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Case Report

Chronic skin ulcers in hemodialysis patient: A fatal case of calciphylaxis ☆,☆☆

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ABSTRACT

Calciphylaxis is a rare and deadly vascular disease with poorly understood pathophysiology and without definitive treatment. Early presentations include skin ulcers with risk factors including end stage renal disease on hemodialysis, hypertension, hyperlipidemia, and diabetes mellitus. In our case, we present an 80-year-old female with multiple risk factors including hemodialysis and clinical features of necrotic and gangrenous skin lesions diagnostic of calciphylaxis who became hemodynamically unstable and ultimately expired secondary to toxic sequelae. We illustrate this case to explore early clinical presentation, limitations of current disease management and treatments, and the role for further studies to improve diagnosis and reduce mortality.

Introduction

Calciphylaxis is a serious arteriolopathy with high possibilities of fatal outcomes. One study demonstrated 6 months survival to be at 50% [1]. Although the pathophysiology remains an uncharted territory, the current understanding highlights mechanisms of microcalcifications and thrombosis within the cutaneous and subcutaneous adipose arterioles through parathyroid hormone, vitamin D, lack of mineralization inhibitory factors, and chronic inflammatory cascades. Its rarity can be demonstrated by its incidence rate of 3.49 per 1000 in the western hemisphere, specifically among patients with end stage renal disease (ESRD) on hemodialysis (HD) which is considered the most prominent risk factor. Although studies are scant, existing literature has identified potential concomitant risk factors among patients with ESRD including diabetes mellitus (DM), female sex, and medication use such as Warfarin, vitamin D, and calcium binders. Early clinical presentation is highlighted by characteristic, significantly painful lesions that begin cutaneously or subcutaneously in areas of increased adiposity, the distal lower extremities being

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Fig. 1 – Right lower extremity with foul-smelling, frank purulent discharge covered in topical cream.

the most affected, then rapidly progressing into necrosis with a black eschar and a possible sequelae of gangrene. The first lesion may represent as purple-like, plaque-like, livedo reticularis or indurative. Diagnosis is mainly clinical and based on the calciphylaxis lesions. Although skin biopsy remains the gold standard for confirmation, it may not be an absolute necessity when clinical suspicion is high based on findings mentioned as above. Treatment is not completely established without evidence-based guidelines due to lack of studies; however, the most common modality is a multidisciplinary approach with pain control, wound care, and early surgical intervention when necessary. While treatment remains challenging in many scenarios, new therapies have been slowly investigated including tissue plasminogen activator, sterile maggot therapy, and vitamin K supplementation [2,3]. We present a case of an 80-year-old patient with ESRD on HD who presented with calciphylaxis progressing into wet gangrene and sepsis requiring urgent surgical intervention [4–6].

Case presentation

The patient was an 80-year-old female with a medical history of ESRD on HD, hypertension, hyperlipidemia, and DM who presented with multiple skin lesions on her upper and lower extremities. She states that the lesions located on the right foot were foul-smelling and purulent with subjective fever for the past 2 days. The lesions started as multiple, hardened painful bumps under the skin that rapidly progressed into bruise-like and dark maroon discoloration with indentation. The patient had been applying topical hydrocortisone, lidocaine wound gel, aloe vera gel, and aquaphor (mineral oil-hydrophil petrolat) daily. Prior to the onset of the skin lesions, the patient had been experiencing severe episodes of diffusely dry, scaly, and itchy skin for weeks. The patient started HD 1 year before presentation; however, she has not been able to tolerate her sessions recently due to recurrent episodes of hypotension requiring early termination. Her medications included Sitagliptin 50 mg once daily, Repaglinide 1 mg 3 times daily, Losartan-Hydrochlorothiazide 100-25 mg once daily, Amlodipine 10 mg once daily, Terazosin 5 mg once nightly, and Sevelamer 800 mg twice daily. Vital signs on admission revealed blood pressure 114/53 mm Hg, heart rate 84 beats per minute, respiratory rate 18 respirations per minute, oxygen saturation of 96% on room air, and temperature of 97.9°F. On physical examination, she was ill-appearing, frail and cachectic, normal heart and lung sounds with multiple skin lesions on bilateral lower extremities and bilateral upper extremities; however, they were all covered with what seemed to be dried, thick layers of white topical agents. Her right lower extremity lesion was foul-smelling with frank purulent discharge concerning for wet gangrene (Fig. 1).

