CASE REPORT

Development of warfarin-induced, non-uremic calciphylaxis following recovery from COVID-19 infection with acute renal injury – A report of a case.

Briana Halle, BA[1], Lisa Ishii, MD[2], Jeffrey P. Zwerner MD, PhD[2], Eva Rawlings Parker, MD [2]

[1]Vanderbilt University School of Medicine, Nashville, Tennessee, USA
[2]Department of Dermatology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Corresponding author: Eva Rawlings Parker, MD, Assistant Professor of Dermatology, Vanderbilt University Medical Center, Department of Dermatology, 719 Thompson Lane, Suite 2630, Nashville, TN 37204-3609, USA (eva.r.parker@vumc.org)

Received: 11/25/2021 Revised: 2/1/2022 Accepted: 2/14/2022 Published: 3/31/2022

Am j Hosp Med 2022 Jan;6(1):2022. DOI: : https://doi.org/10.24150/ajhm/2022.001

Herein we report a case of an obese female presenting with calciphylaxis after a prolonged hospital course due to COVID-19, with multiple complications including now-recovered acute renal failure and deep venous thrombosis requiring treatment with warfarin. Two months after discharge, she presented with new, painful, ulcerated plaques on the thighs and was diagnosed with calciphylaxis. Throughout the COVID-19 pandemic, cutaneous manifestations of SARS-CoV-2 infection have been increasingly characterized, yet non-uremic calciphylaxis is infrequently observed. Despite its rarity, our case highlights the importance of clinician awareness of the potential association of COVID-19 as an additional trigger for calciphylaxis, especially in patients with multiple risk factors. We also urge physicians to be aware of delayed onset in the presentation of calciphylaxis after renal recovery.

Keywords: calciphylaxis, COVID-19, acute renal injury, adverse drug reaction, anticoagulants

INTRODUCTION

Calciphylaxis results from thrombotic occlusion in narrowed arterioles and is characterized by painful ischemic ulcers with black eschar and associated livedo, purpura, or reticular erythema.[1,2] The highest incidence is seen with end-stage renal disease (ESRD), although calciphylaxis in the setting of normal kidney function is reported.[1,3] Classic histopathology reveals microvascular calcification and thrombosis in subcutaneous and dermal vessels; additional characteristics include ulceration, panniculitis, bulla formation, and epidermal necrosis.[1,3,4]

We report a patient with a recent history of SARS-CoV-2 infection complicated by acute kidney injury (AKI) with associated renal failure who developed calciphylaxis two months after renal recovery. A review of non-uremic risk factors associated with calciphylaxis and the possibility of a delayed-onset presentation of calciphylaxis after COVID-19 infection are discussed.

CASE PRESENTATION

A 39-year-old Caucasian female, with a medical history pertinent for obesity, diabetes mellitus, and a recent 7-week hospitalization for COVID-19, presented two months after discharge with painful, violaceous plaques on the thighs with increasing lesion burden and progressive ulceration. Her previous hospitalization was prolonged and complicated by hypoxemic respiratory failure necessitating extracorporeal membrane oxygenation, AKI presumed secondary to acute tubular necrosis in the setting of septic shock, and deep vein thrombosis treated with warfarin for one month and then transitioned to ongoing therapy with apixaban. Specifically, during her prior admission for Sars-CoV-2 infection, her renal function acutely declined over 24 hours, marked by decreased urine output, worsened eGFR to 40 ml/min/1.73m^2, and elevated creatinine, more than doubling from 0.68 to 1.46 mg/dL (range 0.57-1.11 mg/dL) with subsequent, progressive worsening of this marker. Other labs were notable for elevated potassium to 6.3 mmol/L (range 3.3-4.8 mmol/L), elevated lactate to 15.8 mmol/L (0.5-2.2 mmol/L), and decreased bicarbonate to 16 mmol/L (22 - 29 mmol/L). Following three weeks of intermittent continuous renal replacement therapy (CRRT) and hemodialysis (HD), she was discharged with stabilized urine output and improving creatinine, down-trending from 4.31 to 4.08 mg/dL (range 0.57-1.11 mg/dL). At the time of readmission two months later for skin lesions, her renal function had normalized.

