CHAPTER **38**

CALCIPHYLAXIS

Robert M. Goecker, DPM

INTRODUCTION

Calciphylaxis is a dreaded complication of chronic renal failure. Calcific uremic arteriolopathy (calciphylaxis) is a rare but serious life threatening complication of chronic renal failure that manifests with painful nonhealing eschars/wounds as a result of a calcification syndrome that predominantly affects relatively small vessels. The small vessel thrombosis leads to thrombotic cutaneous ischemia, and necrotic skin ulcerations. Most cases of calciphylaxis are characterized by rapid progression of these tender subcutaneous nodules or cutaneous plaques to full thickness tissue necrosis that often leads to secondary infection and high mortality rate. Intractable skin necrosis sometimes causes lethal sepsis because it progresses rapidly. This condition is being increasingly recognized and reported as a contributing factor to death in dialysis patients. This article will attempt to increase podiatric awareness as well as review the diagnosis and management of these difficult wounds.

HISTORY/OVERVIEW

Calciphylaxis (calcific uremic arteriolopathy) is being reported with increasing frequency especially over the last few years.[1-24] The devastating complication of medial vascular calcification of the small arterioles with resulting skin necrosis is leading to significant morbidity and mortality in both diabetic and non-diabetic patients undergoing renal replacement therapy. The first clinical presentation of a calciphylaxis-like process associated with uremia was first recorded by Bryant and White in 1898. Selve in 1962 coined the term calciphylaxis based on what he thought was a hypersensitivity reaction. He hypothesized that sensitizers such as PTH or Vitamin D might cause vascular ossification and calcification. However, this was incorrect as there is no immunoglobulin mediated allergy.[1] Hafner et al in 1995 termed this phenomenon as uremic small artery disease to describe skin necrosis and acral gangrenous changes as a consequence of intimal arterial hyperplasia, arteriolar medial calcification, and thrombosis in the arteries of the subcutaneous tissue in the hands and feet.[2] The more appropriate description of the condition is calcific uremic arteriolopathy.[3] This newer descriptive terminology is preferred but calciphylaxis is entrenched in the literature.[4] The pathognomic skin lesions are caused by a small vessel vasculopathy. The intimal arterial hypertrophy, arteriolar medial calcification and small vessel thrombosis leads to cutaneous ischemia, and necrotic skin ulcerations. The full thickness tissue necrosis often leads to secondary infection and potential lethal sepsis because it progresses rapidly. This condition is being increasingly recognized. Prevalence of 1-4% has been estimated in various hemodialysis populations.[5,6] The mortality rate for proximal lesions has been reported as high as 63% compared with a 23% rate for distal lesions.[2] There has been no correlation between the age at onset and outcome of the disease. Pathogenesis is related to vascular calcium deposition and raised serum phosphate levels.

Calciphylaxis has been recognized with chronic kidney failure (end-stage renal disease on hemodialysis) or renal transplant patients due to disturbance of calcium and phosphate metabolism. Many cases occur within the first year of dialysis treatment. A high phosphate diet and many times hyperparathyroidism also act as sensitizers and lead to a high calcium-phosphate product with resultant precipitation of Ca-P crystals. This results in vascular ossification/calcification of the media and internal elastic lamina of the small to medium sized arteries and arterioles with intimal proliferation and at times arterial occlusion. There seems to be a positive correlation between the length of azotemia and intensifying vascular calcification. Non-uremic causes or other triggering events previously described include alcoholic liver disease, corticosteroids, immunosuppression, malignancy, connective tissue disease, protein C and S deficiencies, albumin infusion, and intravenous iron dextran. Obesity has also been described as a risk factor due to the potential decreased blood flow to areas of large amounts of adipose tissue. There is a slight female preponderance due to a higher percentage of fat in the subcutaneous tissue. Diabetic patients with chronic renal failure have increased risk of acral necrosis due to extensive vascular calcifications. Vascular insufficiency may exist as well.[1]

CLINICAL PRESENTATION

First of all it is very important to recognize the clinical presentation of the skin color changes and the neuropathic type of pain before the ulcerations develop. If the ulcerations develop there is an increased risk of sepsis and premature death. The skin lesions usually present a painful, violaceous (livedo reticularis like) discoloration and evolve into well demarcated non-healing ulcers that become necrotic and gangrenous (Figure 1). The lesions can occur proximally (trunk, buttock, thighs) or distally (calves, forearms, acral sites [hands, feet, fingers, toes]). The more proximal lesions have a poorer prognosis due to the larger potential bulk of the necrotic and infected tissue. The wounds tend to develop in sites of previous trauma even as small as simple scratches. As these wounds progress and are debrided they tend to present on a granulating bed with enlargement at the periphery of the ulcer (Figure 2).[4] Histopathology reveals extensive medial calcification of small to medium sized arteries/arterioles with intimal proliferation. The deposition of the calcium is either segmental or circumferential and leads to atrophy of the smooth muscle fibers of the media. The arterial lumen is usually preserved. There may also be subcutaneous calcification with ischemic epidermolysis.[1]

