Unexpected skin necrosis of the thighs

The patient was initially told she had cellulitis and sent home with a combination antibiotic. Three weeks later, she returned with necrotic lesions.

A 62-YEAR-OLD WOMAN sought care at our clinic for painful skin lesions that had developed on her thighs 5 days earlier. She had received ongoing treatment at our clinic over the past few years for diabetes, hyperlipidemia, hypertension, and sarcoidosis. In the last 2 years, she’d had 2 hospitalizations for acute renal failure, with a creatinine value as high as 3.8 mg/dL and a persistent glomerular filtration rate consistent with stage 3 chronic kidney disease.

The medications she was taking included glyburide, pravastatin, and lisinopril. During the 2 years prior to her recent clinic visit, she’d had some intermittently elevated calcium readings. Repeat calcium levels each time were normal. In addition, her parathyroid hormone levels fluctuated between low, high, and normal. Her technetium sestamibi scan was negative for hyperparathyroidism. The patient was unemployed and gave no history of recent travel, injuries, or exposure to animals.

On examination, we noted large, poorly demarcated, warm, indurated erythematous lesions on her lateral thighs. She was given a diagnosis of cellulitis and treated with trimethoprim/sulfamethoxazole 160/800 mg twice daily for 10 days. During follow-up visits 3 and 7 days later, she indicated that the lesions were less painful and they appeared to be less swollen.

Three weeks later, the patient returned to the clinic with skin sloughing that had produced necrotic lesions with black eschar on the bases (FIGURE 1). In addition, new lesions appeared on her anterior thighs. An initial punch biopsy of the lesions revealed no significant pathologic abnormality.

WHAT IS YOUR DIAGNOSIS?

HOW WOULD YOU TREAT THIS PATIENT?

FIGURE 1

What started as indurated plaques...
Diagnosis: Calciphylaxis
Calciphylaxis is an uncommon disorder of vascular calcification and thrombosis resulting in skin necrosis.1 It most commonly occurs in people with end-stage renal disease (ESRD) on hemodialysis, but in nonuremic patients the most frequent cause is primary hyperparathyroidism.2,3 Similar vascular calcifications may be observed in milk alkali syndrome, rickets, collagen diseases, and hypervitaminosis D. Progression to necrosis in these cases is extremely rare.3 There are only a few documented cases of calciphylaxis associated with sarcoidosis, hypercalcemia, and non-ESRD.4

Female sex and diabetes appear to be risk factors.2 The presence of autoimmune disorders is a major feature in patients without ESRD.2,3 Although this patient did not have a previously diagnosed autoimmune disorder, an antinuclear antibody (ANA) test and lupus anticoagulant values were later found to be positive. In patients with autoimmune disorders, prednisone administration is associated with an increased risk of calciphylaxis.3 A hypercoagulable state can also underlie development of calciphylaxis. Our patient did have a mild protein C and S deficiency.

The prognosis of patients diagnosed with calciphylaxis is very poor. The mortality rate is reported to be as high as 60% to 80%.6

What to do when the biopsy isn’t helpful
This case points out an important pathologic rule: If the biopsy doesn’t correlate with the observed disease, additional biopsies are indicated. Calciphylaxis is diagnosed on tissue biopsy.

Although this patient didn’t have a previously diagnosed autoimmune disorder, ANA and lupus anticoagulant values were later found to be positive.

4 other possibilities comprise the differential diagnosis
Several conditions may present with erythema or necrosis similar to that of calciphylaxis (TABLE).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Characteristics</th>
</tr>
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<tbody>
<tr>
<td>Warfarin-induced skin necrosis</td>
<td>Painful, erythematous, edematous lesions; rapidly progressive; petechiae, hemorrhagic bullae, then necrotic eschar</td>
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<tr>
<td>Cutaneous anthrax</td>
<td>Small painless, pruritic papules; advances to bullae; finally erodes to painless necrotic lesions with black eschar</td>
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<tr>
<td>Cholesterol embolization</td>
<td>Majority with livedo reticularis, cyanosis, or gangrene; smaller percentage with cutaneous ulceration, purpura, petechiae, or painful, firm erythematous nodules</td>
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<tr>
<td>Vasculitis</td>
<td>Palpable purpura; biopsy of most affected area is necessary for diagnosis</td>
</tr>
<tr>
<td>Calciphylaxis</td>
<td>Painful erythematous papules, plaques, nodules, or ulcerations in areas with high adiposity; may progress to necrosis</td>
</tr>
</tbody>
</table>

Is it calciphylaxis or something else?1,3,7-9
Meticulous wound care, adequate pain control, and special attention to the prevention of secondary infection are all essential to the care of patients with calciphylaxis.

Management is mainly supportive

If you have a patient with calciphylaxis, address predisposing conditions such as hyperparathyroidism, hypercalcemia, and renal dysfunction\(^1\) (strength of recommendation [SOR]: C). In addition, discontinue calcium and vitamin D supplementation\(^6\) (SOR: C). Finally, the patient will need meticulous wound care with adequate pain control; special attention to prevention of secondary infection is essential\(^1,6\) (SOR: C).

Our patient was one of the lucky ones

We treated this patient’s hypercalcemia, which was noted on admission to the hospital, with zoledronate and corrected her hypophosphatemia. Her renal function significantly improved with aggressive hydration.

With correction of electrolytes and normalization of kidney function, lesion progression was arrested. Granulation tissue developed in the lesions and split-thickness expanded skin grafts were performed on the large lesions (FIGURE 2). Fortunately, this patient survived despite the usual high rate of mortality.

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References


FIGURE 2

Good granulation beds, followed by closure

After aggressive treatment of renal dysfunction, correction of electrolyte abnormalities, and meticulous wound care, the patient’s lesions developed good granulation beds and showed signs of healing (A). The second image (B), taken 9 months after the patient first sought treatment for the lesions, shows the wounds after skin grafting.