

Review Article

A case series and clinical update on calciphylaxis

鈣化防禦症的病例系列和臨床更新

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Calciphylaxis is a rare disorder characterised by microvascular calcification and thrombosis often leading to rapidly progressing ulceration and tissue necrosis. It most commonly affects patients with chronic renal disease. Clinical findings are variable although painful lower limb lesions are characteristic. Some cases can be diagnosed on clinical grounds. However there are useful diagnostic adjuncts. Differential diagnosis includes atherosclerotic vascular disease, pyoderma gangrenosum, vasculitis, necrobiosis lipoidica and warfarin necrosis. Sadly, treatment remains largely supportive. There is a need for heightened interest and targeted research.

鈣化防禦症是一種罕見的疾病，其特徵為微血管的鈣化和血栓形成，常導致快速惡化的潰瘍並組織壞死。此病最常見於慢性腎病患者，其臨床表現多樣化，最具代表性的當是疼痛的下肢損傷。部份病例可經臨床診斷，亦有可靠的診斷輔助檢查。鑑別診斷包括動脈粥樣硬化性血管疾病、壞疽性膿皮病、血管炎、脂性漸進性壞死和華法林壞死。可悲的是，治療大多只限於支持性質，故提高醫學界對此病的興趣並進行針對性的研究實是刻不容緩。

Keywords: Amputation, calciphylaxis, diabetes, mortality, renal failure

關鍵詞：截肢、鈣化防禦症、糖尿病、死亡率、腎衰竭

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Introduction

Calciphylaxis is a rare and potentially fatal medical problem that may result in painful ulcers of the skin, characterised by microvascular calcification and thrombosis often leading to tissue necrosis. It has been well described in patients with end stage kidney disease, with a reported incidence of 1% per year among those on haemodialysis and a one-year survival rate of approximately 45%.^{1,2}

Treatment is essentially supportive with the mortality rate increasing to over 80% once ulceration develops, largely as a result of sepsis.³ We now present three cases of calciphylaxis that demonstrate the at times rampant nature of the disease and highlight the importance of early diagnosis and appropriate intervention. There is also a need of further research, which will hopefully bring about more positive outcomes for patients devastated by calciphylaxis.

Case 1

A 47-year-old gentleman with dialysis-dependent renal failure secondary to diabetic nephropathy, presented to hospital with a 4-week history of worsening pain in bilateral lower leg ulcers that had been present for several months. His medical history was significant for type two diabetes mellitus and hypertension. Examination revealed two ulcers on his left medial leg and one on his

right posterior leg that were tender to palpation, well-demarcated with associated central necrosis and surrounding erythema (Figure 1a). Peripheral pulses were present bilaterally.

Significant laboratory investigations revealed a serum calcium of 2.26 mmol/L (normal range 2.10-2.60), phosphorus of 2.00 mmol/L (0.75-1.50 mmol/L), calcium phosphate index of 4.52 mmol/L (<4 mmol/L), creatinine of 948 μ mol/L (60-110 μ mol/L), blood urea nitrogen of 26.5 mmol/L (3.0-8.0 mmol/L) and a parathyroid hormone (PTH) level of 45.2 pmol/L (2.0-6.0 pmol/L). Plain radiographic examination demonstrated extensive vascular calcification of his lower limb vessels (Figure 1b). Doppler arterial brachial index demonstrated normal triphasic waveforms bilaterally. Punch biopsy of the ulcerated skin was performed which revealed extensive vascular medial dystrophic calcification within the subcutaneous tissue, consistent with calciphylaxis.

