Nonuremic Calciphylaxis Triggered by Rapid Weight Loss and Hypotension

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PRACTICE POINTS
- Calciphylaxis is a potentially fatal disease caused by metastatic calcification of cutaneous small- and medium-sized blood vessels leading to ischemia and necrosis.
- Calciphylaxis most commonly is seen in patients with renal disease requiring dialysis, but it also may be triggered by nonuremic causes in patients with known risk factors for calciphylaxis.
- Risk factors for calciphylaxis include female gender, white race, obesity, alcoholic liver disease, primary hyperparathyroidism, connective tissue disease, underlying malignancy, protein C or S deficiency, corticosteroid use, warfarin use, diabetes, iron or albumin infusions, and rapid weight loss.
- The term calcific uremic arteriolopathy should be disregarded, as nonuremic causes are being reported with increased frequency in the literature.

Calciphylaxis, otherwise known as calcific uremic arteriolopathy, is characterized by calcification of the tunica media of the small- to medium-sized blood vessels of the dermis and subcutis, leading to ischemia and necrosis. It is a deadly disease with a 1-year mortality rate of more than 50%. End-stage renal disease (ESRD) is the most common risk factor for calciphylaxis, with a prevalence of 1% to 4% of hemodialysis patients with calciphylaxis in the United States. However, nonuremic calciphylaxis (NUC) has been increasingly reported in the literature and has risk factors other than ESRD, including but not limited to obesity, alcoholic liver disease, primary hyperparathyroidism, connective tissue disease, and underlying malignancy. Triggers for calciphylaxis in at-risk patients include use of corticosteroids or warfarin, iron or albumin infusions, and rapid weight loss. We report an unusual case of NUC that most likely was triggered by rapid weight loss and hypotension in a patient with multiple risk factors for calciphylaxis.

Case Report
A 75-year-old white woman with history of morbid obesity (body mass index, 40 kg/m²), unexplained weight loss of 70 lb over the last year, and polymyalgia rheumatica requiring chronic prednisone therapy presented with painful lesions on the thighs, buttocks, and right shoulder of 4 months’ duration. She had multiple hospital admissions preceding the onset of lesions for severe infections resulting in sepsis with hypotension, including *Enterococcus faecalis* endocarditis, extended-spectrum beta-lactamase bacteremia, and *Pseudomonas aeruginosa* pneumonia. Physical examination revealed large well-demarcated ulcers and necrotic eschars with surrounding...
violaceous induration and stellate erythema on the ante-
rior, medial, and posterior thighs and buttocks that were
exquisitely tender (Figures 1 and 2).

Notable laboratory results included hypoalbuminemia
(1.3 g/dL [reference range, 3.5–5.0 g/dL]) with normal
renal function, a corrected calcium level of 9.7 mg/dL
(reference range, 8.2–10.2 mg/dL), a serum phosphorus
level of 3.5 mg/dL (reference range, 2.3–4.7 mg/dL), a
calcium-phosphate product of 27.3 mg²/dL² (reference
range, <55 mg²/dL²), and a parathyroid hormone level of
49.3 pg/mL (reference range, 10–65 pg/mL). Antinuclear
antibodies were negative. A hypercoagulability evaluation
showed normal protein C and S levels, negative lupus
anticoagulant, and negative anticardiolipin antibodies.

Telescoping punch biopsies of the indurated borders of
the eschars showed prominent calcification of the small-
and medium-sized vessels in the mid and deep dermis,
intravascular thrombi, and necrosis of the epidermis and
subcutaneous fat consistent with calciphylaxis (Figure 3).

After the diagnosis of calciphylaxis was made,
the patient was treated with intravenous sodium
thiosulfate 25 mg 3 times weekly and alendronate 70 mg
weekly. Daily arterial blood gas studies did not detect
metabolic acidosis during the patient’s sodium thiosulfate
therapy. The wounds were debrided, and we attempted
to slowly taper the patient off the oral prednisone.

Unfortunately, her condition slowly deteriorated second-
ary to sepsis, resulting in septic shock. The patient died
3 weeks after the diagnosis of calciphylaxis was made. At
the time of diagnosis, the patient had a poor prognosis
and notable risk for sepsis due to the large eschars on the
thighs and abdomen as well as her relative immunosup-
pression due to chronic prednisone use.