Pertinent laboratory findings included elevated white cell count 20.9 $\times$ 10^3/mcL (reference rage 4.80-10.80 $\times$ 10^3/mcL), hemoglobin 8.0 g/dL (reference range 12.0-16.0 g/dL), potassium 4.2 mmol/L (reference range 3.5-5.1 mmol/L), calcium 8.4 mg/dL (reference range 8.6-10.3 mg/dL), phosphorus 2.6 mg/dL (reference range 2.5-4.5 mg/dL), creatinine 1.8 mg/dL (reference range 0.50-1.20 mg/dL), and BUN 21 mg/dL (ref-

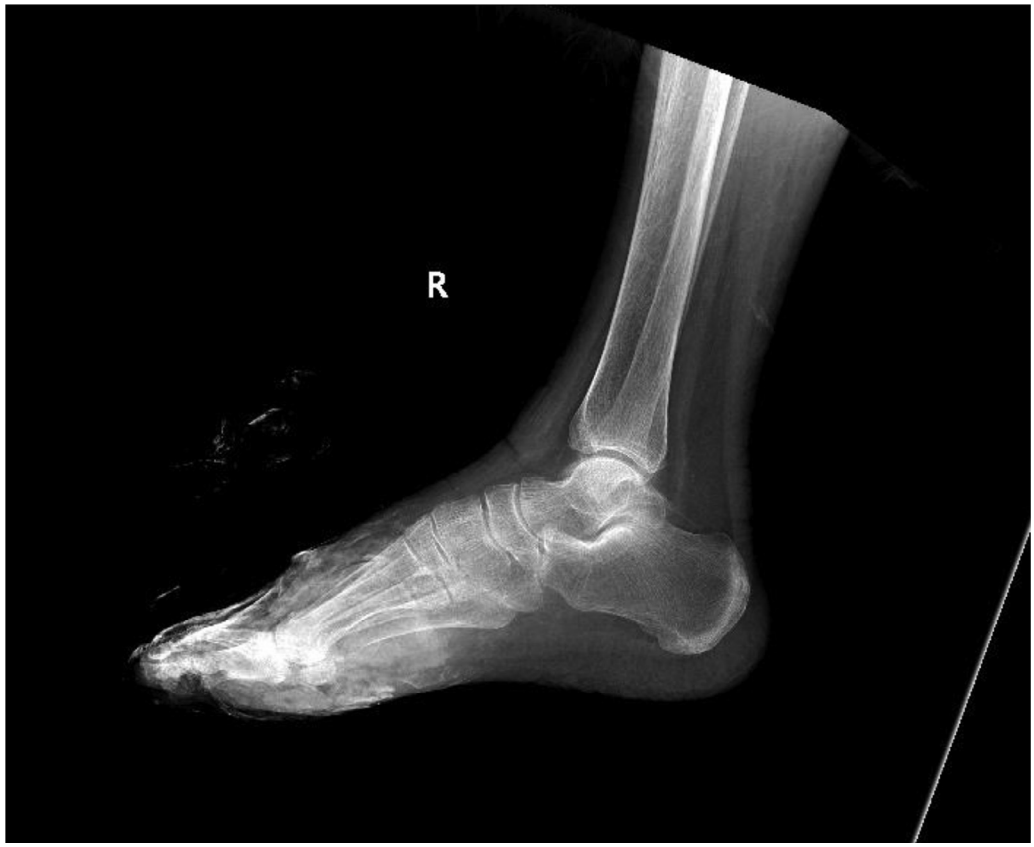

Fig. 2 – Radiographic imaging of the right lower extremity showing radiodense material on the cutaneous tissues likely secondary to therapeutic ointment, obviates full assessment of the osseous structure without loss of articular cartilage at the first MTP and lytic osseous focus.

