Calciphylaxis: a favorable outcome with hyperbaric oxygen

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Abstract: A 66-year-old female with diabetes mellitus and end-stage renal disease presented with painful bilateral lower extremity livedo reticularis and necrotic ulcerations. Her distal lower extremity pulses were intact and plethysmographic studies confirmed relatively normal large vessel arterial perfusion. Extensive laboratory analysis was remarkable for an elevated calcium × phosphorous product and parathyroid hormone level. An ulcer biopsy revealed small vessel medial calcinosis, and calciphylaxis was subsequently diagnosed. Despite aggressive wound debridements, antibiotics and subtotal parathyroidectomy, her ulcers failed to improve significantly prompting a trial of hyperbaric oxygen therapy. After 7 weeks of hyperbaric treatments, her ulcers had essentially healed.

Key words: calciphylaxis; hyperbaric oxygen; ulcerations

Introduction

The calcifying panniculitis of renal failure or ‘calciphylaxis’ is an uncommon necrotizing cutaneous abnormality, which is classically found in patients with end-stage renal disease associated with secondary hyperparathyroidism. The disorder should be suspected when a dialysis patient presents with rapidly enlarging and painful, symmetrical lower extremity ischemic ulcerations, with biopsy evidence of small vessel medial calcinosis. Unfortunately, treatment is often unsatisfactory and mortality rates are high. This paper presents the second reported case of calciphylaxis, which was successfully treated with hyperbaric oxygen.

Case report

A 66-year-old female with diabetes mellitus-induced end-stage renal disease presented with a 2-week history of a spontaneous painful, nodular ‘rash’ on her calves. Additional past medical and surgical history included CAD, HTN, atrial fibrillation, and a left arm arteriovenous fistula. She had undergone hemodialysis three times a week for 2 years. Medications included digoxin, ferrous sulfate, calcium carbonate, ASA, multivitamins and casanthranol/docusate sodium (no insulin or sulfonylurea therapy). The patient had never smoked and did not drink alcohol.

The initial examination revealed two small right lateral calf ulcerations with peripheral necrosis and surrounding tender, indurated livedo reticularis. Livedoid changes were also present on the contralateral calf. No pedal atheroembolic phenomena were identified and the femoral, popliteal, dorsalis pedis, and posterior tibial arterial pulses were 2+. The abdominal aorta was not palpably aneurysmal. Ankle/brachial indices were greater than 1.0 bilaterally (inaccurate due to calcified vessels); however, the plethysmographic ankle waveforms were markedly pulsatile with a dicrotic notch suggesting well-preserved large vessel arterial perfusion.

The ulcers were debrided and antibiotics with topical wound care were prescribed. The patient returned 1 month later with increasingly painful calves and several new ulcers, which were now present bilaterally. Repeat examination revealed multiple, bilateral large ulcerations covered with thick necrotic eschar (Figures 1 and 2). Subcutaneous periwound tender induration was also palpated.

Abnormal laboratory tests included the following: intact PTH 913 pg/ml; calcium (corrected) 10.9 mg/dl; phosphate 7.4 mg/dl; calcium × phosphate product 80.6; creatinine 5.3 mg/dl; BUN 68 mg/dl; hemoglobin 9.1 g/dl; hematocrit 29.7%; albumin 3.3 g/dl; and erythrocyte sedimentation rate 42 mm/h. The succeeding laboratory tests were negative or normal: white blood cells, platelets, glucose, total protein, prothrombin time, partial thromboplastin time, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, amylase, uric acid, antinuclear antibody, rheumatoid factor, hepatitis B antigen, hepatitis C antibody, complement 3 and 4, serum protein electrophoresis, cold agglutinins, cryoglobulins, α-1 antitrypsin, anticardiolipin antibodies, lupus anticoagulant, total and functional protein C and S, and antithrombin III.

Wound biopsy revealed subcutaneous arterioles with medial calcification and intimal fibrous hyperplasia combined with dermal and epidermal ischemic necrosis. No evidence of necrotizing vasculitis was identified. Plain film radiography of the right tibia/ibula showed extensive calcification throughout the tibioperoneal arteries. Patchy areas of subcutaneous small artery calcification were identified within the ulcerated areas. No osteomyelitis was present.