DIFFERENTIAL DIAGNOSIS

Calciphylaxis is one of several potential cutaneous pseudovasculitities meaning it is capable of simulating cutaneous authentic vasculitis.[7] These lesions must be distinguished from a vasculitic skin rash. Biopsy and negative serology can rule out a vasculitic skin rash. Skin biopsy soon after the presentation is imperative for diagnosis and to avoid potentially harmful treatments such as corticosteroids and immunosuppressant medications.[8] Other potential differential diagnoses include cutaneous infarcts from cryoglobulinemia (ruled out by absence of cryoglobulin), cholesterol emboli (smaller nonhealing vascular ulcerations with livedo reticularis), pancreatic panniculitis (usually pre-tibial with altered serum amylase that rapidly normalize), coumadin necrosis (elevated PT/INR) and cardiac myxoma.

TREATMENT

Patients with calciphylaxis have poor healing potential due to ischemia and comorbid factors such as diabetes mellitus, renal failure, peripheral vascular disease, and obesity. No standard treatment has been established for this syndrome. The initial goal of the treatment is prevention of infection and pain management.[9] Early recognition and multi-disciplinary treatment is required. Prophylaxis with rigorous control of the uremia and prevention of secondary hyperparathyroidism is important. A multidisciplinary approach will first include normalizing the calcium and phosphorous product. A low phosphate diet along with vitamin D analog supplements and phosphate binders will be prescribed. Parathyroidectomy has been described with success by several reports.[2,10-12] However, others have not recommended routine parathyroidectomy unless there is severe hyperparathyroidism.[13] Weenig et al reported increased survival rates with debridement but not with parathyroidectomy.[14] While maximizing the metabolic status a thorough evaluation of the vascular perfusion is required. Appropriate revascularization is performed if needed. Then attention is directed to the difficult necrotic wounds.

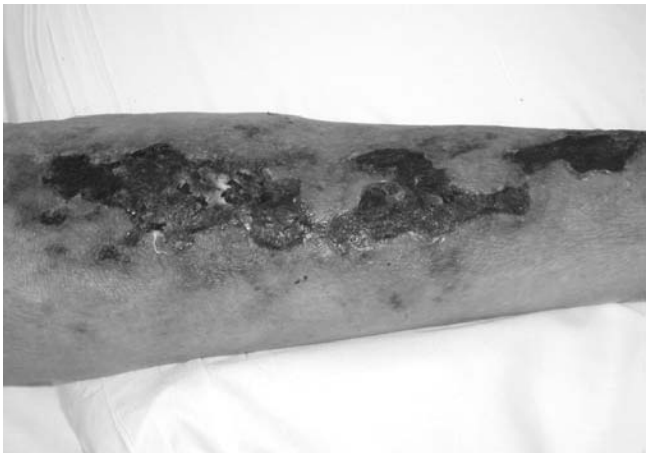

Figure 1. Calciphylaxis. Progressive blackened eschar with surrounding extending violaceous skin changes.

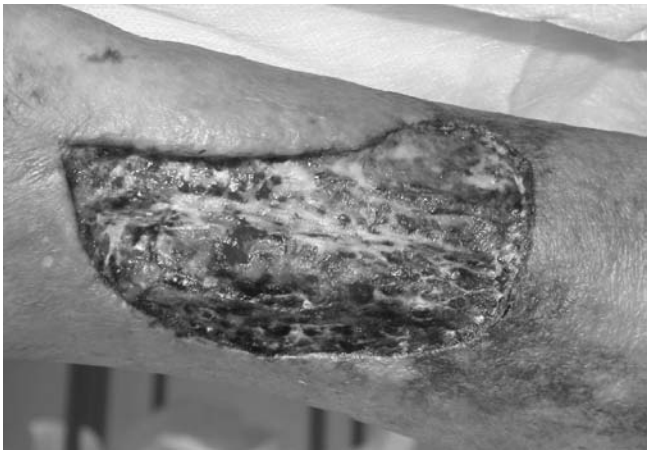

Figure 2. Calciphylaxis wound post debridement with a granulating base that is enlarging at the periphery of the ulcer. Note the violaceous preischemic changes in the skin at the wound edges.

