Calciphylaxis: a favorable outcome with hyperbaric oxygen

Steven M Dean[a] **and Howard Werman**[b]

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 white 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 atheroem-

bolic phenomena were identified and the femoral, popliteal, dorsalis pedis, and posterior tibial arterial pulses were 2+/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/fibula 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

[a]Grant Wound Care Center®, Grant Hospital, Columbus, OH, USA and [b]Department of Emergency Medicine — Hyperbaric Oxygen Division, The Ohio State University College of Medicine and Public Health, Columbus, OH, USA

Address for correspondence: Steven M Dean, Vascular Services of Ohio, Inc., 81 East Wilson Bridge Road, Worthington, OH 43085, USA.

Figure 1   Right lateral calf ulcerations with livedo reticularis (pre-HBO therapy).
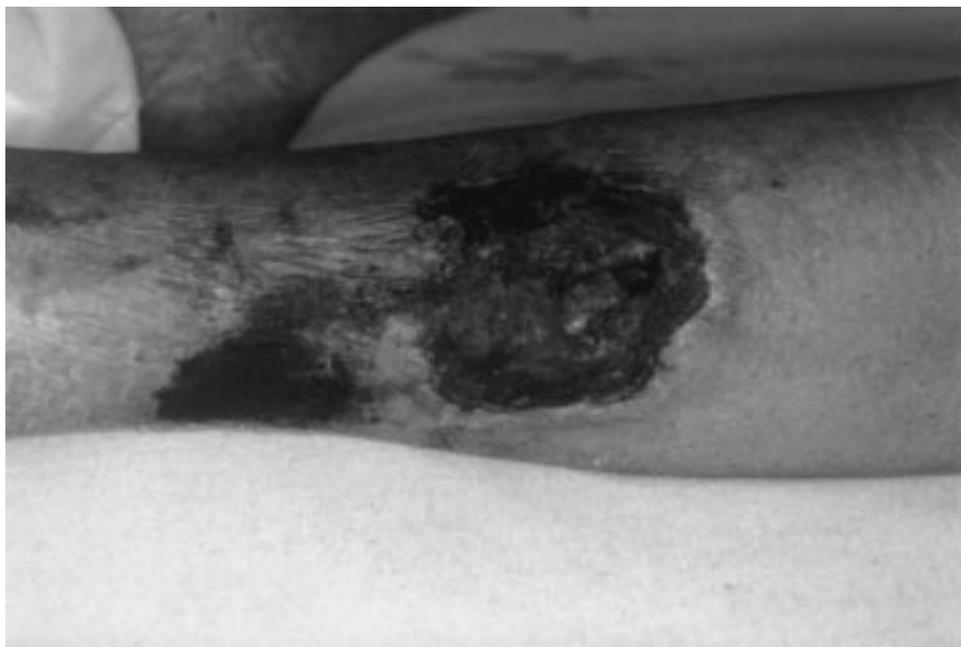

Figure 2   Left lateral calf ulcerations with eschar (pre-HBO therapy).

