

CLINICAL IMAGE

NON-HEALING LEG LESION

Melissa Hubley, DO, PGY-3

Tower Health Reading Hospital Family Medicine Residency, Reading, PA

INTRODUCTION

A 58-year-old female with a past medical history significant for end-stage renal disease on hemodialysis and type 2 diabetes mellitus presented to the emergency room with cough and fatigue that was attributed to a viral upper respiratory tract infection and missed dialysis sessions. However, she was incidentally noted to have a one-week history of a painful, non-healing lesion on the right leg. (Figure 1) The patient denied any history of trauma or injury preceding the development of the leg lesion. Additionally, she denied fever, as well as redness or warmth of the affected leg. Physical examination was significant for two large, violaceous plaques with irregular borders on the posterior calf. A small central eschar was noted in the proximal lesion. The skin was otherwise intact. No notable erythema or exudate was surrounding the lesion. Bloodwork done in the emergency room demonstrated a white blood cell count within normal range.

FIGURE 1:

Right posterior calf lesion on initial presentation



CORRESPONDENCE:

Melissa Hubley, DO | Melissa.hubley@towerhealth.org

Three weeks later, the patient was re-admitted to the hospital with multifocal pneumonia. During this admission, she was found to have worsening of her right posterior calf lesion. (Figure 2) Physical examination revealed that a majority of the distal lesion was now encased in necrotic, black eschar. As before, there was no significant warmth to the touch, erythema or purulent exudate of the lesion. The radiograph was negative for bony destructive changes.

FIGURE 2:

Right posterior calf lesion three weeks later



QUESTIONS:

1. What is the most likely diagnosis?
 - A. Squamous cell carcinoma
 - B. Venous ulcers
 - C. Calciphylaxis
 - D. Pressure ulcers
2. Which patient population is at the highest risk for this diagnosis?
 - A. End-stage renal disease
 - B. Congestive heart failure
 - C. Coronary artery disease
 - D. Diabetes mellitus
3. What is the treatment of choice for this condition?
 - A. Warfarin
 - B. Intravenous sodium thiosulfate
 - C. Vitamin D
 - D. All of the above

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ANSWERS:

1. What is the most likely diagnosis?

Correct Answer:

C.) Calciphylaxis

The most likely diagnosis for this patient's leg lesion is calcific uremic arteriolopathy or calciphylaxis. Calciphylaxis is a rare syndrome seen primarily in patients with end-stage renal disease, characterized by areas of intense pain and ischemic necrosis of the subcutaneous fat and dermis.¹⁻³ Calcification of arterioles and capillaries in these regions is thought to lead to chronic ischemia. Clinically, this presents as changes to the overlying skin. Lesions can initially present in various ways but rapidly progress to characteristic necrotic ulcers with black eschars.^{1,4-6} In this patient, medical history and the unique physical appearance of the lesions are suggestive of calciphylaxis.

Differential includes cellulitis, skin carcinoma, venous ulcers, arterial ulcers, pressure ulcers, diabetic ulcers and pyoderma gangrenosum. There was no leukocytosis, erythema/warmth or purulent exudate on examination suggestive of cellulitis. Squamous cell carcinoma typically appears as a smooth or hyperkeratotic papule/plaque with central ulceration in a sun-exposed region.⁷ The location in this patient would be atypical for a squamous cell carcinoma. Melanoma presents in a variety of ways and is beyond the scope of this current article. Venous ulcers are often irregular, shallow and located over bony prominences, such as the medial malleolus.⁸ In this patient, the lesion was located on the posterior calf, not a typical location of a venous ulcer.

Additionally, the patient was ambulatory upon presentation, making pressure ulcers of the posterior calf unlikely. This patient had diabetes, so diabetic ulceration was on the differential. However, one would expect a diabetic ulcer to develop on the plantar aspect of the foot, likely in the setting of extensive callus formation.⁹ The history provided in this case did not fit this description.

Similar to this patient's lesion, arterial ulcers can produce eschars; however, this patient did have palpable pulses. Notably, throughout several admissions, the patient underwent a comprehensive vascular evaluation with no significant findings seen in the ipsilateral extremity.

