Nonuremic calciphylaxis manifesting with diffuse dermal angiomatosis

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INTRODUCTION
Calciphylaxis is a vasculopathy characterized by vascular calcification, ischemia, and subsequent skin necrosis. While uremic calciphylaxis presents in the setting of end-stage renal disease, nonuremic calciphylaxis (NUC) is associated with a variety of factors, including liver disease, warfarin or systemic corticosteroid use, hypercoagulability, and autoimmune diseases. Diffuse dermal angiomatosis (DDA) is a variant of reactive angioendotheliomatosis that is triggered by local ischemia or vascular inflammation, causing the upregulation of vascular endothelial growth factor. Prior reports have demonstrated a rare association of uremic calciphylaxis with DDA.1-3 Both DDA and calciphylaxis present with painful, purpuric plaques/nodules with necrotic eschars. These similarities can pose a diagnostic and treatment conundrum. We present a case of NUC with histopathologic features of DDA that was responsive to treatment with sodium thiosulfate (STS).

REPORT OF A CASE
A 41-year-old woman with alcoholic hepatitis and acute kidney injury presented with a 3-month history of painful, indurated, subcutaneous nodules, without overlying cutaneous changes and plaques, with overlying retiform purpura and central black eschars, on the abdomen and both thighs (Fig 1). The patient was a smoker without a history of cardiovascular disease or warfarin use.

The initial skin biopsy demonstrated the proliferation of thin-walled vessels in a mixed lobular and diffuse pattern throughout the dermis and subcutis (Fig 2). Von Kossa staining was negative for calcium. After the patient was admitted, a repeat biopsy demonstrated similar findings. An additional, deeper biopsy with sampling of the subcutis also showed zones of diffuse, small vessels surrounded by pericytes in the dermis. Von Kossa staining in the last 2 biopsies showed focal calcium deposition on elastin fibers (Fig 3). Magnetic resonance imaging and plain films demonstrated only soft tissue edema and focal skin thickening, without vessel calcification.

Given the suspicion for NUC due to the recent alcoholic hepatitis and acute renal injury, the patient was started on 2.5 mg rivaroxaban daily, then increased to 5 mg daily. This was subsequently dose reduced and ultimately discontinued due to acute anemia from hemorrhoids. As the patient had no history of deep vein thromboses despite numerous thrombotic challenges (4 pregnancies and oral contraceptive use), the low protein C was deemed to have been acquired from liver dysfunction.

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was started on STS infusions (25 g, thrice weekly). Upon treatment initiation, the patient reported a significant reduction in pain. Within 1 week, there was softening of the induration surrounding her lesions and improved healing at the existing ulcers.

DISCUSSION

NUC classically affects individuals who are women, White, overweight, or taking warfarin. Our patient met 3 of these criteria and had alcoholic liver disease, which has also been associated with NUC. Vitamin K antagonism is one of the most common concomitant conditions reported with NUC; notably, patients with liver disease are at risk of vitamin K deficiency from malabsorption and malnutrition. It is posited that aberrant matrix Gla protein activity, a key inhibitor of calcification activated by vitamin K, may be a driving force in NUC pathogenesis. Liver disease has also been shown to impact the expression of nuclear factor-κB, receptor activator of NF-κB ligand, and osteoprotegrin, which are involved in extraskeletal mineralization. Additionally, decreased protein C levels, as seen in our patient, and decreased protein S levels can occur in the setting of liver disease and may promote local hypercoagulability, leading to NUC.

The incidence of NUC is rising, but its diagnosis remains challenging. DDA may be a feature of calciphylaxis, with studies demonstrating histopathologic features of DDA in biopsies from patients with calciphylaxis. A recent report highlighted a case with clinical features of uremic calciphylaxis with histopathology suggestive of DDA. Our case uniquely demonstrates that NUC may present with histopathologic features of DDA and without diagnostic features of calciphylaxis yet still respond to STS treatment.

Ischemia appears to be critical in both calciphylaxis and DDA development. While calciphylaxis and DDA are associated, the sequence of events in which they cooccur is unclear. Two possibilities have been posited. First, the conditions that induce initially low-grade local ischemia promote vascular endothelial growth factor production, resulting in DDA, serving as a harbinger of the frank ischemia of calciphylaxis. Second, the vascular occlusion of larger dermal vessels in calciphylaxis causes a compensatory increase in vascular endothelial growth factor that promotes the development of DDA.

There are limited reliable tools to aid in the diagnosis of NUC. We recommend maintaining a high degree of clinical suspicion for NUC in patients with appropriate clinical features. Biopsy sensitivities range from 20% to 86%, influenced by factors such as biopsy location and technique. Often, biopsies are nondiagnostic due to inadequate sampling or nonspecific histologic features. Although incisional biopsies are recommended, these may not be appropriate when considering patient comfort, infection risk, and wound healing. Plain films, computed tomography, and ultrasound can be
useful diagnostic modalities, along with contrast-based vascular imaging to detect calcification.9-11 Given our patient’s acute renal injury, contrast-based imaging was not pursued.

This case suggests that empiric calciphylaxis treatment can be initiated in the correct clinical context. Treatments for calciphylaxis are limited. The efficacy of STS has been demonstrated widely, although no randomized controlled trials exist.12,13 The use of STS in NUC has also been demonstrated and is associated with a survival benefit.12,14 Our patient’s improvement on STS builds on this prior evidence. STS is thought to act as a chelating agent, dissolving calcium deposits in the blood vessels.12 It is also proposed to have antioxidant properties, ultimately restoring nitric oxide production in endothelial cells to promote vasodilation. Another proposed mechanism includes hydrogen sulfide, an STS metabolite, exerting vasodilatory, antiinflammatory, and analgesic effects.13 Gastrointestinal side effects can preclude patients from receiving optimal doses, and supportive therapies, such as antiemetics, are often required.

NUC carries high morbidity and mortality risks yet remains difficult to diagnose. This case asserts that DDA may be considered a diagnostic clue in presentations suspicious for NUC and prompt the timely initiation of therapies.

Conflicts of interest
None disclosed.

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