Despite a 2-month treatment regimen of weekly surgical wound debridements, parenteral antibiotics, normalizing
the calcium × phosphate product with low calcium dialysate and phosphate binders, her ulcers continued to increase in size and number. As a result, she underwent an uncomplicated subtotal parathyroidectomy. Over the next month only minimal ulcerative improvement transpired; therefore, she began a trial of 29 hyperbaric oxygen (HBO) treatments in a monoplace chamber (from 10 September to 26 October 1996). Each treatment was undertaken at 2.4 atmospheres absolute (ATA) for a total of 90 min. Weekly wound debridements were continued. Within just 3 weeks of commencing HBO therapy, her ulcers began to decrease in size and the bases became moist instead of dry and necrotic. In addition, the surrounding induration softened and the livedo resolved. After approximately 7 weeks of hyperbaric treatment her ulcers had essentially healed, although some residual hyperpigmented staining was apparent (Figure 3). No evidence of ulcer recrudescence ensued during an 11-month follow up, but unfortunately the patient died secondary to cardiac arrest.

**Discussion**

Calciphylaxis is a potentially devastating ulcerative cutaneous disease. Other designations include the vascular...
calcification–cutaneous necrosis syndrome,\textsuperscript{1} calcific azotemic arteriopathy,\textsuperscript{2} uremic small artery disease with medial calcinosis and intimal calcification,\textsuperscript{3} and the uremic gangrene syndrome.\textsuperscript{4} Fortunately the condition is rare. In a letter to the editor, Goldsmith related that only 157 cases had been reported between 1899 and 1996.\textsuperscript{5} However, the true prevalence is probably higher on account of under-reporting and misdiagnosing the skin manifestations of calciphylaxis as typical atherosclerotic ulcerations. For instance, a recent 15-month cross-sectional retrospective review of 242 hemodialysis patients revealed a calciphylaxis prevalence of 4\% (10 patients).\textsuperscript{6}

Although traditionally described in the setting of end-stage renal disease associated with secondary or tertiary hyperparathyroidism, calciphylaxis has also been reported in non-dialysis azotemic patients with such diverse etiologies as primary hyperparathyroidism,\textsuperscript{7,8} Crohn’s disease,\textsuperscript{9} or AIDS.\textsuperscript{10} Calciphylaxis without azotemia has rarely been recorded following successful renal allografting,\textsuperscript{11–13} and Fader recently published a stereotypical case in a cirrhotic patient with a creatinine value of 1.1 mg/dl.\textsuperscript{14} Women are more often affected.\textsuperscript{3,15,16}

Clinically, the disorder often begins with painful violaceous mottling of the skin resembling livedo reticularis

\textbf{Figure 3} Right (a) and left (b) lateral calves after 7 weeks of HBO therapy. Residual staining present but the ulcer bases have undergone re-epithelialization.
followed by the rapid formation of subcutaneous nodules and plaques which can evolve into ischemic ulcerations. The lower extremities are most commonly affected although the upper extremities, buttocks, abdomen, or trunk can also be involved. Unusual sites of involvement include the penis, neck, breast, and even the tongue. Although such widespread ischemic lower extremity ulcers usually connote severe underlying peripheral arterial occlusive disease, the distal pulses are often well preserved in this condition.

Typical pathologic findings include calcium deposition within dermal sized blood vessels (arterioles and venules) and the subcutaneous tissue. Superimposed intimal hyperplasia, a lymphohistiocytic infiltrate, and/or fibrin microthrombi can also occur. Interestingly, Fischer and Morris reviewed the histopathological findings in three cases of calciphylaxis and noted the presence of an associated giant cell reaction. No evidence of fibrinoid necrosis exists. Diagnostically, an incisional biopsy is preferred since the typical calcific findings can be focal and therefore missed by a punch biopsy.

Plain film radiography often reveals calcium outlining the small, medium and large-sized arteries. Small vessel involvement, defined as a diameter less than 0.5 mm, is probably the most specific radiographic finding in calciphylaxis.

