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Title

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Journal

Dermatology Online Journal, 28(6)

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Publication Date

2022

DOI

10.5070/D328659739

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An unexpected case of non-uremic calciphylaxis in a patient with multiple risk factors

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Abstract

A 58-year-old woman with a history of morbid obesity, asthma, and prior warfarin use presented to the hospital with shortness of breath and a three-month history of painful, ulcerated ulcers with retiform purpura of her bilateral distal extremities. A punch biopsy specimen demonstrated focal necrosis and hyalinization of the adipose tissue with subtle arteriolar calcium deposition, findings consistent with calciphylaxis. We discuss the presentation of non-uremic calciphylaxis and review the risk factors, pathophysiology, and interdisciplinary management approach of this rare disease.

Keywords: calciphylaxis, non-uremic, retiform purpura

Introduction

Calciphylaxis is a microvascular occlusion disorder characterized by metastatic arteriolar calcification and cutaneous necrosis. This disease is predominantly seen in patients with advanced renal disease, yet non-uremic cases are also described. We present a patient with non-uremic calciphylaxis who had been admitted for acute exacerbation of heart failure with a history of morbid obesity, asthma, and prior warfarin use. This case illustrates the particular diagnostic challenge of non-uremic calciphylaxis.

Case Synopsis

A 58-year-old woman with a history of diastolic heart failure, asthma, morbid obesity, and warfarin use was

admitted to the hospital with an acute heart failure exacerbation characterized by shortness of breath and leg edema. Medications included atorvastatin, aspirin, apixaban, albuterol, budesonide, bumetanide, gabapentin, hydralazine, losartan, and omalizumab. Of note, the patient was previously on warfarin for 6 years and switched to apixaban one year prior to presentation. Relevant admitting laboratory tests include brain natriuretic peptide 1568pg/mL (normal: <100pg/mL), blood urea nitrogen 20mg/dL (normal: 6 to 24mg/dL), creatinine of 1.15mg/dL (normal: 0.7 to 1.3mg/dL), aspartate aminotransferase (AST) 12U/L (normal: 8 to 33U/L), alanine transaminase (ALT) 9U/L (normal: 7 to 55U/L), calcium 8.8mg/dL (normal: 8.6 to 10.3mg/dL), phosphate 3.3mg/dL (normal: 2.8 to 4.5mg/dL), white blood cell count of $8.4 \times 10^9/L$ (normal: 4.5 to $11.0 \times 10^9/L$) with elevated neutrophils and normal eosinophilia, prothrombin time 13.9 (normal: 11 to 13.5 seconds), partial thromboplastin time 75 (normal: 21 to 35 seconds), platelets $261 \times 10^9/L$ (normal: 150 to $400 \times 10^9/L$), and international normalized ratio (INR) 1.19 (normal: 0.8 to 1.1).

The patient reported recurrent, painful ulcers of her lower extremities for three months prior to admission to wound care clinic, which was presumed to be related to stasis dermatitis secondary to chronic heart failure. The patient's acute lower extremity edema aggravated painful, chronic ulcerations and retiform purpura of the left lower extremity (**Figure 1**). Upon admission, she was started on a 5-day course of cefazolin for suspected cellulitis, later broadened to vancomycin due to



Figure 1. Ulcer with surrounding retiform purpura of the left dorsal foot during early presentation in the setting of pitting edema.

persistence of symptoms. A dermatologist was consulted and the patient subsequently underwent a telescope punch biopsy of the left leg wound, demonstrating focal necrosis and hyalinization of the adipose tissue along with subtle calcium deposit consistent with calciphylaxis (**Figure 2**).