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
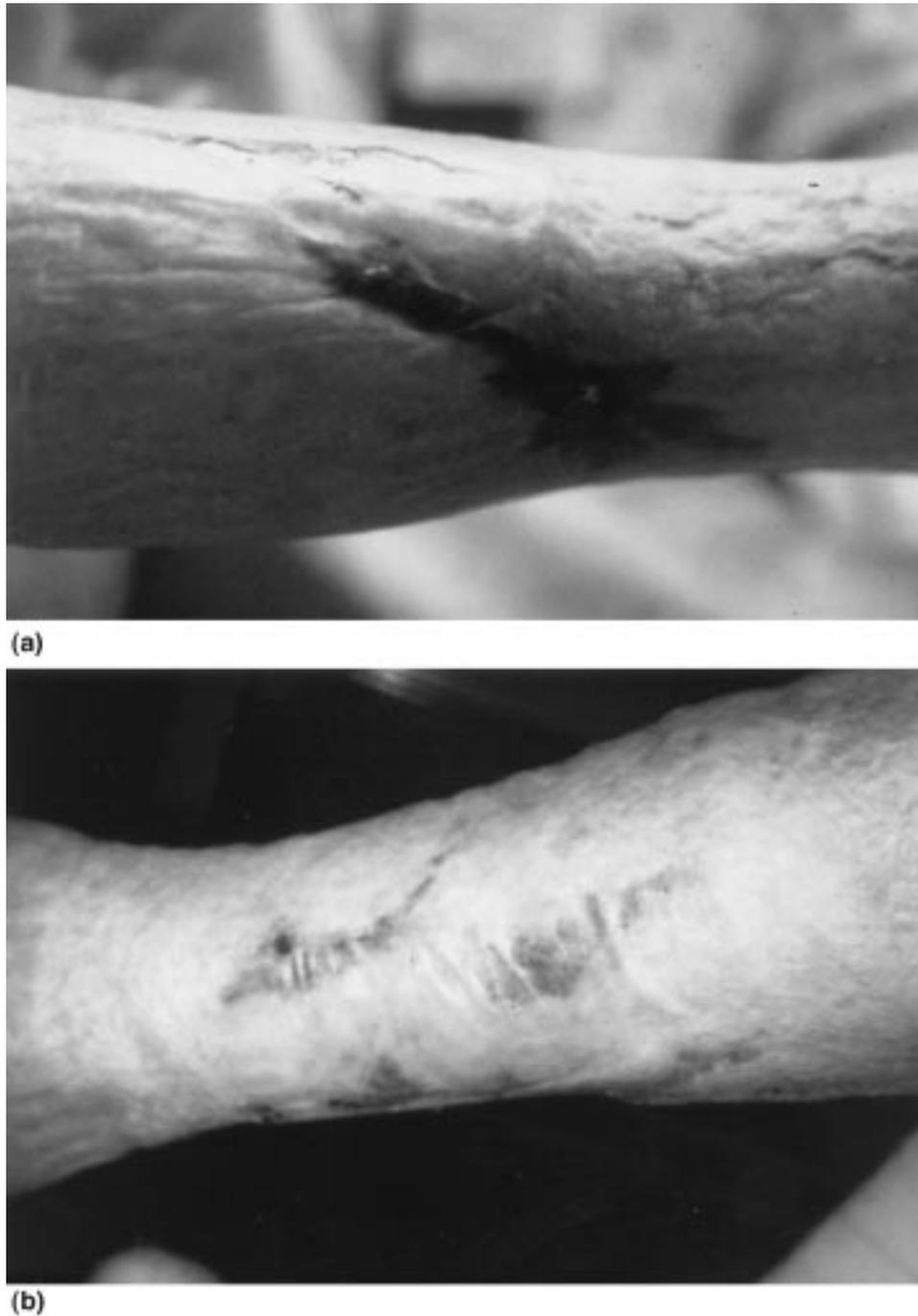
Figure 3 Right (a) and left (b) lateral calves after 7 weeks of HBO therapy. Residual staining present but the ulcer bases have undergone re-epithelialization.

calcification–cutaneous necrosis syndrome,[1] calcific azotemic arteriopathy,[2] uremic small artery disease with medial calcinosis and intimal calcification,[3] and the uremic gangrene syndrome.[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.[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).[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,[7,8] Crohn's disease,[9] or AIDS.[10] Calciphylaxis without azotemia has rarely been recorded following successful renal allografting,[11–13] and Fader recently published a stereotypical case in a cirrhotic patient with a creatinine value of 1.1 mg/dl.[14] Women are more often affected.[3,15,16]

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

followed by the rapid formation of subcutaneous nodules and plaques which can evolve into ischemic ulcerations.[17] 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,[17–20] neck,[1] breast,[21,22] and even the tongue.[23] 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.[24–26]

