

Calciphylaxis in Renal Hyperparathyroidism: A Case-based Review

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ABSTRACT

Calciphylaxis is a rare fatal condition associated with chronic renal failure, with a prevalence of about 4%. The condition is associated with microcalcification of small- and medium-sized arteries, leading to skin ischemia, necrosis, and gangrene. Any part of the body may be involved, but it is predominant in the lower extremities. Severe pain is usually associated with ulcers and may be difficult to manage. Although parathyroidectomy may improve the symptoms, the prognosis remains dismal with a high mortality. We present a case of severe calciphylaxis associated with renal hyperparathyroidism and briefly review the literature on the condition.

Keywords: Calciphylaxis, Hyperparathyroidism, Renal.

How to cite this article: Tan S, Yuan NK, Lim DGZ, Parameswaran R. Calciphylaxis in Renal Hyperparathyroidism: A Case-based Review. *World J Endoc Surg* 2016;8(2):156-159.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriopathy, is a rare and fatal condition with an incidence of 1% in patients with end-stage renal disease (ESRD) and renal transplant patients.^{1,2} The condition was first reported by Bryant and White,³ and the word calciphylaxis was coined by Selye in 1962,⁴ initially believing it be a hypersensitivity reaction. It is characterized by ischemic ulcers of the skin secondary to microvascular calcification and occlusion, first described by Hafner et al² in 1995.

It is a challenging and fatal condition with a less well understood pathogenesis. Most patients present with painful ulcers, predominantly involving the trunk and proximities.⁵ Secondary infections are common in the

ulcers and lead to sepsis.⁶ The condition is associated with high mortality^{7,8} and can be difficult to treat even with parathyroidectomy.

CASE REPORT

A 58-year-old Malay lady with ESRD on hemodialysis presented with 1 month history of worsening bilateral thigh pain. Physical examination revealed tender erythematous areas that were treated as tinea cruris with topical creams initially. Over a course of 2 months, these developed rapidly into eschars followed by nonhealing ulcers (Fig. 1). Lesions of similar nature appeared over her abdomen and left lateral upper arm. Diagnosis of calciphylaxis was made on histopathological examination of the ulcer (Fig. 2). Arterial duplex scan revealed



Fig. 1: Inner panel – violaceous rash over the lower abdominal wall; outer panel – large painful ischemic ulcer with slough and eschar and superadded infections

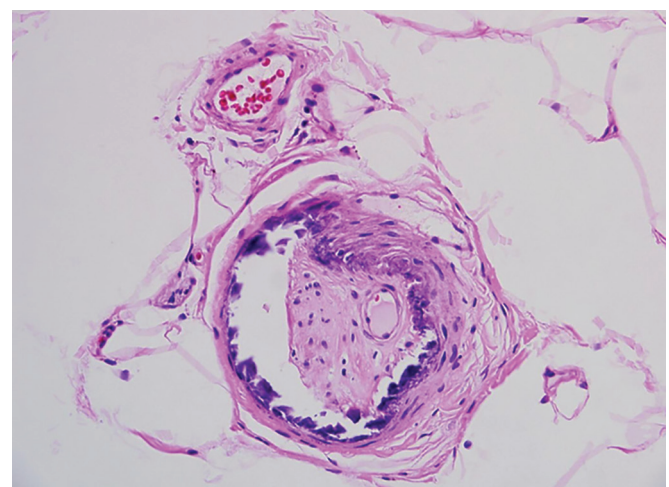


Fig. 2: Calcification of the wall of the blood vessel is seen (hematoxylin and eosin)

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diffusely calcified arteries of the lower limbs. She was treated medically with intensive wound care, analgesia, cinacalcet, low calcium dialysate, sodium thiosulfate, phosphate binders, and surgically with a total parathyroidectomy with brachioradialis autoimplantation under general anesthesia. Serum parathyroid hormone, calcium, and phosphate levels had improved; however, the ulcers persisted and worsened. Her condition deteriorated, and she passed away soon after secondary to overwhelming sepsis from multiple sources.