On physical examination, well-defined, violaceous, indurated, retiform plaques with peripheral erythema were noted on the bilateral thighs (Figures 1-2). Many of the lesions were exquisitely painful and demonstrated central ulceration. She was afebrile and hemodynamically stable. Labs were significant for mild anemia, leukocytosis, thrombophilia, elevated inflammatory markers, and positive antinuclear antibody. Other pertinent laboratory values including renal function were unremarkable (Table 1). Bone scintigraphy demonstrated soft tissue uptake in the medial thighs. Punch biopsy of skin from the edge of an ulcer revealed epidermal necrosis with ulceration and dermal inflammation without evidence of vasculitis or vasculopathy. No intravascular thrombi were noted within dermal vessels. Tissue cultures for bacteria, fungus, and mycobacteria were negative.

Given the constellation of clinical and histopathologic findings, the patient was diagnosed with calciphylaxis. Sodium thiosulfate 25g by intravenous infusion was initiated. She was instructed to perform daily wound care with Dakin’s solution, mupirocin 2% ointment, and non-adherent dressings. Following the commencement of therapy, her clinical status stabilized, and the cutaneous lesions demonstrated improvement with reduced size and less induration.

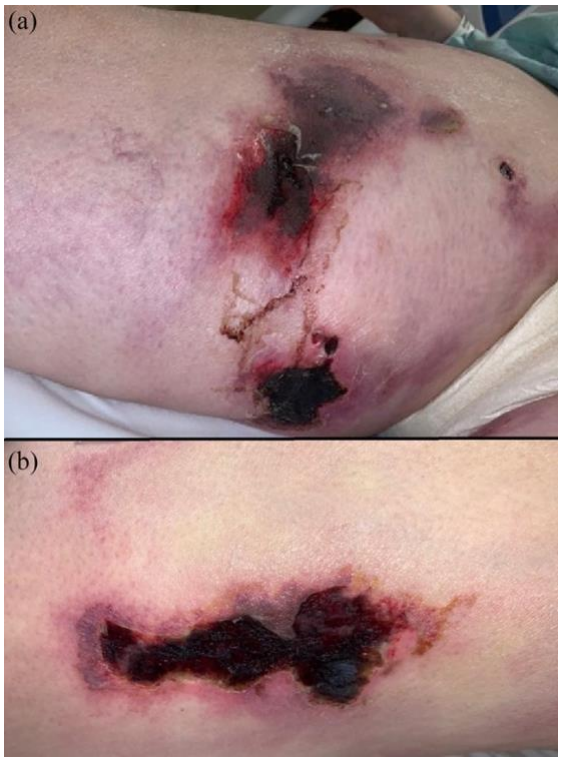

Figure 1. Clinical photographs of the right medial thigh in Panel (a) and the right lateral thigh in Panel (b). Both panels demonstrate indurated, violaceous retiform plaques with large areas of ulceration.

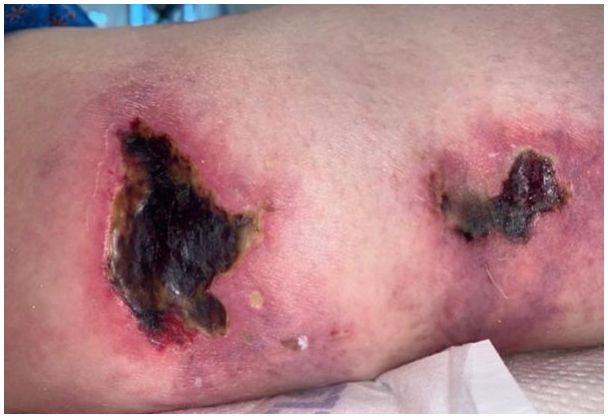

Figure 2. Clinical photograph from the left medial thigh showing large, erythematous, and purpuric plaques with central angulated ulcers with hemorrhagic eschar.

Table 1. Pertinent laboratory results with reference ranges.