The decision to debride is based on the patient's total clinical picture. Debridement is not indicated in dry noninfected wounds. There are reports of debridement leading to worsening of the wound similar to what is seen in pyoderma gangrenousum.[15] Some of these calciphylaxis wounds may be difficult to debride due to location or too painful to debride. Medicinal maggot therapy is an alternative to sharp debridement. A report has described the use of maggot therapy and 800 mg/day of oral pentoxyfillin with complete healing after about 6 months of therapy with better tolerance.[16]

A newer very promising treatment also exists with intravenous sodium thiosulfate. The optimum dose and length of treatment is yet to be determined however, there are several reports with high success rates in treating this potentially lethal condition.[17-19] Sodium thiosulfate is known to be a chelator of cations and has been used in acne treatments, as an antidote for cyanide toxicity, and chemoprotectant against cisplatin and carboplatin toxicity. It also is an effective antioxidant agent. Its dual role as an antioxidant and a chelator of cations such as calcium excess makes it an excellent choice for treatment and future research. It has shown promise in treating this difficult condition especially with hyperbaric oxygen therapy.[4,17] Bisphosphonates may also be effective in treating calciphylaxis and arteriosclerosis oblitterans by reducing the formation of ectopic calcification around blood vessels. A report noted improvement in calciphylaxis wounds with the combination of etidronate disodium and sevelamer hydrochloride.[15]

Aggressive wound care with debridement is required when there is drainage, infection and when the eschar does not cover the entire wound. When these wounds are draining, infected or extensive it requires multiple different wound modalities including diligent wound care, frequent debridement, hyperbaric oxygen therapy, negative pressure wound therapy and skin grafting to improve healing and limb salvage.

Negative pressure wound therapy has been described as being valuable in wounds resulting from calciphylaxis although there may be issues with enlarging wound edge and extensive contiguous wounds that make it difficult to protect the areas of intact skin surface.[20] Hyperbaric oxygen therapy has also been reported as a successful treatment in patients with calciphylaxis.[17,21] The author has utilized aggressive and frequent debridement with negative pressure wound therapy and hyperbaric oxygen therapy with success in healing these difficult wounds (Figures 3-5). These difficult wounds will require a combination of therapies facilitate healing including both medicinal and surgical treatments.[22-24]

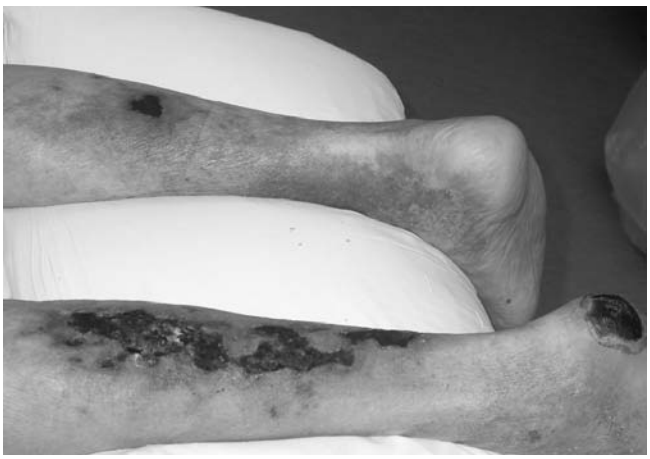

Figure 3A. Calciphylaxis wound. Blackened eschar with surrounding extending violaceous skin changes.

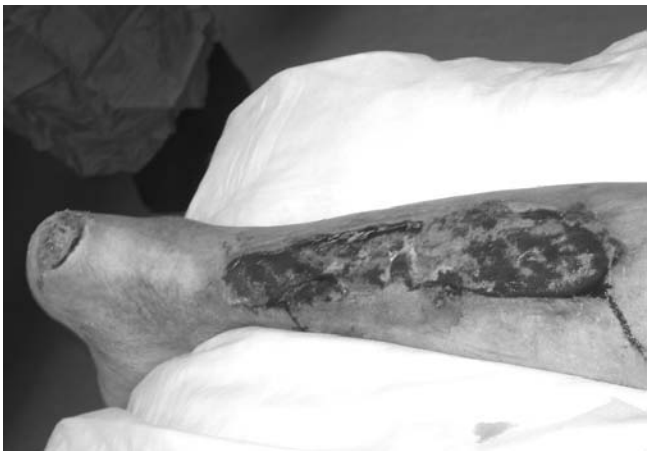

Figure 3B. Post debridement healthy wound ready for split-thickness skin graft assisted by negative pressure wound therapy and hyperbaric oxygen therapy.

