A case of nonuremic calciphylaxis of the penis responding to sodium thiosulfate therapy

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INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare but often fatal disease characterized by vascular calcification that subsequently causes thrombosis and tissue ischemia, leading to painful cutaneous ulceration and necrosis. It most commonly affects the lower extremities and only in exceedingly rare cases, involves the genitalia.[1] Genital involvement is rare due to the rich vascular network that protects against ischemia.[2] Although most commonly seen in patients with hemodialysis-dependent end-stage renal disease, calciphylaxis can occur in the absence of severe renal dysfunction, which is known as nonuremic calciphylaxis (NUC). Risk factors associated with calciphylaxis include female sex, Caucasian race, obesity, hyperparathyroidism, malignancy, alcoholic liver disease, connective tissue disease, autoimmune disease, diabetes, and protein C or S deficiencies. Also, predisposing medical treatments include corticosteroids, warfarin, and albumin or blood transfusions.[1,3] Although a skin biopsy is the current gold standard for the diagnosis of calciphylaxis, there is growing evidence for the usefulness of radiographic imaging, particularly when biopsies are nondiagnostic or contraindicated. Here, we report an unusual case of NUC affecting the penis that was diagnosed with computed tomography (CT) findings that were specific in this clinical scenario. The patient gave consent for his photographs and medical information to be published in print and online with the understanding that this information may be publicly available.

Abbreviations used:

CT: computed tomography
NUC: nonuremic calciphylaxis
STS: sodium thiosulfate

CASE REPORT

A 57-year-old man with a past medical history of poorly controlled diabetes and essential hypertension was evaluated for a 4-month history of painful penile ulceration. Physical examination revealed a 2.3 cm wide circumurethral ulcer of the glans penis with an overlying yellow-green crust (Fig 1). In the 6 years prior to presentation, serum calcium and creatinine levels were measured at least annually and were normal. The patient was normophosphatemic as well. The patient's laboratory reports were significant for decreased parathyroid hormone-related protein (9 pg/mL; normal range, 11-20 pg/mL), normal parathyroid hormone, elevated total protein on urine protein electrophoresis without abnormal bands (Bence-Jones proteinuria), and elevated hemoglobin A1C (9.0%). Tangential shave biopsy of the ulceration as well as 2 subsequent punch biopsies demonstrated ulceration with necrotizing inflammation and no evidence of malignancy. Due to the nonspecific histologic findings, the patient was initially prescribed ciprofloxacin to help cover for the potential of *Pseudomonas aeruginosa* infection in differential diagnosis. One month after initial presentation, the ulcer had progressed proximally with worsening necrosis and pain. A contrast-enhanced CT scan of

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Fig 1. Gross image of ulcerating calciphylaxis of the glans penis prior to treatment.

the pelvis was then ordered, which revealed atherosclerosis without hemodynamically significant stenosis of arterial structures and soft tissue calcification of the penile vasculature and corpus cavernosa (Fig 2). Doppler ultrasound confirmed diffuse atherosclerotic disease without significant stenosis of either the cavernosal or dorsal arteries of the penis (Fig 3).

Following the diagnosis of NUC, treatment was initiated with 25 g of intravenous sodium thiosulfate (STS) twice weekly for 2 weeks before the frequency was increased to thrice weekly. Wound cleansing and debridement were performed, and 90-minute sessions of hyperbaric oxygen therapy were started. Hyperbaric oxygen therapy was discontinued after the fifth treatment due to patient-reported pain with hyperbaric oxygen sessions. After 18 weeks of STS therapy, the ulcer was fully healed (Fig 4). The frequency of STS therapy was reduced to once weekly for the next 2 months before discontinuation, given the cessation of disease activity. Although the ulcer had healed, the patient continued to experience pain of the inguinal folds, scrotum, and penile shaft. Alongside continued use of acetaminophen, nortriptyline 50 mg was prescribed for severe pain flares and tramadol 10 mg was prescribed for nightly use. The patient continues to be seen by the pain management clinic.

DISCUSSION

The diagnosis of NUC was largely based on clinical presentation, radiologic findings, and exclusion of other conditions that can present similarly.

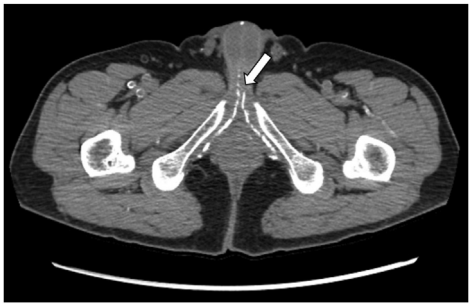

Fig 2. Bilateral calcification of the dorsal arteries visualized by noncontrast CT in the axial view (marked by an *arrow*). *CT*, Computed tomography.

The most likely underlying condition associated with the patient's NUC was diabetes mellitus. Biopsies and serologies did not show any evidence of infectious causes, and atherosclerotic disease was ruled out by the results of both the CT and Doppler ultrasound studies. Normal parathyroid hormone, normal urine protein electrophoresis, and negative antinuclear antibody status made hyperparathyroidism, malignancy, and autoimmune disease less likely. The patient had no prior exposure to warfarin, corticosteroids, or transfusions and was not female, Caucasian, or overweight.