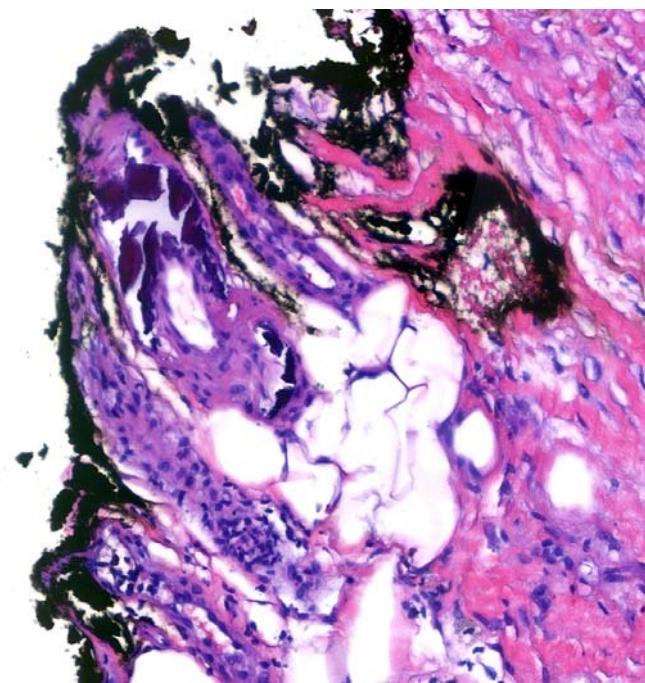


Figure 2. Left leg biopsy. Focal necrosis and hyalinization of the adipose tissue along with subtle calcium deposit compatible with calciphylaxis. H&E, 400X.

Additional workup included elevated beta-2 microglobulin 5.38mg/L (normal: 1.1 to 2.4mg/L), negative anticardiolipin antibodies, negative lupus anticoagulant, negative rheumatoid factor, negative anti-nuclear antibodies, negative anti-double stranded deoxyribonucleic acid antibodies (dsDNA), negative anti-ribosomal P antibodies, negative anti-Sjögren syndrome type A (SSA) and anti-Sjögren syndrome type B (SSB) antibodies, anti-streptolysin O 52IU/mL (normal: <200IU/mL), complement factors C3 and C4 within normal limits (normal C3: 80-178mg/dl, C4: 12-42mg/dl), anti-neutrophil cytoplasmic antibody screen negative, and negative cryoglobulins. The patient also had HbA1c 5.8% (normal: HbA1c <5.7%), Vitamin D 25-OH of 10.25ng/mL (normal: 20 to 50ng/mL), parathyroid hormone of 68pg/mL (normal: 14 to 65pg/mL), and negative human immunodeficiency virus, hepatitis B virus, and hepatitis C virus antibody screens. Urine toxicology was negative. Ankle-brachial index was 0.93 on the right leg and 0.87 on the left leg, showing high pressures consistent with calcified vessels. A left foot computed tomography scan showed soft tissue edema and diffuse calcification suggestive of calcified microvessels (**Figure 3**).

On hospital day 25, the patient was started on intravenous thiosulfate 25g for three days a week (Monday/Wednesday/Friday). On hospital day 38, the patient was discharged to a rehabilitation facility with continued improvement in her lower extremity ulcers (**Figure 4**). The patient was continued on sodium thiosulfate 25g for three days a week (Monday/Wednesday/Friday) for 14 weeks, resulting in full resolution of her lower extremity ulcers.

Case Discussion

Calciphylaxis is a microvascular occlusion disorder characterized by metastatic arteriolar calcification and cutaneous necrosis. It classically presents as painful, violaceous reticular plaques and nodules that commonly progress to necrotic ulcerations with retiform purpura on the abdomen, buttocks, and distal extremities [1]. The clinical presentation of ulcers and retiform purpura can resemble other



Figure 3. 3-Dimensional rendering of computed tomography scan without contrast of left leg showing curvilinear calcifications that represent calcified microvessels.



Figure 4. Lower extremity wound on follow-up 62 days after initial presentation.

disease entities. The differential diagnosis for this presentation includes microvascular occlusion disorders (disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, heparin-induced thrombocytopenia, warfarin-induced skin necrosis), embolic disease (cholesterol and septic emboli), intravascular protein deposition (cryoglobulinemia, cryofibrinogenemia), vasculitis, or infectious etiologies [2]. Clinical suspicion is important for an early diagnosis. In this case, non-uremic calciphylaxis was diagnosed based on the clinical presentation, histopathology, and radiologic data.