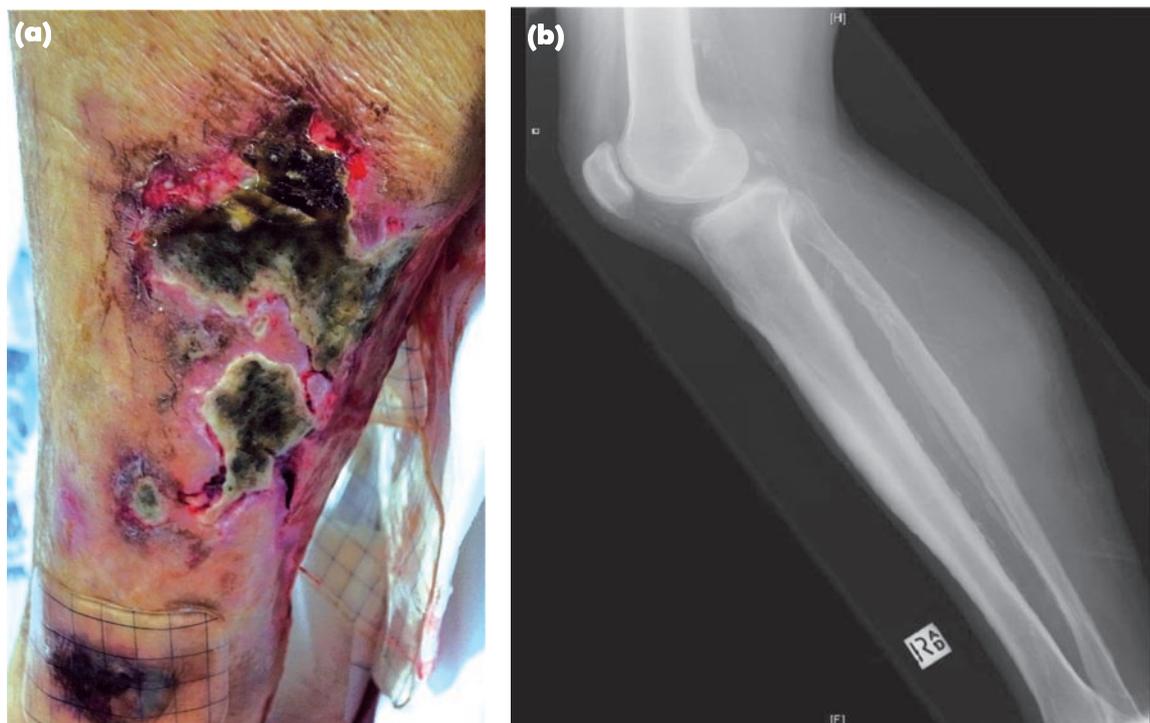


Figure 1. (a) Calciphylaxis lesions on the right medial thigh and leg. (b) Plain radiograph demonstrating calcification of the right lower leg vessels.

Surgical debridement of the lower limb ulcers followed with intra-operative histopathology demonstrating extensive necrosis involving the epidermis and dermis and calcification of the vessel walls, confirming a diagnosis of calciphylaxis. Intra-operative tissue culture was positive for coliforms, enterococcus species and coagulase negative staphylococcus and following debridement the patient was commenced on broad-spectrum intra-venous antibiotics. Medical management consisted of sodium thiosulphate infusions post regular haemodialysis, up-titration of his regular oral phosphate binder, local wound care and regular analgesics. The patient was discharged home after a 17-day hospital admission with daily dressing changes and sodium thiosulphate infusions three times weekly. His lower limb ulcers remained stable. However, he died 16 months later from end stage renal failure.

Case 2

A 41-year-old gentleman with end stage renal failure presented to hospital with a two-week history of lethargy and anorexia, and a three-day history of a rapidly progressing and atraumatically induced painful ulcer on the right lateral leg. His medical background included chronic kidney disease secondary to infective glomerulonephritis at age 17 years and three subsequent renal transplants complicated by rejection. He also had a history of multiple fractures secondary to metabolic bone disease associated with chronic hyperparathyroidism. On examination there was a solitary necrotic, well-demarcated tender ulcer on the right lateral leg (Figure 2a). Laboratory investigations demonstrated calcium of 2.27 mmol/L, phosphorus of 1.39 mmol/L, calcium phosphate index of 2.70, creatinine of



Figure 2. (a) Necrotic well demarcated ulcer on the right lateral leg secondary to calciphylaxis. (b) Plain radiograph of the right leg demonstrating extensive vascular and soft tissue calcification of a patient with biopsy proven calciphylaxis.