Comment
Background on Calciphylaxis—Calciphylaxis is a rare but
deadly disease that affects both ESRD patients receiving
dialysis and patients without ESRD who have known risk factors for calciphylaxis, including female gender, white race, obesity, alcoholic liver disease, primary hyperparathyroidism, connective tissue disease, underlying malignancy, protein C or S deficiency, corticosteroid use, warfarin use, diabetes, iron or albumin infusions, and rapid weight loss.\textsuperscript{36-31} Although the molecular pathogenesis of calciphylaxis is not completely understood, it is believed to be caused by local deposition of calcium in the tunica media of small- to medium-sized arterioles and venules in the skin.\textsuperscript{12} This deposition leads to intimal proliferation and progressive narrowing of the vessels with resultant thrombosis, ischemia, and necrosis. The cutaneous manifestations and histopathology of calciphylaxis classically follow its pathogenesis. Calciphylaxis typically presents with livedo reticularis as vessels narrow and then progresses to purpura, bullae, necrosis, and eschar formation with the onset of acute thrombosis and ischemia. Histopathology is characterized by small- and medium-sized vessel calcification and thrombus, dermal necrosis, and septal panniculitis, though the histology can be highly variable.\textsuperscript{12} Unfortunately, the already poor prognosis for calciphylaxis worsens when lesions become either ulcerative or present on the proximal extremities and trunk.\textsuperscript{4,13} Sepsis is the leading cause of death in calciphylaxis patients, affecting more than 50% of patients.\textsuperscript{2,3,14} The differential diagnoses for calciphylactic-appearing lesions include warfarin-induced skin necrosis, disseminated intravascular coagulation, pyoderma gangrenosum, cholesterol emboli, and various vasculitides and coagulopathies.

\textbf{Risk Factors—}Our case demonstrates the importance of risk factor minimization, trigger avoidance, and early intervention due to the high mortality rate of calciphylaxis. Selye et al\textsuperscript{15} coined the term \textit{calciphylaxis} in 1961 based on experiments that induced calciphylaxis in rat models. Their research concluded that there were certain sensitizers (ie, risk factors) that predisposed patients to medial calcium deposition in blood vessels and other challengers (ie, triggers) that acted as inciting events to calcium deposition. Our patient presented with multiple known risk factors for calciphylaxis, including obesity (body mass index, 40 kg/m\textsuperscript{2}), female gender, white race, hypoalbuminemia, and chronic corticosteroid use.\textsuperscript{16} In the presence of a milieu of risk factors, the patient’s rapid weight loss and episodes of hypotension likely were triggers for calciphylaxis.

Other case reports in the literature have suggested weight loss as a trigger for NUC. One morbidly obese patient with inactive rheumatoid arthritis had onset of calciphylaxis lesions after unintentional weight loss of approximately 50% body weight in 1 year\textsuperscript{17}; however, the weight loss does not have to be drastic to trigger calciphylaxis. Another study of 16 patients with uremic calciphylaxis found that 7 of 16 (44%) patients lost 10 to 50 kg in the 6 months prior to calciphylaxis onset.\textsuperscript{14} One proposed mechanism by Munavalli et al\textsuperscript{10} is that elevated levels of matrix metalloproteinases during catabolic weight loss states enhance the deposition of calcium into elastic fibers of small vessels. The authors found elevated serum levels of matrix metalloproteinases in their patients with NUC induced by rapid weight loss.\textsuperscript{20}

A meta-analysis by Nigwekar et al\textsuperscript{3} found a history of prior corticosteroid use in 61% (22/36) of NUC cases reviewed. However, it is unclear whether it is the use of corticosteroids or chronic inflammation that is implicated in NUC pathogenesis. Chronic inflammation causes downregulation of anticalcification signaling pathways.\textsuperscript{18-20} The role of 2 vascular calcification inhibitors has been evaluated in the pathogenesis of calciphylaxis: fetuin-A and matrix gla protein (MGP).\textsuperscript{21} The activity of these proteins is decreased not only in calciphylaxis but also in other inflammatory states and chronic renal failure.\textsuperscript{16-20} One study found lower fetuin-A levels in 312 hemodialysis patients compared to healthy controls and an association between low fetuin-A levels and increased C-reactive protein levels.\textsuperscript{22} Reduced fetuin-A and MGP levels may be the result of several calciphylaxis risk factors. Warfarin is believed to trigger calciphylaxis via inhibition of gamma-carboxylation of MGP, which is necessary for its anticalcification activity.\textsuperscript{23} Hypoalbuminemia and alcoholic liver disease also are risk factors that may be explained by the fact that fetuin-A is synthesized in the liver.\textsuperscript{24} Therefore, liver disease results in decreased production of fetuin-A that is permissive to vascular calcification in calciphylaxis patients.

There have been other reports of calciphylaxis patients who were originally hospitalized due to hypotension, which may serve as a trigger for calciphylaxis onset.\textsuperscript{25} Because calciphylaxis lesions are more likely to occur in the fatty areas of the abdomen and proximal thighs where blood flow is slower, hypotension likely accentuates the slowing of blood flow and subsequent blood vessel calcification. This theory is supported by studies showing that established calciphylactic lesions worsen more quickly in the presence of systemic hypotension.\textsuperscript{26} One patient with ESRD and calciphylaxis of the breasts had consistent systolic blood pressure readings in the high 60s to low 70s between dialysis sessions.\textsuperscript{27} Due to this association, we recommend that patients with calciphylaxis have close blood pressure monitoring to aid in preventing disease progression.\textsuperscript{28}

