases of calciphylaxis per 10,000 patients on chronic hemodialysis (HD) from 2002-2011.[14] More importantly, this group described increasing incidence rates (3.7 per 10,000 dialysis patients before 2007, 5.7 per 10,000 patients after 2007). Whether this rise in incidence is due to improved recognition of the disease or increased use of calcium-based phosphate binders is unclear. Although primarily associated with chronic kidney disease, calciphylaxis has also been diagnosed in patients with normal renal function, calcium, and phosphate pathways.[15,16] Other identified risk factors include female gender,[17] diabetes mellitus, liver disease[13] and obesity[18] among others.[19-21] Calciphylaxis is not thought to be an inevitable sequela of renal disease; as such, it is considered separate from renal osteodystrophy.[22]

The purpose of this review is to analyze the literature regarding the pathophysiology, risk factors, clinical presentation, diagnostic features and treatment modalities for this exceptionally uncommon illness. Recommended treatments are subsequently proposed for optimal treatment.

PATHOPHYSIOLOGY

Selye et al[23] first described calciphylaxis in rodents as a hypersensitivity-like condition, wherein after sensitization by a calcifying factor, second exposure resulted in local calcification, inflammation and sclerosis. Subsequently, similar lesions were reported in uremic humans; these ischemic, ulcerated wounds were sufficiently similar in their characteristics to Selye's rats that they were termed lesions of calciphylaxis. Although similar to renal osteodystrophy in that there is abnormal calcium deposition, calciphylaxis involves calcification of the tunica media of arterioles and subcutaneous capillaries (<0.6 mm in diameter), as opposed to the deposition in medium-sized vessels common to osteodystrophy.[24]

The formation of calciphylaxis lesions likely requires 2 key steps: (1) medial calcification and intimal fibrosis of the arterioles and (2) thrombotic occlusion due to progressive calcification and endothelial dysfunction. Dysfunction of the regulatory mechanisms that manage calcium, phosphate and parathyroid hormone (PTH) levels results in vascular calcification. Dystrophic

vascular calcification is divided into 2 main categories, according to lesion location and its association with atherosclerosis.[25] The more common is calcification of the intima, in conjunction with or secondary to the formation of atherosclerotic plaques. Conversely, calciphylaxis is characterized by calcification of arteriole media. However, both forms involve calcium hydroxyapatite and matrix vesicles within the calcified vessel walls.[26]

Owing to the association between calcium and phosphate regulation and calciphylaxis, it is unsurprising that the majority of cases of calciphylaxis occur in patients suffering from kidney disease.[12] Phosphorus can rise to pathologic levels in kidney disease because of impaired excretion, and has historically been noted to cause the expression of procalcific genes.[27] Recent research has elaborated the process by which calcium is deposited in vessel walls further. Under the currently accepted model for vascular calcification, lesion pathogenesis begins with the transformation of vascular smooth muscle cells (VSMCs) into osteoblast-like phenotypes.[28] This occurs through interaction amongst the constituents of uremia—hyperphosphatemia, uremic toxins, and reactive oxygen species and the decrease of matrix gla protein (MGP), a potent calcification inhibitor. To some extent, the calciphylaxis is still influenced by the renal system, as hyperphosphatemia is thought to trigger VSMCs transformation to an osteoblastic cell type.[29]

Bone morphogenetic protein-4 and osteopontin, normal constituents in bone repair and development, are also expressed in lesional biopsies of patients with calciphylaxis and are thought to serve as makers of osteoblastic transformation.[30] The activity of bone morphogenetic protein-4 in catalyzing extraskeletal calcification is dependent on reactive oxygen species, which act through nuclear factor kappa B (NFkB) to spur the calcification process.[31] Alternatively, NFkB can be upregulated through loss of constituent inhibitors, such as osteoprotegerin.

However, medial calcification and sub-intimal fibrosis of arterioles alone is likely not sufficient to cause calciphylaxis. The role of hypercoagulability in the development of calciphylaxis is gaining increasing attention. In 1 cohort of patients with CUA, up to 38% and 43% of reported cases had decreased levels of proteins C and S, respectively, on laboratory evaluation.[32] The same study has reported cases of calciphylaxis in patients with multiple hypercoagulable states. Evidence for the role of hypercoagulability in calciphylaxis is further supported by histopathologic findings demonstrating thrombosis in 38 of 44 patients (86%) in 1 cohort, with no inflammatory infiltrates suggestive of a vasculitic process.[19]

The induction of local hypercoagulability may also lead to discrete prothrombotic regions. Inflammatory cytokines, including TNF-alpha, IL-1 and IL-6, may reduce anti-thrombotic responses such as protein C and S receptor expression, thrombomodulin expression, and vascular heparin-like molecules, promoting thrombosis.[33] Similarly, other factors linked to calciphylaxis (later) are thought to enhance thrombosis by reducing anti-thrombotic processes or enhancing prothrombotic mechanisms, as opposed to inducing calcification.

This is further supported by the rise of calciphylaxis in patients with normal kidney function, a phenomenon called nonuremic calciphylaxis. A systemic review of nonuremic calciphylaxis[32] identified associations between calciphylaxis and the following medical diseases: primary hyperparathyroidism (27.8% of available cases), cholangiocarcinoma, chronic myeloid leukemia, melanoma and other malignancies (22.2%), alcoholic liver disease (16.7%) and connective tissue diseases (11.1%). Disease characteristics are virtually identical to CUA. The presence of calciphylaxis in patients with normal renal function and mineral bone axes imply that hyperphosphatemia may not be an absolute requirement for lesion induction.

CLINICAL PRESENTATION

History

Patients with calciphylaxis typically present with significant pain and chronic nonhealing wounds. The wounds themselves show signs of poor healing, including black eschar. Furthermore, the open, chronic wounds are often secondarily super-infected, leading to erythema, edema and purulent discharge. Left untreated, these wounds can progress to systemic infections, with all of the associated complications.[4] Although the cutaneous complications are often the patient's primary concern, vascular calcification has also been noted in skeletal muscle, brain, lungs, intestines and other organ systems,[34,35] suggesting a more systemic process. Interestingly, many cases of systemic calciphylaxis lack vascular thrombosis of the involved organs on histopathology, bringing into question whether these cases represent metastatic calcification rather than calciphylaxis.

There has been a significant effort toward understanding the characteristics that predispose patients to calciphylaxis. Individual studies are often limited owing to the sheer rarity of the disease, and thus prone to limitations in sample size, demographic heterogeneity and selection bias. However, the summation of these works reveals several recurring connections between certain factors and the development of calciphylaxis.

The most commonly associated risk factors involve mineral components of the renal system. Hyperphosphatemia, an elevated calcium-phosphorus product, hyperparathyroidism and vitamin D deficiency are significantly associated with calciphylaxis.[36] Initial investigation into calciphylaxis likely started with these factors due to the increased rates in patients with chronic kidney disease. A variety of medications are associated with increased risk for developing calciphylaxis. Calcium