301 $\mu\text{mol/L}$, blood urea nitrogen of 22.9 mmol/L and PTH level of 61.7 pmol/L . A radiograph of the right lower leg demonstrated extensive vascular calcification of the anterior and posterior tibial and peroneal arteries and their superficial branches (Figure 2b). Incisional skin biopsy demonstrated ulceration and necrosis extending down to the subcutis and calcification of small and medium-sized arteries within the dermis and subcutis consistent with a diagnosis of calciphylaxis.

The patient was commenced on sodium thiosulphate and cinacalcet and re-commenced on haemodialysis with the aim of normalising calcium and phosphate levels. Despite enthusiastic medical therapy, progressive ulceration with necrosis occurred and an attempt at surgical excision of the lesion was pursued. Microscopic appearance of the excisional biopsy demonstrated dermal and fat necrosis with a neutrophilic infiltrate with associated calcified vessels present deep to the ulcer. A muscle biopsy demonstrated findings consistent with an inflammatory myositis. Repeated wound debridement and vacuum assisted dressings ensued over the following two weeks. Unfortunately, there was no clinical improvement and the decision was made to proceed with an above knee amputation. To date there has been no recurrence of painful skin ulcers post-amputation.

Case 3

A 59-year-old non-metropolitan gentleman with dialysis dependent chronic kidney disease presented to hospital with a 3-month history of an increasingly painful penile problem. He had a history of chronic renal failure secondary to interstitial nephritis. He underwent a renal transplant 11 years ago and this was complicated by rejection. Other significant history included type two diabetes mellitus and previous parathyroidectomy. On examination a well-demarcated necrotic tender lesion on the glans

penis involving the urethral meatus was noted (Figure 3a). Lower limb peripheral pulses were present bilaterally. Laboratory studies demonstrated a serum calcium of 2.19 mmol/L , phosphorus of 2.23 mmol/L , calcium phosphate index of 4.88 mmol/L , creatinine of 614 $\mu\text{mol/L}$, PTH level of 1.1 pmol/L and a negative autoantibody screen and syphilis antibody.