Traditionally, skin biopsy with histopathologic assessment was considered the most reliable method of diagnosis. The telescope punch biopsy technique can be used to sample deeper tissue in the subcutis. This biopsy technique involves an initial 6mm punch biopsy to capture epidermis and dermis. A 4mm punch biopsy is then telescoped into the center of the 6mm defect, capturing deeper subcutis [3]. However, histopathologic evaluation may be equivocal and often requires multiple biopsies which can delay treatment [4]. Radiologic imaging may provide a more rapid diagnosis of calciphylaxis in

cases in which skin biopsy pathology is equivocal or pending [5]. Imaging studies, including X-ray and computed tomography, have been suggested to be comparable to histopathology to diagnose calciphylaxis [5,6]. Plain radiography is reported to have a 90% specificity for netlike patterns of calcification [7]. Bone scintigraphy is a highly sensitive (89%) and specific (97%) tool as well [8]. Additional studies report that mammography, ultrasound, and magnetic resonance imaging may play an important role in detecting this disease [9,10].

In our patient, the presence of bilateral ulcers and leg edema from acute on chronic heart failure and the previous diagnosis of stasis dermatitis caused a delay in the identification of this condition (>3 months). Understanding risk factors may improve initial recognition of this disease. Pertinent risk factors for non-uremic calciphylaxis in our patient included female gender, morbid obesity, and a history of corticosteroid and warfarin use. Additional associations include malignancy, liver disease, connective tissue disease, diabetes mellitus, and

derangements in calcium and phosphate homeostasis [11,12]. Identifying risk factors and the underlying etiology is important, as some associations portend a more favorable prognosis. For example, patients with warfarin-associated calciphylaxis have a favorable prognosis [13], whereas patients with nephrogenic calciphylaxis experience worse survival outcomes [14]. In the setting of nephrogenic calciphylaxis, one-year mortality rates are high [11,12,15-17] and up to 50% of patients are bedridden or wheelchair bound [18]. Patients experience chronic, debilitating pain that may influence their quality of life [19].

Notably, our patient had been on warfarin for 6 years and had been switched to apixaban one year prior to this presentation. Warfarin use increases the risk of calciphylaxis by a factor of 3 to 13 [2]. Warfarin uses may precede the onset of calciphylaxis by one to 168 months[13]. The pathogenesis of warfarin-associated calciphylaxis is not fully understood, but evidence supports warfarin's inhibition of vitamin K-dependent matrix Gla protein, which promotes vascular calcification [20]. Warfarin also decreases protein S secretion in endothelial cells, which may promote local coagulopathy [20]. Warfarin-associated calciphylaxis has a more favorable prognosis, with a lower mortality rate (17%) than uremic calciphylaxis (50-80%), [13].

Treatment for calciphylaxis is centered on inhibiting the progression of vascular calcification and correcting the underlying etiology. Strategies to inhibit and decalcify vessels include correcting electrolyte abnormalities and utilizing medications such as sodium thiosulfate and vitamin K. The benefit of sodium thiosulfate has been more thoroughly studied in patients with nephrogenic calciphylaxis.

However, smaller case series have suggested that sodium thiosulfate may also be an effective treatment for non-uremic calciphylaxis, as noted in this case [21]. Regardless of the treatment employed, patient care involves a collaborative, interdisciplinary approach. The interdisciplinary team may include dermatologists, nephrologists, wound care specialists, pain and palliative care physicians, nutritionists, radiologists, and surgical specialists [22]. These specialists played an integral role in diagnosing nonuremic calciphylaxis in our case and developing our treatment plan.

Conclusion

Herein, we describe nonuremic calciphylaxis in a 58-year-old woman presenting with multiple risk factors (morbid obesity, corticosteroid use, and history of warfarin use). This case illustrates the diagnostic challenges of nonuremic calciphylaxis and reviews the risk factors, pathophysiology, differential diagnosis, diagnostic workup, and treatment for this disease. Histopathologic evaluation and radiologic data can be used to diagnose calciphylaxis. Management includes local wound care and systemic sodium thiosulfate. Multidisciplinary collaboration between dermatologists, nephrologists, radiologists, wound care specialists, pain and palliative care physicians, and surgical subspecialists is essential. Increased awareness of this rare disease can lead to an earlier diagnosis and improved patient outcomes.

Potential conflicts of interest

The authors declare no conflicts of interest.

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