2. Which patient population is at the highest risk for this diagnosis?

Correct Answer:

A.) End-stage renal disease

Calciphylaxis is most often seen in patients with end-stage renal disease, although it can occur in earlier stages of chronic kidney disease and occasionally patients with normal renal function.¹⁻³ Diabetes mellitus is also a risk factor for calciphylaxis,^{1,10} but it is not as strongly associated with the condition as end-stage renal disease. Notably, calciphylaxis is rare; even in patients with risk factors, most never develop the condition.¹

3. What is the treatment of choice for this condition?

Correct Answer:

B.) Intravenous sodium thiosulfate

Although treatment remains under investigation, sodium thiosulfate is often given in the treatment for calciphylaxis.^{1,6,11} Warfarin is associated with an increased risk of developing calciphylaxis and should be discontinued.^{6,10} Additionally, vitamin D supplementation should be stopped during treatment.¹

DISCUSSION

Calciphylaxis, or calcific uremic arteriolopathy, is a rare, life-threatening syndrome that primarily affects patients with end-stage renal disease.¹⁻³ Although the exact pathogenesis is unknown, in calciphylaxis, calcification of arterioles and capillaries in the subcutaneous fat and dermis leads to chronic ischemia.¹ Subsequent endothelial injury and microthrombosis cause further occlusion of associated vessels. This presents clinically as painful, ischemic skin lesions. Lesions can initially present in various ways, including induration, livedo reticularis or violaceous, plaque-like subcutaneous nodules.⁴⁻⁶ These initial lesions classically progress to necrotic ulcers with black eschars.^{1,4-6}

Calciphylaxis is rare, with an annual incidence of 35 per 10,000 patients on hemodialysis in the United States.¹⁰ Risk factors include end-stage renal disease, diabetes mellitus, female sex, obesity, hyperphosphatemia, hypercalcemia, hyperparathyroidism and warfarin use, among others.^{1,6,10}

However, most patients with risk factors do not develop calciphylaxis. It is thought that an inciting event in patients with underlying risk factors likely triggers the development of calciphylaxis, such as repetitive trauma from subcutaneous injections.¹⁰ However, in many cases, no clear trigger is identified.¹

Diagnosis may be made via clinical suspicion alone in patients with classic presentation. Skin biopsies may be used to confirm clinical suspicion; however, this practice is often discouraged due to the risk of developing new non-healing ulcers and sampling error.⁶

Treatment remains under investigation. Modalities include wound care, pain control and infection prevention. Additionally, correction of abnormal calcium and phosphate levels should be undertaken, including stopping vitamin D supplements, intensifying dialysis regimens and using low/non-calcium-containing phosphate binders.^{1,6} Warfarin should also be held and vitamin K supplementation considered.

Although there are no approved therapies for calciphylaxis, one medication often given in the treatment of calciphylaxis is sodium thiosulfate. Sodium thiosulfate works by increasing the solubility of calcium.¹¹ It is administered intravenously at the end of every hemodialysis session. Efficacy has been demonstrated in case studies, but randomized controlled trials are currently under investigation.¹

Despite advancements in treatment, calciphylaxis remains a life-threatening syndrome with high morbidity and mortality. The one-year mortality rate is estimated to be 45–52% in those with end-stage renal disease.^{8,10,12}

CONCLUSION

In this case, nephrology was consulted and the patient was started on intravenous sodium thiosulfate. Calcium-based medications were held. Biopsy was not recommended due to the risk of poor wound healing. Due to the development of metabolic acidosis, sodium thiosulfate was later replaced with an intralesional form administered by vascular surgery. Wound care also followed the patient throughout admission, and she remained on a pain regimen for symptomatic relief.

Unfortunately, despite aggressive treatment, the patient had minimal improvement on the sodium thiosulfate and ended up being re-admitted multiple times over several months for uncontrolled pain and later infection. Ultimately, the ulcer continued to progress, leading to wasting the limb, loss of ambulation and an above-the-knee amputation approximately five months after the initial presentation. A few months following amputation, the patient opted to pursue hospice and stop dialysis.

Calciphylaxis is a rare, life-threatening syndrome with a very high mortality rate and limited treatment options. The purpose of this photographic clinical case is to aid in the early identification and treatment of this rapidly progressive syndrome.

AUTHOR DISCLOSURES:

No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

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