erence range 6.0-23.0 mg/dL). Two sets of blood cultures showed no growth and urinalysis was unremarkable. A full assessment of bone and soft tissue on radiographic imaging of the right lower extremity was obstructed by dense layers of dried topical creams that amalgamated with the necrotic lesion (Fig. 2). Surgery was consulted and the patient underwent emergent right-sided below-the-knee amputation on admission for source control and was placed on an appropriate antibiotics regimen including vancomycin 1 g daily for 3 days and piperacillin-tazobactam 2.25 g every 8 hours for 10 days with improvement. However, her ability to tolerate HD steadily declined within 1 week of admission due to intradialytic hypotension requiring pressor support. All of her home blood pressure medication was stopped and midodrine was started but the patient still could not tolerate it. As a result of incomplete HD sessions, she developed bilateral pleural effusions leading to flash pulmonary edema and respiratory distress prompting intubation on day 11 of admission. Concurrently, the patient was found to have COVID-19 infection with CT of chest with contrast findings concerning for superimposed pneumonia, cultures grew pseudomonas and was treated with meropenem 1 g daily for 7 days (Fig. 3). Prior to hospitalization, the patient received 1 dose of the monovalent COVID vaccine. Subsequently, she remained afebrile and repeated blood cultures negative. Broad infectious investigation for her acute decompensation was unrevealing; transthoracic echocardiogram with an ejection fraction of 60% without evidence of endocarditis. Her hemoglobin was stable around her baseline. The patient was successfully extubated 5 days after intubation, and 2 days later, her supplemental oxygen requirement was titrated down to room air. After family discussions about the viability of on-going HD and the patient's guarded prognosis, they elected to withdraw care on day 23 of admission, including skin biopsy, and pursue comfort care, and ultimately the patient passed away 5 days later on day 28 of admission. Family declined to autopsy.

Discussion

One of the most challenging aspects of calciphylaxis is the treatment, mainly due to the absence of evidence-based clinical trials. The majority of treatment methodologies have been anecdotal, stemming from retrospective case reports, case series, and cohort studies. However, the common denominator among all articles has been a multidisciplinary approach to focus on wound care and pain control with the ultimate goal to prevent systemic infection and complications [7]. Two of the main reasons contributing to the lack of clinical trials are the ambiguity of the disease's pathophysiology in addition to its high morbidity and mortality, the latter being 40% at 6