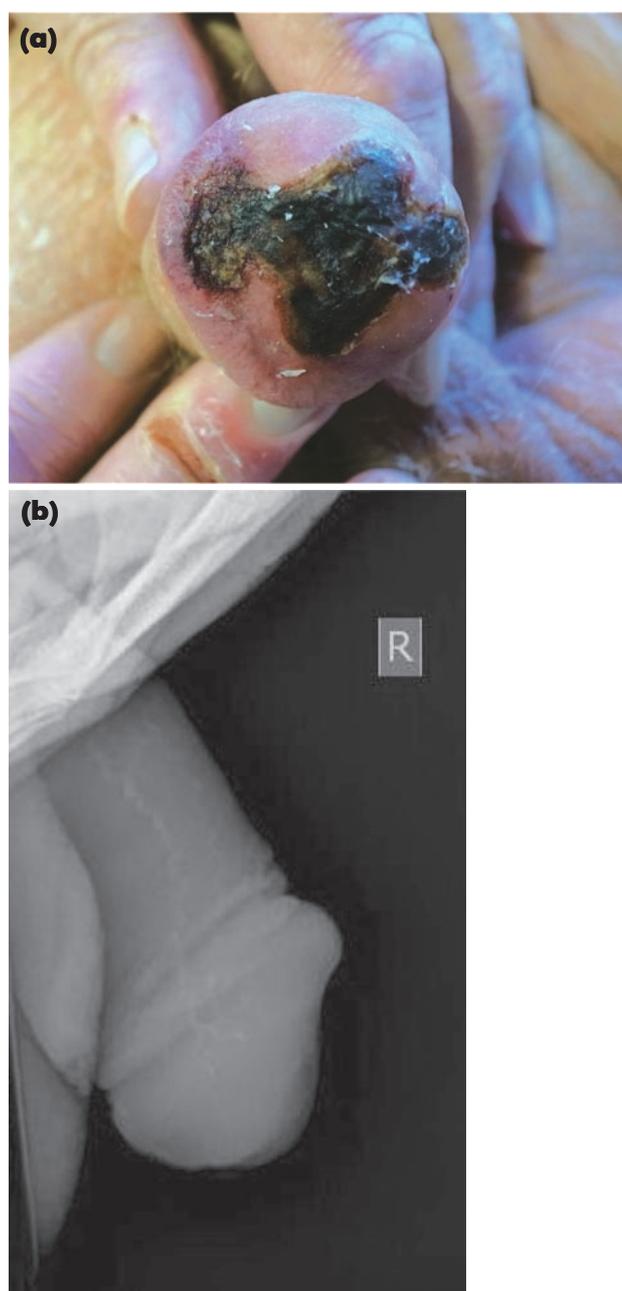


Figure 3. (a) Penile calciphylaxis. (b) Calcification of the penile vessels in a patient with penile calciphylaxis.

A pelvic X-ray demonstrated moderate calcification of the pelvic and penile vessels (Figure 3b). A pelvic angiogram was subsequently undertaken which showed extensive calcification of the external iliac and bilateral femoral arteries. Incisional skin biopsy showed no definite histological evidence of calciphylaxis. A further biopsy was discussed as the clinical picture was suggestive of calciphylaxis but was refused by the patient. Nevertheless, with the clinical presentation, biochemical data and imaging findings, it was felt that calciphylaxis was the most likely clinical challenge, despite the non-definitive penile histology. The patient was commenced on sodium thiosulphate infusions and haemodialysis was up titrated to five times weekly. Local wound care was commenced with topical steroid ointment and non-adhesive dressings. Consideration was given to hyperbaric oxygen therapy but was not pursued due to geographical and travel limitations. Surgical debridement and possible partial penectomy were discussed. However, the patient opted for continuation of non-surgical management instead. The patient was commenced on broad-spectrum antibiotics and analgesics and was discharged home following a three-week hospital admission. He is being followed up by colleagues in his local area.

Discussion

Calciphylaxis, or calcific uraemic arteriopathy, is an uncommon disorder frequently associated with chronic kidney disease, affecting approximately 4% of the dialysis dependent population, with an increased incidence over the past ten years.^{2,4} Selye et al first described the term in 1962. Then in 1976, Gipstein et al. published the first case series in human subjects and hypothesised that the underlying pathophysiology consisted of calcium deposition within the media of small and medium-sized arteries, subintimal proliferation and fibrosis leading to ischaemic necrosis.^{5,6}

Although the cause of calciphylaxis remains unclear, the risk factors have been well described and include diabetes mellitus, obesity, female gender, Caucasian race, hypoalbuminaemia and hypercoagulable states.^{1,4,7} Biochemical disturbances such as elevated serum calcium and phosphate, calcium phosphate index and parathyroid hormone have also been implicated. However normal or even low levels are often found in patients with the disease and thus do not preclude a diagnosis of calciphylaxis.⁷ In our case series, all three patients had normal serum calcium levels and two patients had elevated serum phosphate and mildly elevated calcium phosphate indices. Both patients who had not undergone previous parathyroidectomy had significantly elevated PTH levels.