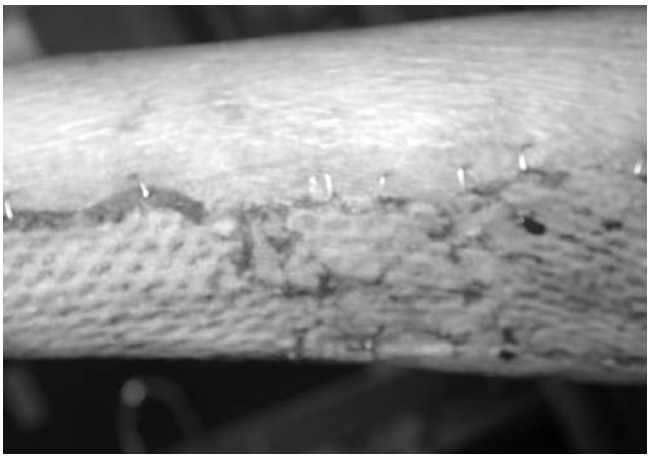

Figure 3C. Healed wound post split-thickness skin graft.

Figure 5A. Calciphylaxis wound after previous debridement. There is a granulating base with subtle changes at the edge of the wound.

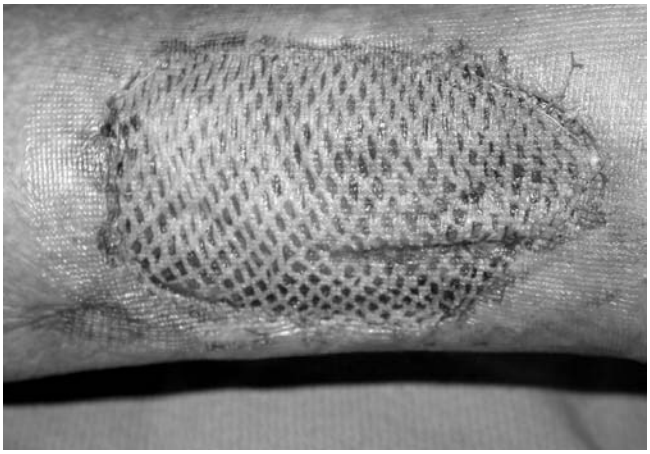

Figure 5B. Healing skin graft with some discoloration at the edge of the graft take. Note the marginal appearance at the edge of the graft.

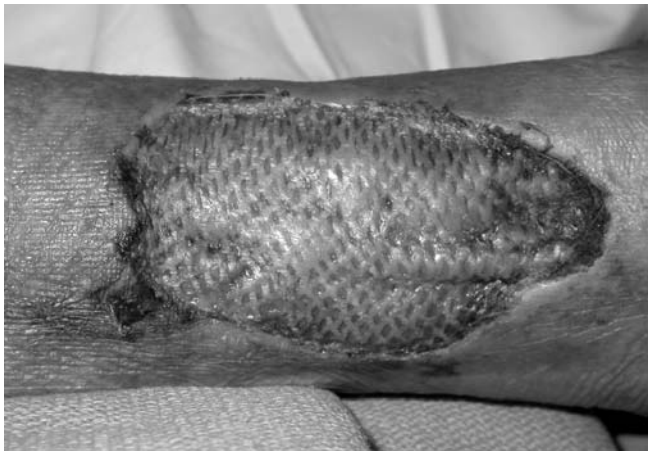

Figure 5C. Healing skin graft. Note the marginal appearance at the edge of the graft.

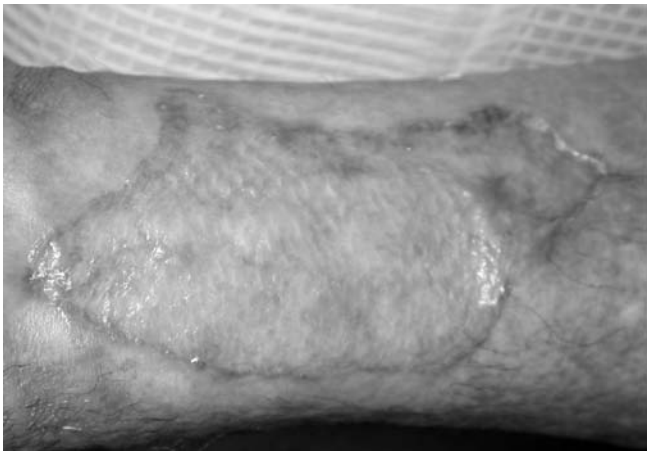

Figure 5D. Healed wound after split-thickness skin graft.