In this case, the CT and ultrasound findings highlight the utility of radiographic imaging in diagnosing calciphylaxis. Calciphylaxis is often diagnosed by the histologic visualization of circumferential calcification of the intima or media of subcutaneous vessels.[4] However, when the penis is the sole site involved, caution with penile biopsies is advised due to the potential of increased morbidity with nonhealing wounds.[5] Although the patient did not experience any negative outcomes associated with the penile biopsies, the biopsies nonetheless were helpful to investigate infectious and malignant etiologies in differential diagnosis.

If biopsy results are pending, nonspecific, or unable to be obtained due to patient refusal or contraindications, radiographic imaging, such as plain radiographs and CT scans, may play an essential role in the work-up. Radiographic imaging has a resolution nearly as fine as histopathology[6] and allows the visualization of microvascular calcifications before cutaneous manifestations appear.[7] On plain radiograph, the pattern of reticular subcutaneous calcification is highly specific for calciphylaxis.[8] On CT, the microvascular calcifications of calciphylaxis can be seen as linear, branching opacities.[9]

In addition, we report the successful treatment of nonuremic penile calciphylaxis with intravenous STS. Proposed mechanisms of STS to treat calciphylaxis include its ability to act as an antioxidant,

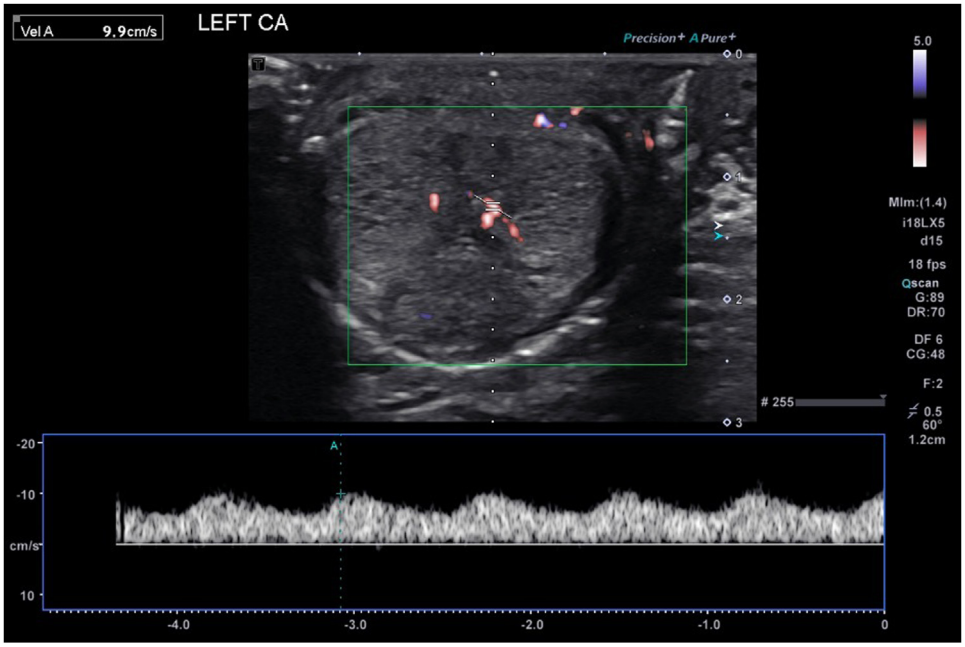

Fig 3. Low resistance blood flow of the left cavernosal artery visualized by pulse wave Doppler.

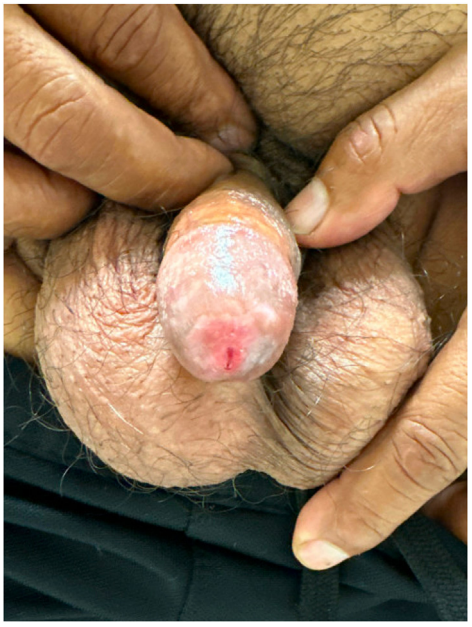

Fig 4. Gross image of healed ulcer on the glans after 7 months of STS therapy. *STS*, Sodium thiosulfate.

vasodilator, and calcium chelator.[10] Although STS is the standard treatment for calciphylaxis, its efficacy has been difficult to analyze due to the rarity of calciphylaxis and the polypharmacy involved in treating comorbid diseases.

The vast majority of penile calciphylaxis cases have overwhelmingly been reported in the setting of end-stage renal disease. This case highlights the importance of keeping calciphylaxis on differential diagnosis even in the absence of severe renal compromise and other common presenting features. Additionally, documentation of the patient's presentation and favorable clinical course reinforces both the diagnostic utility of radiographic imaging in the absence of positive histopathologic findings and the use of STS as a therapeutic approach for NUC. More research and clinical trials are required to determine optimal imaging protocols in diagnostic work-up.

Conflicts of interest

None disclosed.

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