The pathogenesis of calciphylaxis remains speculative and traditionally thought to involve perturbations of parathyroid hormone, phosphate and calcium, yet their participation is not absolute. In one recent review of 40 calciphylaxis cases, 82% had elevated parathyroid hormone, two-thirds manifested hyperphosphatemia, but only one-third had an elevated calcium x phosphorous product and 20% had hypercalcemia. By applying data from experimental rat models, Seyle believed the pathophysiology involved three consecutive stages: sensitization, latency and challenging. Factors such as hyperphosphatemia, hypercalcemia, an elevated calcium x phosphorous product, increased parathyroid hormone, and/or vitamin D are thought to ‘sensitize’ the tissues. After a ‘latent’ period, exposure to a ‘challenging’ agent induces local or systemic calcium precipitation. Potential challengers include iron salts, albumin, trauma, cytotoxic medications and/or glucocorticoids. Nevertheless, Seyle’s theory may not be entirely germane in humans since his rat models primarily demonstrated extra-vascular and not vascular calcification, and ischemic skin ulcerations were not common.

Hypercoagulability may also play a pathologic role. For example, functional protein S or C deficiency has been documented in several cases. Dereure et al recently reported a case of calciphylaxis associated with a circulating anticoagulant (lupus anticoagulant). The presence of proximal clinical involvement (e.g. ulcerations on the abdomen/trunk and proximal to the knees) suggests a poorer prognosis than distally located lesions (distal to the knees and elbows). One report showed that 40 out of 53 (75%) subjects with distal involvement survived, whereas only 11 of 42 (26%) patients with a proximal distribution lived (p = 0.0001).

Treatment of calciphylaxis is traditionally unsatisfactory with mortality rates ranging from 50% to 100%. Death usually results from sepsis and inanition. Primary therapy consists of providing supportive measures such as nutrition, dietary control of calcium and phosphorous, wound care with frequent debridements, and antibiotics. Other treatment modalities include low calcium dialysate, phosphates, and parathyroidectomy. Hyperbaric oxygen, and although controversial, even glucocorticoids.

Ulcer progression and death, despite parathyroidectomy, has been noted by several investigators. Hafner’s retrospective literature review of 95 calciphylaxis patients clearly showed a survival advantage post-parathyroidectomy. Thirty eight out of 58 (65%) patients treated with parathyroidectomy survived, whereas only 13 of 37 (35%) patients survived without the surgery (p = 0.007). Nonetheless, selection bias may account for the favorable surgical results since patients severely afflicted with calciphylaxis may not have been appropriate surgical candidates.

Glucocorticoid use is highly debatable since it is thought to act as a calciphylactic challenger or precipitant; however, Elamin recently reported complete ulcer healing with a combination of a 10-day course of prednisone followed by cimetidine for 3 months.

Finally, Vassa et al adjunctively utilized hyperbaric oxygen following skin grafting in a patient with combined distal and proximal calciphylaxis-induced skin necrosis. Complete ulcer and skin graft healing occurred in 2 months.

This study represents the second published report of successfully treated calcifying panniculitis with hyperbaric oxygen therapy. Healing occurred within approximately 2 months, obviating the need for any additional management such as skin grafting. Hyperbaric oxygen therapy promotes wound healing by producing an elevation of the partial pressure of oxygen within diseased tissue. The cycle of tissue hypoxia and hyperoxia is thought to be crucial in the process of neovascularization. It is proposed that macrophages within hypoxic tissues produce lactate, a potent stimulus for fibroblast migration as well as an angiogenesis factor. Hyperbaric oxygen treatments increase tissue oxygen tension which further stimulates collagen matrix leading to improved angiogenesis. Other effects of improved tissue oxygen tension, may contribute to wound healing in areas of local ischemia associated with calciphylaxis. These include improved phagocytosis by neutrophils, reduction in local tissue edema, inhibition of bacterial proliferation, and increased production of superoxide dismutase, an oxygen free-radical scavenger.

Conclusion

Hyperbaric oxygen appears to be an ideal adjunctive therapy for ulcerative cutaneous disorders such as calciphylaxis where underlying small vessel ischemia is contributory. Increasing tissue oxygen tension could potentially benefit other disease states that are sometimes complicated by small vessel ischemic ulcerations such as warfarin necrosis, the antiphospholipid antibody syndrome, vasculitis and atheroemboli.

Considering the often dismal outcome of conventionally treated calciphylaxis, novel therapies are needed. The preliminary results with hyperbaric oxygen are certainly encouraging. Larger trials addressing new treatment

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approaches such as hyperbaric oxygen are needed, though they may prove difficult due to the rarity of the disease.

References