Laboratory Test	**Reported Value for Patient**	**Reference Range**
Creatinine	0.74 mg/dL	0.57 - 1.11 mg/dL
Estimated glomerular filtration rate	>60 ml/min/1.73m^2	>60 ml/min/1.73m^2
Blood urea nitrogen	16 mg/dL	7 - 21 mg/dL

Parathyroid hormone	47 pg/mL	16 - 77 pg/mL
Total serum calcium	8.8 mg/dL	8.4 - 10.5 mg/dL
Serum phosphorus	4.2 mg/dL	2.3 - 4.7 mg/dL
White blood cells	12.3 x 10^3/mcL	3.9 - 10.7 x 10^3/mcL
Hemoglobin	9.0 gm/dL	11.8 - 16.0 gm/dL
Hematocrit	29%	36 - 43%
Platelets	614 x 10^3/mcL	135 - 371 x 10^3/mcL
C-Reactive protein	59.2 mg/dL	0 - 5.0 mg/dL
Erythrocyte sedimentation rate	56 mm/hr	2 - 37 mm/hr
C3 level	153 mg/dL	88 - 201 mg/dL
C4 level	26 mg/dL	10 - 40 mg/dL
Anti-nuclear antibody	1:320, speckled/smooth pattern	Negative
Anti-neutrophil cytoplasmic antibody	Negative	Negative
Anti-dsDNA antibody	Negative	Negative
Cryoglobulins	Negative	Negative
Rheumatoid factor	Negative	Negative

DISCUSSION

To the authors' knowledge, this is only the second reported case of non-uremic calciphylaxis following COVID-19.[5] The pathogenesis of calciphylaxis is thought to be multifactorial, involving an imbalance of calcium and phosphate levels that results in the formation and deposition of calcium-phosphate crystals contributing to chronically narrowed vessels.[2] Traditionally, calciphylaxis occurs in the setting of renal failure, which disrupts the normal concentrations of these electrolytes due to decreased renal phosphate excretion and secondary hyperparathyroidism. Other disorders that impact this mineral balance are associated with calciphylaxis including primary parathyroid dysfunction and hyperthyroidism.[2]

The development of calciphylaxis in non-uremic patients is theorized to occur through a series of unique mechanisms. An association between bone mineral loss and vascular calcification has been noted, suggesting the potential influence of regulators of bone mineralization and resorption on the development of calciphylaxis.[2] One such regulator is nuclear factor kappa-beta activation, a transcription factor induced by infection and inflammation, whose overactivity is

associated with atherosclerosis, vascular mineral deposition, and bone mineral loss.[2] Other documented risk factors for non-uremic calciphylaxis include obesity, diabetes mellitus, malignancy, systemic corticosteroid use, hyperparathyroidism, Caucasian race, and female gender.[1,3,6] Prothrombotic states are also implicated.[1,5,7,8] Warfarin use is associated with as much as a 13-fold increased risk of calciphylaxis. As a vitamin K antagonist, warfarin is thought to predispose to calciphylaxis through a reduction in levels of matrix-gla protein, an inhibitor of microvascular calcification whose carboxylation is vitamin K-dependent.[1]

While calciphylaxis has been reported in uremic patients and less commonly in non-uremic cases, the impact of transient renal failure on the development of calciphylaxis is less clear, as only two previous reports of calciphylaxis presenting after renal recovery are documented in the literature.[9,10] With the onset of calciphylaxis two months after renal recovery, along with the presence of other risk factors, this case suggests the potential role transient renal failure may play in the development of calciphylaxis, especially when concurrent precipitating events and comorbidities exist. The temporal correlation of transient uremia, even with subsequent recovery and normalization of renal function, with the development of calciphylaxis should be investigated in more depth to elucidate its significance as an etiologic driver in this disease.