The clinical presentation of calciphylaxis can be variable in its early stages. Patients often have painful lesions, including reticulate purpura, violaceous plaques and livedo reticularis.⁷ The lesions are most commonly distributed over the lower extremities and often rapidly progress to ulceration with central necrosis and finally gangrene. Ulceration can be deep involving the underlying fascia and an inflammatory myositis is frequently observed as was noted in the second case of this series. Differential diagnosis includes vasculitis, warfarin induced skin necrosis, atherosclerotic vascular disease, pyoderma gangrenosum and necrobiosis lipoidica diabetorum. Factors that favour a diagnosis of calciphylaxis include the rapidly progressive nature of the lesions, severity of pain and presence of peripheral pulses.

While calciphylaxis most commonly presents in those with chronic kidney disease, it has also been described in other patient populations. In a recent systematic review by Nigwekar et al, they noted that primary hyperparathyroidism, alcoholic liver disease, malignancy and connective tissue diseases were the most commonly reported risk factors associated with non-uraemic calciphylaxis.⁸

Interestingly, preceding corticosteroid use was associated with 61% of these cases and the majority of patients had normal calcium, phosphate and parathyroid hormone levels, suggesting additional factors are involved in its pathogenesis. In our case series all patients had a history of chronic kidney disease. However, one must be mindful to include calciphylaxis as a differential when examining a patient with a painful ulcer even if there is no history of renal impairment.

Management continues to be the most challenging aspect for clinicians caring for these patients and while it remains largely supportive, should be instigated early and follow a multidisciplinary approach. Medical treatment options that have been recently studied in retrospective studies and case series with varying degrees of success have focused primarily on normalising serum calcium, phosphate and parathyroid hormone levels.

Cinacalcet, a calcimimetic agent utilised in CKD patients with secondary hyperparathyroidism, acts by reducing serum calcium and phosphate levels by sensitising the calcium-sensing receptor to calcium. It was shown to decrease the risk of calciphylaxis in a recent study that examined 3,883 dialysis patients with hyperparathyroidism treated with cinacalcet versus placebo (6 versus 18 cases, $P=0.009$).⁹ However, evidence regarding its role in treatment of established cases of calciphylaxis is lacking, with only a few case reports published demonstrating beneficial effects in most patients with concomitant hyperparathyroidism.¹⁰

Bisphosphonate therapy has shown promising results in recent a prospective case series of eight patients diagnosed with calciphylaxis, demonstrating lesion stabilisation within four weeks and complete resolution within six months of commencing treatment in all patients.² Its

mechanism is thought to extend beyond its effects on osteoclast inhibition and calcium homeostasis, as well as through inhibition of macrophage activity and reduction in pro-inflammatory cytokines.¹¹ Systemic corticosteroids have also been trialled with mixed results noted in the literature. A small case control study recently outlined the beneficial effect of steroids in the treatment of calciphylaxis in the non-ulcerative form.³ Other studies however have reported systemic steroid use as an independent risk factor in the development of calciphylaxis and high mortality rates have been noted in non-uraemic cases when treated with systemic corticosteroid therapy.^{7,8}

Sodium thiosulphate remains the most widely utilised medical treatment for calciphylaxis even though the precise therapeutic mechanism is unclear. Initially its proposed mechanism was through the formation of water-soluble calcium thiosulphate complexes and thus inhibition of calcium phosphate precipitation.¹¹ More recent studies however suggest that its also displays anti-oxidant and vasodilatory properties, which may account for the rapid pain relief that patients often report when commenced on this treatment.¹² In the largest observational study to date that assessed the efficacy of sodium thiosulphate in 53 patients with calciphylaxis, over 70 percent of patients treated had improvement or complete resolution of their disease.¹²

The role of parathyroidectomy in calciphylaxis is controversial. Its utility in the treatment of calciphylaxis has generally focused on patients with secondary hyperparathyroidism and resultant hypercalcaemia and elevated calcium phosphate index. Smaller case series have demonstrated a reduction in mortality following parathyroidectomy.¹³ However, two larger retrospective studies demonstrated no survival benefit among those who underwent the procedure.^{1,14} Thus, there has now been a

trend towards medical management of hyperparathyroidism with cinacalcet over parathyroidectomy, due to the potential risks associated with surgery including wound infection and poor wound healing in this patient population.