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.[2,10,24,26,27] Interestingly, Fischer and Morris reviewed the histopathological findings in three cases of calciphylaxis and noted the presence of an associated giant cell reaction.[24] 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.[17]

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.[24,27–29]

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.[15]

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 × 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.[30,31] Potential challengers include iron salts, albumin, trauma, cytotoxic medications and/or glucocorticoids.[2,11,25,32–36] Nevertheless, Seyle's theory may not be entirely germane in humans since his rat models primarily developed *extravascular* 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.[16,37,38] Dereure et al recently reported a case of calciphylaxis associated with a circulating anticoagulant (lupus anticoagulant).[39]

The presence of proximal clinical involvement (e.g. ulcerations on the abdomen/trunk and proximal to the knees and elbows) confers a poorer prognosis than distally located lesions (distal to the knees and elbows).[3,15,27] 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).[3]

Treatment of calciphylaxis is traditionally unsatisfactory with mortality rates ranging from 50% to 100%.[3,15,17,40–42] Death usually results from sepsis and inanition.[43] 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,[1] phosphate binders,[11] parathyroidectomy,[3,11,25,36,40,44,45] diphosphonates,[46,47] hyperbaric oxygen,[48] and although controversial, even glucocorticoids.[49]

Ulcer progression and death, despite parathyroidectomy, has been noted by several investigators,[7,9,11,25,27,34,50] yet Hafner's retrospective literature review of 95 calciphylaxis patients clearly showed a survival advantage post-parathyroidectomy.[3] 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.[49]

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.[48]

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.[51] 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,[52] reduction in local tissue edema,[53] inhibition of bacterial proliferation,[54] and increased production of superoxide dismutase,[55] 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

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

References

1 Lipsker D, Chosidow O, Martinez. F. Low-calcium dialysis in calciphylaxis. *Arch Dermatol* 1997; **133**: 798–99.

2 Wilkinson SP, Stewart WK, Parham DM, Guthrie W. Symmetric gangrene of the extremeties in late renal failure: a case report and review of the literature. *Q J Med* 1988; **67**(252): 319–41.

3 Hafner J, Keusch G, Wah 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.

4 Torok L, Kozepessy L. Cutaneous gangrene due to hyperparathyroidism secondary to chronic renal failure (uremic gangrene syndrome). *Clin Exp Dermatol* 1996; **21**: 75–77.

5 Goldsmith DJ. Diabetes, tissue infarction, and calciphylaxis (letter). *Am J Med* 1997; **102**: 171.

6 Angelis M, Wong LL, Myers SA, Wong LM. Calciphylaxis in patients on hemodialysis: a prevalence study. *Surgery* 1997; **122**(6): 1083–89.

7 Khafif RA, Delima C, Silverberg A et al. Acute hyperparathyroidism with systemic calcinosis. *Arch Intern Med* 1989; **149**: 681–84.

8 Winkelmann RK, Keating FR. Cutaneous vascular calcification, gangrene and hyperparathyroidism. *Br J Dermatol* 1970; **83**: 263–68.

9 Barri YM, Graves GS, Knochel JP. Calciphylaxis in a patient with Crohn's disease in the absence of end-stage renal disease. *Am J Kidney Dis* 1997; **29**(5): 773–76.

10 Cockerell CJ, Dolan ET. Widespread cutaneous and systemic calcification (calciphylaxis) in patients with the acquired immunodeficiency syndrome and renal disease. *J Am Acad Dermatol* 1992; **26**: 559–62.

11 Gipstein RM, Coburn JW, Adams DA. et al. Calciphylaxis in man. *Arch Intern Med* 1976; **136**: 1273–80.

12 Wenzel-Seifert K, Harwig S, Keller F. Fulminant calcinosis in two patients after kidney transplantation. *Am J Nephrol* 1991; **11**: 497–500.

13 Massry SG, Gordon A, Coburn JW et al. Vascular calcification and peripheral necrosis in a renal transplant patient: reversal of lesions following subtotal parathyroidectomy. *Am J Med* 1970; **49**: 416–22.

