Clinical Column

Calciphylaxis: Overview for the vascular nurse

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Have you cared for a middle-aged patient on dialysis who developed black, leathery skin patches on her legs? Did she report intense pain and tell you they started out as small, tender bumps and areas of skin discoloration when they first appeared? If yes, you may have encountered a patient with calciphylaxis. This article will provide the vascular nurse with an overview of the condition as it pertains to renal patients with the condition.

Calciphylaxis is a severely painful and life-threatening condition characterized by cutaneous ischemia and skin necrosis.[1] It is a poorly understood vascular calcification disorder associated with a high 1-year mortality rate of 45%-80%, with prognosis being especially poor if ulcerated lesions are present.[2] The condition occurs most frequently in patients with end-stage renal disease (ESRD) who are receiving hemodialysis or who have recently received a kidney transplant.[3] The term calcific uremic arteriolopathy (CUA) has been coined for this population, and the term calciphylaxis is used for non-ESRD patients with the disorder.[3] An estimated 15%-20% of patients with calciphylaxis do not have renal disease.[4] Name ambiguity is pervasive, and most clinicians still refer to CUA as calciphylaxis.[3]

Calciphylaxis was first described in 1961 by Selye in his research with laboratory rats, and the name implies calcification of the dermis and a phylactic or adaptive reaction to an agent.[2,5] Even though calciphylaxis in humans is not a hypersensitivity reaction and it refers to calcification of small dermal and subcutaneous arteries (and not dermal calcification), the name calciphylaxis has remained.[2,5] The focus of this article is calciphylaxis in patients with ESRD, and the term CUA will be used for the purposes of this overview.

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CLINICAL PRESENTATION

Persons with CUA often present with exquisitely painful skin lesions located in areas of dense adiposity, most commonly the thighs, abdomen, and buttocks.[4] However, the early phase of CUA may present as unremarkable small papules (even without exterior skin changes) or erosions and supports a theory that subcutaneous changes happen before any apparent overlying skin changes.[4] Some authors have encountered patients who have pain which precedes any CUA skin lesions.[3] CUA is often classified as proximal (thighs, buttocks, trunk), distal (calves, forearms), or acral (hands, feet fingers, toes).[5] Many atypical sites are also described, including genitalia, tongue, breasts, neck, and more.[5] Persons with both proximal and distal disease have demonstrated the highest mortality.[6]

Terms commonly used to describe the painful CUA lesions include the following:[7]

- Livedo racemosa (also known as livedo reticularis; reddish blue, net-like mottling of skin on the limbs and trunk)[8]
- Hemorrhagic patches
- Indurated plaques
- Necrotic cutaneous ulcer
- Hemorrhagic bullae

See Figure 1 for cutaneous images of calciphylaxis in early and later stages.[6]

CUA lesions exhibit poor wound healing and are often complicated by blistering, ulcerations which demonstrate black eschar, and superimposed infections.[2,3] Early diagnosis is often missed due to an unclear clinical presentation and possibly to misleading educational materials that provide only photographic representation of late-stage CUA.[4] Recognition in the early stage can allow prompt implementation of potentially lifesaving treatments.[6] Although skin manifestations dominate the clinical picture, cutaneous findings may be part of a larger systemic process which leads to arterial calcifications of many vascular beds.[2,9] Calcifications of skeletal muscles, intestines, mesentery, lungs, and optic nerve have also been reported.[9] Wound infection and sepsis are the most common causes of death in a CUA patient.[4]

INCIDENCE AND PREVALENCE

The incidence of CUA is on the rise over the past decade and may affect up to 5% of dialysis-dependent patients.[6,10] It is not an