Further complicating our case, calciphylaxis has been associated with COVID-19, potentially suggesting precipitation of calciphylaxis by SARS-CoV-2 infection.[11] Calciphylaxis is hypothesized to develop from local or systemic hypercoagulable states inciting thrombosis in chronically calcified, narrowed vessels.[1] Infection with the SARS-CoV-2 virus results in significant inflammation, abnormal coagulation parameters, and endothelial damage through the virus' tropism for ACE2 receptors, disrupting intrinsic antithrombotic properties and leading to a vasculopathic state.[12] Thus, the thrombotic vasculopathy seen with COVID-19 may contribute to the development of calciphylaxis in patients with concurrent risk factors such as the patient described herein who is an obese, diabetic, Caucasian female with recent warfarin use.[11] However, the timing of calciphylaxis with SARS-CoV-2 infection is less consistent. Previous reports of uremic-associated disease describe its development within a month following COVID-19 diagnosis.[5,11,13] In our case, the manifestations of calciphylaxis began much later, presenting 3 months after infection and 2 months after recovery of renal function and discontinuation of warfarin.

Given the high mortality rate,[3,6,8] early diagnosis of calciphylaxis remains paramount. Clinicians should maintain a heightened index of suspicion for calciphylaxis in patients with a history of COVID-19. Additionally, careful consideration of the risk-benefit ratio for warfarin use in patients with known comorbidities may assist in preventing calciphylaxis in at-risk patients. We urge physicians to be aware of the possibility of a delayed-onset presentation of calciphylaxis and recommend that at-risk patients be closely monitored.

Notes
There were no sources of funding for this work.

Potential conflicts of interest: The authors have no conflicts of interest to declare.

References

1. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med. 2018;378(18):1704–1714. doi: 10.1056/NEJMra1505292

2. Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor κ-B. J Am Acad Dermatol. 2008;58(3):458–471. doi: 10.1016/j.jaad.2007.12.006

3. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from Nonuremic Causes: A Systematic Review. Clin J Am Soc Nephrol. 2008;3(4):1139–1143. doi: 10.2215/CJN.00530108

4. Bahrani E, Perkins IU, North JP. Diagnosing Calciphylaxis: A Review With Emphasis on Histopathology. Am J Dermatopathol. 2020;42(7):471–480. doi: 10.1097/DAD.0000000000001526

5. Mathur N, Duffy RF, Chinn B, et al. Nonuremic calciphylaxis in a COVID-19 patient. Int J Dermatol 2021;60(9):1154-1155. doi: 10.1111/ijd.15661

6. Bajaj R, Courbebaisse M, Kroshinsky D, Thadhani RI, Nigwekar SU. Calciphylaxis in Patients With Normal Renal Function: A Case Series and Systematic Review. Mayo Clin Proc. 2018;93(9):1202–1212. doi: 10.1016/j.mayocp.2018.06.001

7. Harris RJ, Cropley TG. Possible role of hypercoagulability in calciphylaxis: review of the literature. J Am Acad Dermatol. 2011;64(2):405–412. doi: 10.1016/j.jaad.2009.12.007

8. Kalajian AH, Malhotra PS, Callen JP, Parker LP. Calciphylaxis With Normal Renal and Parathyroid Function: Not as Rare as Previously Believed. Arch Dermatol. 2009;145(4): 451-458. doi: 10.1001/archdermatol.2008.602

9. Azarchi, S; Sunseri, M; Kramer, P; Smith, J. Calciphylaxis After Acute Kidney Injury. Abstract presented at Hospital Medicine 2017, May 1-4, 2017; Las Vegas, NV. Abstract 341. J Hosp Med. 2021;12(Suppl2). https://shmabstracts.org/abstract/calciphylaxis-after-acute-kidney-injury/

10. Oda T, Sawada Y, Yamaguchi T, et al. Calciphylaxis following acute renal injury: a case and literature review. Springerplus. 2016;5(1):1043. doi:10.1186/s40064-016-2740-1

11. Bitar C, Chan MP, Harms PW, et al. Cutaneous manifestations of hospitalized coronavirus disease 2019 patients: a report of six cases with clinicopathologic features and viral RNA in situ hybridization. J Eur Acad Dermatol Venereol. 2020;34(11):e656–e659. doi:10.1111/jdv.16741

12. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033–2040. doi: 10.1182/blood.2020006000

13. Abutaki FH, Alfaraj D, Alshahrani A, Elsharkawy T. Warfarin-Induced Calciphylaxis in a COVID-19 Patient. Cureus. 2020;12(12):e12249. doi: 10.7759/cureus.12249