Atypical Warfarin-Induced Calciphylaxis Outside a Typical Presentation of End-Stage Renal Disease on Hemodialysis

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ABSTRACT

We present a case report highlighting a 47-year-old woman who developed warfarin-induced calciphylaxis. She initially developed bilateral leg wounds secondary to restraint straps from helicopter transportation to a higher level of care for treatment of critical aortic stenosis. She was started on warfarin following surgical implantation of a mechanical aortic valve. After her wounds failed to heal, a punch biopsy of the wounds demonstrated ulceration, altered vasculature, and soft tissue calcification. The pathology confirmed the clinical concern for calciphylaxis, which is most often diagnosed in patients with a history of end-stage renal disease on hemodialysis. However, our patient did not demonstrate evidence of renal disease prior to the onset of calciphylaxis. Her wounds began to heal after treatment with sodium thiosulfate and changing her anticoagulation from warfarin to rivaroxaban.

INTRODUCTION

Calciphylaxis is a rare ischemic skin lesion caused by calcium-mediated obstruction of dermal and subcutaneous microvasculature. Its pathogenesis is not well-known but is hypothesized to be due to an imbalance between mineral and bone transcription factors within vascular endothelial cells.[1] It is most commonly observed in patients with end-stage kidney disease, diabetes mellitus type 2, hypoalbuminemia, autoimmune disease, liver diseases, or malignancies. It also has been associated with medications, including warfarin, corticosteroids, calcium-based phosphate binders, or activated vitamin D.[2] While assessing dermatologic lesions during warfarin administration, histological analysis via punch biopsy is essential, as warfarin-induced skin necrosis can commonly present similarly to calciphylaxis. Warfarin-associated calciphylaxis is more common in female patients and usually occurs below the knee. The time between initiating warfarin therapy and the onset of calciphylaxis is, on average, 32 months. Furthermore, survival rates among patients with warfarin-associated calciphylaxis are distinctly improved from patients with comorbidities, specifically end-stage kidney disease.[3]

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CASE REPORT

A 47-year-old woman presenting with dyspnea, bilateral lower extremity edema, pulmonary vascular congestion, and a right-sided pleural effusion was admitted with suspected acute heart failure. A transthoracic echocardiogram demonstrated a mildly dilated right ventricle, a reduced ejection fraction of 20% to 25%, mild thickening of the mitral valve, and a normal tricuspid valve. Most concerning was a severely calcified and stenotic aortic valve with severely restricted movement. She was diagnosed with symptomatic critical aortic stenosis and was admitted to a critical access facility without cardiothoracic surgery capacity. Given the urgency of her clinical condition, she was airlifted to an appropriate facility. During air transport, she suffered bilateral pressure wounds from safety straps. She subsequently underwent a surgical aortic valve replacement with a metal valve. Warfarin was started after surgery as is the standard of care with mechanical heart valves.

Approximately 1 month after her aortic valve replacement and initiation of warfarin therapy, the patient presented to the emergency department concerned about nonhealing wounds on her legs. The pressure wounds from her helicopter transport had worsened since discharge. They were dark purple, increasingly tender, and growing larger in diameter. One spot appeared ulcerated with surrounding erythema, while other smaller locations appeared flat without ulceration. She did not endorse any sys temic symptoms.

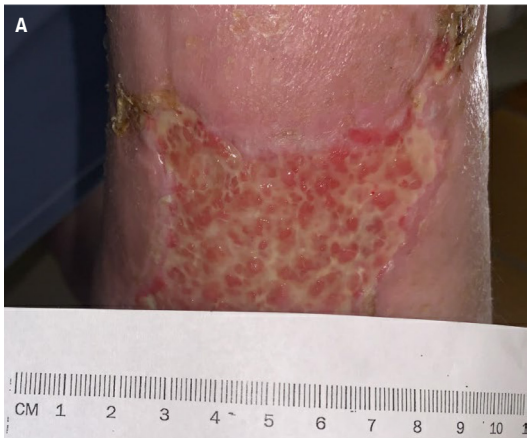
She was diagnosed with bilateral leg cellulitis and started on oral antibiotics.

Over the next month, more lower leg lesions developed, and her original wounds worsened, despite the antibiotics. A vascular workup found a normal ankle-brachial index and no evidence of vascular insufficiency. Further workup for endocrine pathologies, liver disease, and malignancy was negative. She was not using exogenous corticosteroids and did not demonstrate adrenal insufficiency.

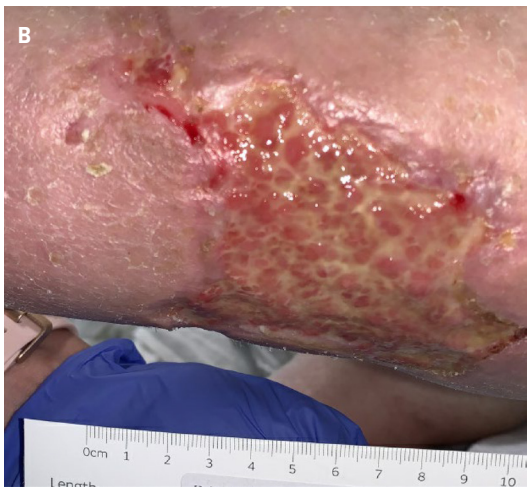
The wound clinic provider performed a punch biopsy of one of the patient's most tender areas of ulceration. The biopsy demonstrated altered vasculature and soft tissue calcification consistent with calciphylaxis. She was referred to dermatology for a second evaluation, and they agreed with the diagnosis of calciphylaxis. Given she had normal kidney function and had never required kidney replacement therapy, warfarin was the most likely cause, despite the low incidence of that complication. Dermatology recommended that she be started on sodium thiosulfate 25 grams intravenously 3 times a week.