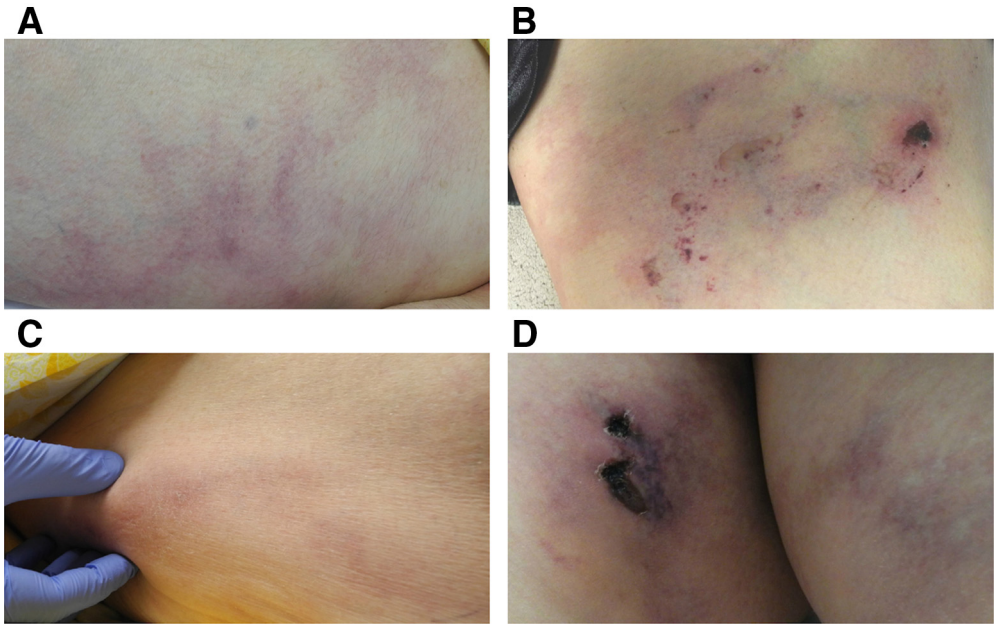

Figure 1. *(A) Top left: early calciphylaxis—right anterior-medial thigh. Erythematous and violaceous broken circles of livedo racemosa signifying active ischemia. (B) Top right: early calciphylaxis—left anterior thigh. Livedo racemosa with bullae formation and crusting from ischemia and subsequent skin necrosis. (C) Bottom left: calciphylaxis as panniculitis—right lateral thigh. Painful indurated subcutaneous plaque with surrounding livedo racemosa. Note the "forked lightening" erythema to the right of the indurated and dimpled plaque. (D) Bottom right: progressive calciphylaxis—bilateral anterior thighs. Slightly more advanced stage than previous pictures. Livedo racemosa is present but has progressed to retiform purpura on right anterior thigh. There is eschar formation from skin that has already necrosed due to ischemic injury. (Jeong HS, BA BBA, Dominguez AR)[6]. Adapted with permission from BMJ Publishing Group.*

inescapable consequence of renal disease and is a separate entity from renal osteodystrophy.[6] The increased incidence of CUA may be attributable to better clinician awareness and the ongoing epidemic of obesity and metabolic syndrome and the subsequent increase in the occurrence of type 2 diabetes mellitus and ESRD.[5] Early and aggressive control of secondary hyperparathyroidism in ESRD may be a contributor as well; these measures include widespread use of calcium-containing phosphorus binders and calcitriol.[5] CUA is most commonly reported in patients in the fifth decade of life, but cases have even been reported in children.[2] There is higher incidence of the condition in women with a 2:1 female predilection reported.[2] As many as 32%-38%, CUA patients are kidney transplant recipients, including persons will a functional graft.[5]

Additional risk factors for CUA include the following:[1–3,6,9,10]

- Hyperphosphatemia
- Elevated calcium-phosphorus product
- Hyperparathyroidism
- Medications including warfarin, calcium-containing phosphorus binders, vitamin D analogs, systemic glucocorticoids
- Hypoalbuminemia
- Hypercoagulable states (eg, protein C, protein S, antiphospholipid syndrome)
- Obesity
- Diabetes mellitus
- Inflammatory and autoimmune conditions
- Liver disease
- Longer dialysis vintage
- Trauma
- Caucasian race
- Elevated aluminum levels
- Iron administration
- Rapid weight loss

Certainly, these risk factors are not consistent across studies, and many cases exist where the CUA patient has low or even normal levels of serum calcium, phosphorus, and parathyroid hormone.[2] Calciphylaxis risk factors in the nonuremic population include primary hyperparathyroidism, alcoholic liver disease, malignancy, connective tissue disease, prior steroid use, and protein C or S deficiency.[10]

DIAGNOSIS

Diagnosing CUA begins with a detailed clinical history which focuses on important risk factors for the condition and the timing of skin lesions.[4] A high index of suspicion is needed to make and confirm the diagnosis.[9,11] Pathogenesis remains unclear, and no diagnostic or serologic test exists for CUA.[9] A definitive diagnosis is generally rendered by cutaneous biopsy, but performing this procedure is controversial as adverse effects have included nonhealing ulcerations, infection, sepsis, and more.[3,4,6] Some clinicians advise biopsy only when the clinical diagnosis is unclear (eg, early-stage findings), and an excisional