REFERENCES

1. Mathur RV, Shortland JR, el-Nahas AM. Calciphylaxis. *Postgrad Med J* 2001;77:557-61.
2. Hafner J, KeuschG, Wahl C, et al. Uremic small-artery disease with medial calcification and intimal hyperplasia (so called calciphylaxis): a complication of chronic renal failure and benefit from parathyroidectomy. *J Am Acad Dermatol* 1995;33:954-62.
3. Coates T, Kirkland GS, Dymock RB, Murphy BF, Brealey JK, Mathew TH, Disney AP. Cutaneous necrosis from Calcific uremic arteriolopathy. *Am J Kidney Dis* 1998;32:384-91.
4. Hayden MR, Tyagi SC, Kolb L, Sowers JR, Khanna R. Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease and calciphylaxis-calcific uremic retinopathy: the emerging role of sodium thiosulfite. *Cardiovasc Diabetol* 2005;4:4.
5. Byrne H, Lloyd S. Calciphylaxis: calcific uremic arteriolopathy—a case study. *J Ren Care* 2007;33:74-7.
6. Angelis M, Wong LL, Myers SA, et al. Calciphylaxis in patients on hemodialysis: a prevalence study. *Surgery* 1997;122:1083-90.
7. Sakr SH, Russell EB, Jasin HE. Systemic lupus erythematous and calciphylaxis. *J Rheumatol* 2004;31: 1851-3.
8. Carlson JA, Chen KR. Cutaneous pseudovasculitis. *Am J Dermatopathol* 2007;29:44-55.
9. Martin R. Mysterious calciphylaxis: wounds with eschar — to debride or not to debride? *Ostomy Wound Manage* 2004;50:68-71.
10. Bronson N, Menon R, Butler J, Gordon I. Parathyroidectomy, excision and skin grafting with topical negative pressure for calciphylaxis ulcers. *J Wound Care* 2007;16:295-7.
11. Milas M, Bush RL, Lin P, Brown K, Mackay G, Lumsden A, Weber C, Dodson TF. Calciphylaxis and nonhealing wounds: the role of the vascular surgeon in a multidisciplinary treatment. *J Vasc Surg* 2003;37:501-7.
12. Arch-Ferrer JE, Beenken SW, Rue LW, Bland KI, Diethelm AG. Therapy for calciphylaxis: an outcome analysis. *Surgery* 2003;134:941-4.
13. Kang AS, McCarthy JT, Rowland C, Farley DR, van Heerden JA. Is calciphylaxis best treated surgically or medically? *Surgery* 2000;128:967-71.
14. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis and outcome. *J Am Acad Dermatol* 2007;57:356-6.
15. Hanafusa T, Yamaguchi Y, Tani M, Umegaki N, Nishimura Y, Katayama I. Intractable wounds caused by calcific uremic arteriolopathy treated with bisphosphonates. *J Am Acad Derrmatol* 2007;57:1021-5.
16. Tittelbach J, Graefe T, Wollina U. Painful ulcers in calciphylaxis - combined treatment with maggot therapy and oral pentoxyfillin. *J Dermatolog Treat* 2001;12:211-4.
17. Cicone JS, Petronis JB, Embert CD, Spector DA. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis* 2004;43:1104-8.
18. Subramabiam K, Wallace H, Sinniah R, Saker B. Complete resolution of recurrent calciphylaxis with long-term intravenous sodium thiosulfite. *Australas J Dermatol* 2008;49:30-4.
19. Tokashiki K, Ishida A, Kouchi M, Tomiyama N, Kohagura K, Iseki K, Takishita S. Successful management of critical limb ischemia with intravenous sodium thiosulfite in a chronic hemodialysis patient. *Clin Nephrol* 2006;66:140-3.
20. Dean SM, Werman H. Calciphylaxis: a favorable outcome with hyperbaric oxygen. *Vasc Med* 1999;63:149-53.
21. Emohare O, Kowal-Vern A, Wiley D, Latenser BA. Vacuum-assisted closure use in calciphylaxis. *J Burn Care Rehabil* 2004;25:161-4.
22. Don BR, Chin AI. A strategy for the treatment of calcific uremic arteriolopathy (calciphylaxis) employing a combination of therapies. *Clin Nephrol* 2003;59:463-70.
23. Parker RW, Mouton CP, Young DW, Espino DV. Early recognition and treatment of calciphylaxis. *South Med J* 2003;96:53-5.
24. Snyder RJ, Beylin M, Weiss SD. Calciphylaxis and its relation to end stage renal disease: a literature review and case presentation. *Ostomy Wound Manage* 2000;46:40-7.