14 Fader DJ, Kang S. Calciphylaxis without renal failure. *Arch Dermatol* 1996; **132**: 837–38.

15 Budisavljevic MN, Cheek D, Ploth DW. Calciphylaxis in chronic renal failure. *J Am Soc Nephrol* 1996; **7**: 978–82.

16 Walsh JS, Fairley JA. Calciphylaxis (letter). *J Am Acad Dermatol* 1996; **35**(5) Pt 1: 786–87.

17 Ivker RA, Woosley J, Briggaman RA. Calciphylaxis in three patients with end-stage renal disease. *Arch Dermatol* 1995; **131**: 63–68.

18 Melikoglu M, Apaydin S, Hamuryudan V et al. Calciphylaxis: a condition mimicking necrotizing vasculitis. *Clin Rheumatol* 1996; **15**: 498–500.

19 McAuley K, Devereux F, Walker R. Calciphylaxis in two non-compliant patients with end-stage renal failure. *Nephrol Dial Transplant* 1997; **12**: 1061–63.

20 Wood JC, Monga M, Hellstrom WJ. Penile calciphylaxis. *Urology* 1997; **50**: 622–44.

21 Morris DJ, Fischer AH, Abboud J. Breast infarction after internal mammary artery havest in a patient with calciphylaxis. *Ann Thorac Surg* 1997; **64**: 1469–71.

22 Ilkani R, Gardezi S, Hedayati H, Schein M. Necrotizing mastopathy caused by calciphylaxis: a case report. *Surgery* 1997; **122**: 967–68.

23 Bedoya RM, Gutierrez JL, Mayorga F. Calciphylaxis causing localized tongue necrosis: a case report. *J Oral Maxillofac Surg* 1997; **55**: 193–96.

24 Fischer AH, Morris DJ. Pathogenesis of calciphylaxis: study of three cases with literature review. *Hum Pathol* 1995; **26**: 1055–64.

25 Duh Q-Y, Lim RC, Clark OH. Calciphylaxis in secondary hyperparathyroidism. *Arch Surg* 1991; **126**: 1213–19.

26 Richardson JA, Herron G, Reitz R et al. Ischemic ulcerations of skin and necrosis of muscle in axotemic hyperparathyroidism. *Ann Intern Med* 1969; **71**: 129–38.

27 Chan YL, Mahony JF, Turner JJ et al. The vascular lesions associated with skin necrosis in renal disease. *Br J Dermatol* 1983; **109**: 85–89.

28 Peterson R. Small vessel calcification and its relationship to secondary hyperparathyroidism in the renal homotransplant patient. *Radiology* 1978; **126**: 627–33.

29 Lazorik FC, Friedman AK, Leyden JJ. Xeroradiographic observations in four patients with chronic renal disease and cutaneous gangrene. *Arch Dermatol* 1981; **117**: 325–28.

30 Seyle H. *Calciphylaxis.* Chicago, IL: University of Chicago Press, 1962.

31 Seyle H, Gabbiani G, Strebel R. Sensitization to calciphylaxis by endogenous parathyroid hormone. *Endocrinology* 1962; **71**: 554–58.

32 Tamura M, Hiroshige K, Osajima A et al. A dialysis patient with systemic calciphylaxis exhibiting rapidly progressive visceral ischemia and acral gangrene. *Intern Med* 1995; **34**: 908–12.

33 Lugo-Somolinos A, Sanchez JL, Mendez-Coll J et al. Calcifying panniculitis associated with polycystic kidney disease and chronic renal failure. *J Am Acad Dermatol* 1990; **22**: 743–47.

34 Rubinger D, Friedlaender MM, Silver J et al. Progressive vascular calcification with necrosis of extremities in hemodialysis patients: a possible role of iron overload. *Am J Kidney Dis* 1986; **7**: 125–29.