The patient's cardiologist recommended discontinuation of warfarin and switching to rivaroxaban. Direct-acting oral anticoagulants (DOACs) typically are not recommended in the setting of mechanical heart valves; however, it was deemed appropriate given her diagnosis of calciphylaxis secondary to warfarin use. In her situation, off-label use of DOACs was necessary despite the mechanical valve. Without discontinuation of warfarin, the lesions were likely to progress. Wounds did appear to show clinical stability without progression once warfarin was discontinued. After starting treatment with sodium thiosulfate and discontinuation of warfarin, her wounds began to heal slowly. Healing only after discontinuing warfarin and starting treatment confirmed the diagnosis. The images included in this report were taken 2 months after she was started on treatment and changed to rivaroxaban (Figure). She continues to be seen by her wound clinic and the prognosis for complete healing is thought to be very good.

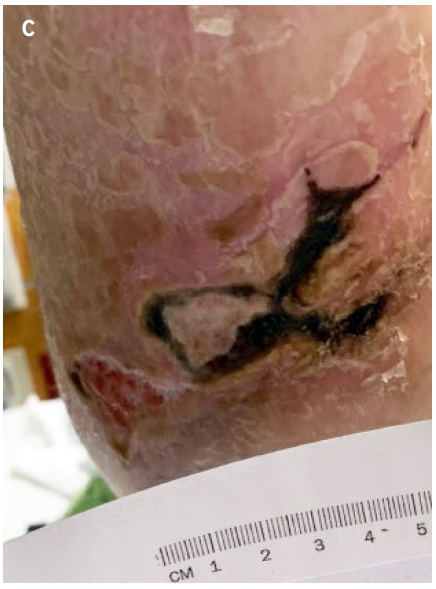
Figure. Clinical Images of Lesions at Presentation



A. Right Posterior Lower Extremity Wound



B. Left Lateral Lower Extremity Wound



C. Right Posterior Lower Extremity Wound

DISCUSSION

Diagnosis of Calciphylaxis

Our patient demonstrated nonhealing leg wounds bilaterally (Figure). She had punch biopsies from both legs that revealed ulcerations with alteration of vasculature, fat necrosis, and soft tissue calcification within medium and large vessels in a mockingbird-like fashion. Inflammatory changes were not noted to be consistent with infectious etiology. Other thrombotic vasculopathies associated with trauma could have a similar appearance, although a nearly symmetric demonstration in the bilateral lower extremities is highly unlikely.

Our patient demonstrated evidence of calciphylaxis within 3 months of starting warfarin therapy, which is remarkably different from the typical 32-month onset. It is also worth highlighting that calciphylaxis in our patient developed on the site of preexisting

wounds rather than spontaneous calciphylaxis. Traditional non-warfarin-induced calciphylaxis is typically irreversible and carries a poor prognosis. It is important to note that warfarin-induced calciphylaxis can be treated effectively with the discontinuation of warfarin and the initiation of sodium thiosulfate.

Use of Warfarin

Warfarin is the anticoagulant of choice in the setting of mechanical heart valves, and for many people, it is well tolerated. Patient adherence and monitoring can be difficult as they require frequent lab monitoring and dietary changes. Warfarin is metabolized by the cytochrome P450 system; medications and foods that interact with the P450 system can interfere with warfarin anticoagulation. For this reason, there is a growing trend to begin using DOACs, such as rivaroxaban and apixaban when possible.

In our patient's case, the initial gold standard of care was administered with the use of warfarin in the setting of mechanical heart valves. Also, given her medical presentation, other diagnoses outside of warfarin-induced calciphylaxis were considered, and warfarin-induced skin necrosis, vasculitis, and infection were excluded as likely causes. This case does raise the question of using DOACs in the setting of a mechanical heart valve. Currently, their use is considered off-label with mechanical valves.[4] Further investigation and research could be appropriate to compare long-term outcomes using DOACs in patients unable to tolerate warfarin therapy. Given the lack of clinical evidence and no Food and Drug Administration approval, it should not be considered standard of care to start a patient first-line on DOACs over warfarin therapy in the setting of mechanical heart valves.

CONCLUSIONS

Calciphylaxis is a rare condition in patients with end-stage kidney disease on hemodialysis and even rarer as a complication of warfarin use. The case described here had several unique aspects that add to the medical literature. The patient's skin lesions appeared to start at the site of existing trauma—a phenomenon not described in the literature to our knowledge. The biopsy showing calciphylaxis was obtained after only 2 months of initiating warfarin therapy, which is sooner than the typical 32-month onset. She appeared effectively anticoagulated on a DOAC in the setting of a metal heart valve, which is not well-described in the literature. This case report suggests that clinicians should always consider calciphylaxis as a complication in people taking warfarin. Further studies are needed to evaluate the efficacy of DOACs for mechanical heart valves.

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