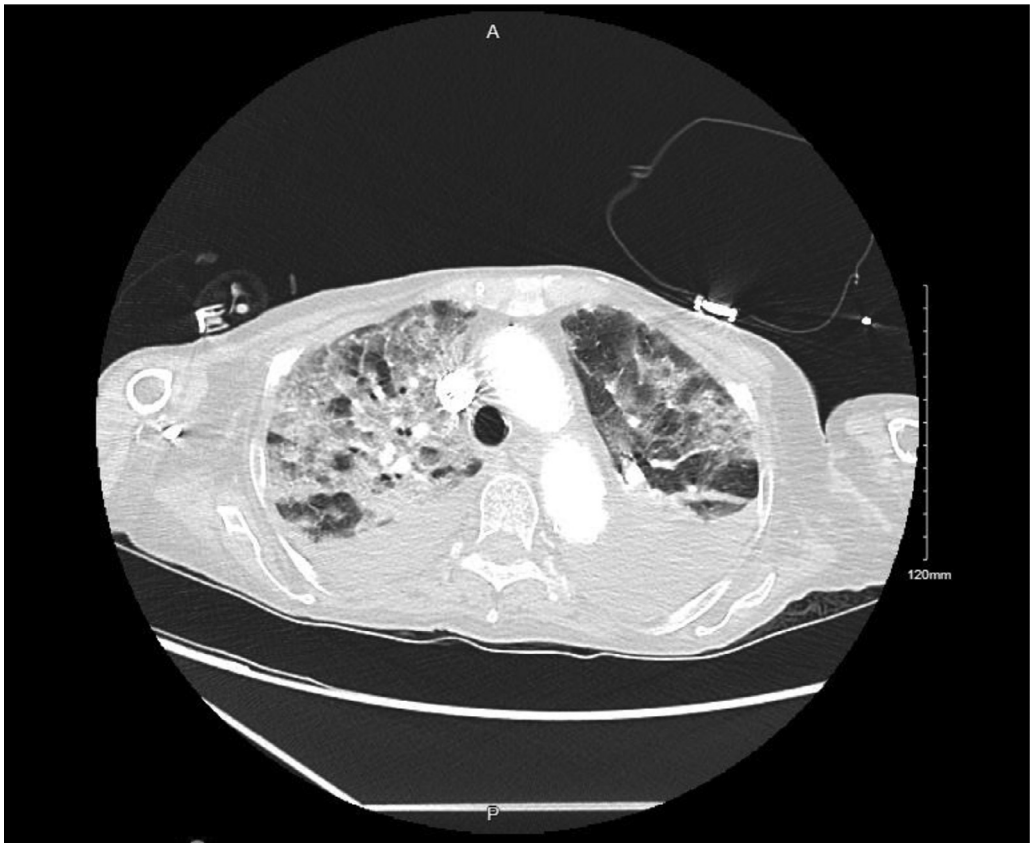

Fig. 3 – Computed tomography with contrast of chest showing multifocal airspace opacities bilaterally representative of infection and/or pulmonary edema with moderate sized bilateral pleural effusions.

months and 44%, respectively, at 1 year, hindering the ability to recruit long-term patients [1]. Among the risk factors, HD is associated with higher rates of morbidity and mortality. In addition, certain medications such as calcium-containing phosphate binders are very likely precipitants and complicators of the disease due to an apparent role of phosphate and calcium derangements among previously reported cases and their outcomes [6,7]. Our patient had both of these risk factors. Skin ulcers are the earliest and only known presenting clinical findings. They may be the initial sign at any stage of their appearance or progression, ranging from subcutaneous painful nodules to necrosis with dry or wet gangrene, the latter being our patient's case.

Infection is a common complication of calciphylaxis and early debridement is associated with relatively better outcomes. In fact, the main driver of calciphylaxis' high morbidity and mortality are superimposed infections [8]. Therefore, thorough infectious workup was completed in our case including blood cultures, chest radiographs, and CT with appropriate treatment for pneumonia, transthoracic echocardiogram to rule out and as well as below the knee amputation by surgery for source control of right lower extremity wet gangrene. Although surgical intervention and aggressive antibiotic therapy hindered and reversed the toxic sequelae of our patient, rapidly declining hemodynamic stability during HD was the ultimate decision maker in her terminal case.

In addition, vitamin K deficiency is thought to be a provoking factor for calciphylaxis in patients with ESRD on HD. Vitamin K activates matrix gamma-carboxyglutamic acid protein leading to inhibition tissue and vascular calcification. Patients with ESRD on HD are recommended to minimize sodium and potassium intake which inadvertently eliminates foods rich in vitamin K [9]. In this case, vitamin K levels were not checked. In a phase 2 randomized placebo-controlled trial, vitamin K supplementation reduced mortality and healed ulcers over weeks [10]. It remains unclear if repletion would have benefited as our patient rapidly deteriorated.

Some of the literature reports calciphylaxis in extra-dermatological tissues such as lung, brain, and muscle as evident on either imaging or histological specimens [11]. It is unclear whether calciphylaxis affects only arterioles or additional levels of vasculature outside of the integumentary system, making this area of pathophysiology worth exploring especially in patients on HD. Our patient's gradual inability to tolerate any form of HD due to intradialytic hypotension, even with pressor support, had led us to a hypothesis that the disease's microcalcifications may have led to arteriolar sclerosis and an inability to increase vascular resistance making dialysis obsolete. This potential area is of great clinical relevance for patients dependent on HD.

Conclusion

Calciphylaxis is a rare disease with a poorly understood pathophysiology. Diagnosis is usually clinical with skin ulcer-

ations typically being the early clinical presentation and the treatment is symptomatic with surgical intervention when needed. Despite attempts to find new treatment measures, outcomes remain poor especially in hemodialysis patients. Further studies are needed to establish a streamlined and evidence-based approach to dealing with calciphylaxis.

Author contributions

Conceptualization: Jawad Shabani, Vaibhav Shah; Writing - original draft preparation: David Song, Jawad Shabani, Vaibhav Shah, Vikash Jaiswal; Writing - review and editing: David Song, Vikash Jaiswal, Akanksha Sharma; Funding acquisition: None.

Patient consent

A written informed consent was obtained from the patients for publication of this case and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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