\textbf{Management—}Calciphylaxis treatment has not yet been standardized, as it is an uncommon disease whose pathogenesis is not fully understood. Current management strategies aim to normalize metabolic abnormalities such as hypercalcemia if they are present and remove inciting agents such as warfarin and corticosteroids.\textsuperscript{29} Other medical treatments that have been successfully used include sodium thiosulfate, oral steroids, and adjunctive bisphosphonates.\textsuperscript{29,31} Sodium thiosulfate is known to cause metabolic acidosis by generating thiosulfuric acid in vivo in patients with or without renal disease; therefore, patients on sodium thiosulfate therapy...
should be monitored for development of metabolic acido-
sis and treated with oral sodium bicarbonate or dialysis
as needed.30,32 Wound care also is an important
element of calciphylaxis treatment; however, the debridem-
ent of wounds is controversial. Some argue that dry intact
eschars serve to protect against sepsis, which is the
leading cause of death in calciphylaxis.2,14,33 In contrast,
a retrospective study of 63 calciphylaxis patients found
a 1-year survival rate of 61.6% in 17 patients receiving
wound debridement vs 27.4% in 46 patients who did
not.2 The current consensus is that debridement should
be considered on a case-by-case basis, factoring in the
presence of wound infection, size of wounds, stability of
eschars, and treatment goals of the patient.34 Future
studies should be aimed at this issue, with special focus
on how these factors and the decision to debride or not
impact patient outcomes.

Conclusion
Calciphylaxis is a potentially fatal disease that impacts
both patients with ESRD and those with nonuremic risk
factors. The term calcific uremic arteriolopathy should
be disregarded, as nonuremic causes are being reported
with increased frequency in the literature. In such cases,
patients often have multiple risk factors, including obesity,
primary hyperparathyroidism, alcoholic liver disease, and
underlying malignancy, among others. Certain triggers for
onset of calciphylaxis should be avoided in at-risk patients,
including the use of corticosteroids or warfarin; iron and
albumin infusions; hypotension; and rapid weight loss.
Our fatal case of NUC is a reminder to dermatologists
treating at-risk patients to avoid these triggers and to keep
calciphylaxis in the differential diagnosis when encounter-
ing early lesions such as livedo reticularis, as progression
of these lesions has a 1-year mortality rate of more than
50% with the therapies being utilized at this time.

REFERENCES
1. Au S, Crawford RL. Three-dimensional analysis of a calciphylaxis
2007;56:569–579.
4. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk
5. Angelis M, Wong LL, Myers SA, et al. Calciphylaxis in patients on
acute, reversible renal failure in the setting of alcoholic cirrhosis. J Am
2007;29:400–403.
8. Baxtolf K, Cerottini JP, Panizzon RG. Lower limb skin ulcerations, intra-
vascular calcifications and sensorimotor polyneuropathy: calciphylaxis
medial calcification and intimal hyperplasia (so-called calciphylaxis):
a complication of chronic renal failure and benefit from parathyroidec-
15. Selye H, Gentile G, Prioreschi P. Cutaneous indolent mottled induced by calciphyl-
renal and parathyroid function: not as rare as previously believed.
17. Malaloh U, Roberts L, Sangka K. Calciphylaxis in a morbidly obese
woman with rheumatoid arthritis presenting with severe weight loss
Heremans-Schmid glycoprotein/fetuin-A is a systematically acting
link inflammation and cardiovascular calcification in hemodialysis
20. Luo G, Duck P, McKee MD, et al. Spontaneous calcification of
1997;385:78–81.
21. Weening RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor
fetuin-A (AHSG) concentrations in serum with cardiovascular mortal-
ity in patients on dialysis: a cross-sectional study. Lancet. 2003;
361:827–833.
23. Wallin R, Cain D, Sane DC. Matrix GLA protein synthesis and gamma-
carboxylation in the aortic vessel wall and proliferating vascular
smooth muscle cells a cell system which resembles the system in bone
24. Sowers KM, Hayden MR. Calcific uremic arteriolopathy: pathophysi-
ology, reactive oxygen species and therapeutic approaches. Oxid Med
but fatal delayed complication of Roux-en-Y gastric bypass surgery.
26. Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in preven-
pain in end-stage renal disease: calciphylaxis with chronic hypoten-
rioles with infarcts of the subcutis and skin (“calciphylaxis”) in chronic
29. Jeong HS, Dominguez AR. Calciphylaxis: controversies in pathogenesis,
30. Bourgeois P, De Haes P. Sodium thiosulfate as a treatment for calciphy-
31. Biswas A, Walsh NM, Tremaine R. A case of nonuremic calciphyl-
32. Selk N, Rodby RA. Unexpectedly severe metabolic acidosis associated
with sodium thiosulfate therapy in a patient with calcific uremic arte-
33. Martin R. Mysterious calciphylaxis: wounds with eschar—to debride or