35 Rees JKH, Coles GA. Calciphylaxis in man. *Br Med J* 1969; **2**: 670–72.

36 Khafif RA, DeLima C, Silverberg A, Frankel R. Calciphylaxis and systemic calcinosis. Collective review. *Arch Intern Med* 1990; **150**: 956–59.

37 Mehta RL, Scott G, Sloand JA et al. Skinnecrosis associated with acquired protein C deficiency in patients with renal failure and calciphylaxis. *Am J Med* 1990; **88**: 252–57.

38 Rostaing L, El Feki S, Delisle MB et al. Calciphylaxis in a chronic hemodialysis patient with protein S deficiency. *Am J Nephrol* 1995; **15**: 524–27.

39 Dereure O, Leray H, Barneon G et al. Extensive necrotizing livedo reticularis in a patient with chronic renal failure, hyperparathyroidism and coagulation disorder regression after subtotal parathyroidectomy. *Dermatology* 1996; **192**: 167–70.

40 Kane WJ, Petty PM, Sterioff S et al. The uremic gangrene syndrome: improved healing in spontaneously forming wounds following subtotal parathyroidectomy. *Plast Reconstr Surg* 1996; **98**: 671–78.

41 Androgue HJ, Frazier MR, Zeluff B, Suki WN. Systemic calciphylaxis revisited. *Am J Nephrol* 1981; **1**: 177–83.

42 Ruggian JC, Maesaka JK, Fishbane S. Proximal calciphylaxis in four insulin-requiring diabetic hemodialysis patients. *Am J Kidney Dis* 1996; **28**(3): 409–14.

43 Bargman JM. Calciphylaxis, calcinosis and calcergy – separate but not equal. *J Rheummatol* 1995; **22**(1): 5–6.

44 Roe SM, Graham LD, Brock WB, Barker DE. Calciphylaxis: early recognition and management. *Am J Surg* 1994; **60**: 81–86.

45 Blumberg A, Weidmann P. Successful treatment of ischaemic ulceration of the skin and axotaemic hyperparathyroidism with parathyroidectomy. *Br Med J* 1977; **1**: 552–553.

46 Raper RF, Ibels LS. Ostoesclerotic myeloma complicated by diffuse arteritis, vascular calcification and extensive cutaneous necrosis. *Nephron* 1985; **39**: 389–92.

47 Whittam LR, McGibbon DH, MacDonald DM. Proximal cutaneous necrosis in association with chronic renal failure. *Br J Dermatol* 1996; **135**: 778–81.

48 Vassa N, Twardowski ZJ, Campbell J. Hyberbaric oxygen in calciphylaxis-induced skin necrosis in a peritoneal dialysis patient. *Am J Kidney Dis* 1994; **23**(6): 878–81.

49 Elamin EM, McDonald AB. Calcifying panniculitis with renal failure: a new management approach. *Dermatol* 1996; **192**: 156–59.

50 Poch E, Almirall J, Alsina M et al. Calciphylaxis in a hemodialysis patient: appearance after parathyroidectomy during a psoriatic flare. *Am J Kidney Dis* 1992; **19**: 285–288.

51 Hunt TK. The physiology of wound healing. *Ann Emerg Med* 1988; **17**: 1265–73.

52 Badwey JA, Karnovsky ML. Active oxygen species and the functions of phagocytic leukocytes. *Ann Rev Biochem* 1980; **49**: 695–726.

53 Hammarlund C, Svedman C, Svedman P. Hyperbaric oxygen treatment of healthy volunteers with u.v.-irradiated blister wounds. *Burns* 1991; **17**: 296–301.

54 Brown GL, Thomson PD, Mader JT et al. Effects of hyperbaric oxygen upon *S. Aureus, P. aeruginosa*, and *C. albicans*. *Aviat Space Environ Med* 1979; **50**: 717–20.

55 Harabin AL, Braisted JC, Flynn ET. Response of antioxidant enzymes to intermittent and continuous hyperbaric oxygen. *J Applied Phys* 1990, **69**: 328–35.