Wound management remains somewhat contentious, lacks general consensus and should be tailored towards the individual patient. That said, smaller non-infected wounds with dry eschar are managed conservatively or with chemical debridement agents, such as topical enzymatic solutions. If larger necrotic areas are present or the wound is infected, surgical debridement is often undertaken, with two recent retrospective studies supporting its use by demonstrating improved survival rates among those who underwent surgical debridement compared with those who did not.^{1,14}

Hyperbaric oxygen therapy (HBOT) has also recently been explored, with the largest case series demonstrating ulcer healing in eight out of nine patients treated with HBOT.¹⁵ Currently it is generally considered second-line treatment due to factors such as cost and access to treatment. Nevertheless, it may be considered early on in patients without secondary hyperparathyroidism. Several other treatments including sterile maggot therapy, renal transplantation and vitamin K have been proposed. Unfortunately the evidence is limited to case reports and should be considered on an individual case basis. In addition, adequate analgesia and nutritional support must be integrated into the management plan of all patients presenting with calciphylaxis.

Ignoring patients suffering from calciphylaxis is heartless medicine: it is akin to turning a deaf ear to a cry for help. Consequently, we must be appropriately tuned in and be receptive and offer a helping hand. Let us join the fight against calciphylaxis and reach for a pain free land of peace and harmony.

References

1. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007;56:569-79.
2. Torregrosa JV, Durán CE, Barros X, Blasco M, Arias M, Cases A, et al. Successful treatment of calcific uraemic arteriopathy with bisphosphonates. *Nefrologia* 2012;32:329-4.
3. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. *Kidney Int* 2002;61:2210-7.
4. Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, et al. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. *Kidney Int* 2001;60:324-32.
5. Selye H, Gabbiani G, Strebel R. Sensitization to calciphylaxis by endogenous parathyroid hormone. *Endocrinology* 1962;71:554-8.
6. Gipstein RM, Coburn JW, Adams DA, Lee DB, Parsa KP, Sellers A, et al. Calciphylaxis in man: a syndrome of tissue necrosis and vascular calcification in 11 patients with chronic renal failure. *Arch Intern Med* 1976;136:1273-80.
7. Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kid Dis* 2015;66:133-46.
8. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol* 2008;3:1139.
9. Floege J, Kubo Y, Floege A, Chertow GM, Parfrey PS. The Effect of Cinacalcet on Calciphylaxis Events in Haemodialysis Patients in the EVOLVE Clinical Trial. *Clin J Am Soc Nephrol* 2015;10:800-7.
10. Velasco N, MacGregor MS, Innes A, MacKay IG. Successful treatment of calciphylaxis with cinacalcet- Calcification of the penile vessels in a patient with penile calciphylaxis: an alternative to parathyroidectomy? *Nephrol Dial Transplant* 2006;21:1999-2004.
11. Raymond CB, Wazny LD. Sodium thiosulfate, bisphosphonates, and cinacalcet for treatment of calciphylaxis. *Am J Health Syst Pharm* 2008;65:1419-29.
12. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E. Sodium thiosulfate therapy for calcific uremic arteriopathy. *Clin J Am Soc Nephrol* 2013;8:1162-70.
13. Giroto JA, Harmon JW, Ratner LE, Nicol TL, Wong L, Chen H. Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism. *Surgery* 2001;130:645-51.
14. Lal G, Nowell AG, Liao J, Sugg SL, Weigel RJ, Howe JR. Determinants of survival in patients with calciphylaxis: a multivariate analysis. *Surgery* 2009;146:1028-34.
15. Basile C, Montanaro A, Masi M, Pati G, De Maio P, Gismondi A. Hyperbaric oxygen therapy for calcific uremic arteriopathy: a case series. *J Nephrol* 2001;15:676-80.