DISCUSSION

Calciophylaxis is a rare and serious type of extraosseous calcification, i.e., characterized by microcalcification of small- and medium-sized vessels, leading to ischemia, and necrosis. It is most commonly seen in 1 to 4% of patients with ESRD on hemodialysis. The condition may also be seen in non-ESRD patients⁹ or in postrenal transplant patients (Perloff et al), where calciophylaxis may set in within a few months to as long as 20 years.¹⁰⁻¹²

The pathogenesis of the condition is less well understood, but may be due to a decreased arteriolar blood flow as a consequence of intimal fibrosis associated with the calcification and thrombus formation within the venules. Hyperparathyroidism, vitamin D therapy, and increased serum phosphate and calcium product have been implicated as causative mechanisms in calciophylaxis. The risk factors for developing calciophylaxis are given in Table 1. The patients had all the risk factors as given in Table 1, except that of hypercoagulable state.

CLINICAL FEATURES

Patients usually present with extremely painful skin necrosis, ranging from small lesions over a large area, with two patterns of distribution: Proximal involving the buttock, abdomen, inner thighs, and limbs,¹³ and distal involving the lower extremities. The lesions usually start as a small area of erythema with a violaceous plaque or frank areas of ulcers and eschar formation, with superinfections.¹³ Uncommonly, patients may present with

systemic calciophylaxis like ischemic myopathy, arthropathy, pancreatitis, and intestinal ischemia.⁷ When the ulcers are present distally, it is important to rule out ischemic vascular pathology.

The diagnosis is confirmed by an adequate skin biopsy with sufficient subcutaneous tissue. Punch biopsy may not be enough and large biopsy may be associated with failure to heal and secondary infection. Biopsy may also help in differentiating from other ulcerative conditions like warfarin necrosis, vasculitis, and nephrogenic systemic fibrosis. Histological examination usually shows arterial medial calcification (Fig. 2), intimal hyperplasia and/or proliferation, adipocyte calcification, and infiltration of inflammatory cells. Acute and chronic calcifying septal panniculitis is the most common finding in both early and late stages of calciophylaxis.¹⁴

TREATMENT

Management of this condition is quite challenging and requires a multidisciplinary approach. Calciophylaxis is associated with a mortality rate of up to 80%. The goals of treatment consist of prevention, infection control and wound care, management of disease progression, and systemic disorder.¹⁴ It is important to maintain the levels of parathyroid hormone, calcium, phosphate, and the calcium-phosphate product within the normal range.^{15,16} Adequate pain management and surgical debridement are also necessary in these groups of patients. Early support from plastic and vascular surgeons may be needed in the treatment of this condition.

Sodium thiosulfate administered intravenously is an emerging and promising drug in the treatment for calciophylaxis.^{17,18} It acts by chelation of calcium and results in dissolution of calcium deposits. In a multicenter retrospective cohort study of 172 hemodialysis patients treated with sodium thiosulfate, the drug was tolerated well in 53 (31%) of patients where data were available.¹⁹ The drug at a dose of 25 gm in 100 mL of normal saline solution is administered intravenously over the last half-hour of each hemodialysis session, and it is the currently recommended dose for an average 70-kg person who is on thrice-weekly hemodialysis therapy.²⁰ The duration of treatment is unclear, but improvement in pain within 1 and 2 weeks after initiation of sodium thiosulfate is an important predictor of long-term response.²⁰ The drug has also been administered intralesionally into the calciophylaxis lesions.²¹

Patients with calciophylaxis have severe pain and managing it can be a challenge. It is not uncommon for patients to be on a cocktail of strong analgesics but are restricted by the type of analgesics that can be used. Commonly used strong opioids like morphine, codeine,

Table 1: Risk factors for the development of calciophylaxis (summarized from references¹⁰⁻¹³)

Female sex
Diabetes
Obesity (body mass index >30)
Hypercoagulable states, such as protein C and S deficiency and antiphospholipid syndrome
Hypoalbuminemia
Increased phosphorus concentration
Medications – warfarin, calcium-based binders, vitamin D analogs, and systemic glucocorticoids

and hydrocodone²² and nonsteroidal anti-inflammatory agents are contraindicated due to the accumulation of neurotoxic metabolites and impact on renal function with small renal reserve. Oxycodone and hydromorphone may be used with close monitoring along with neuro-pathic agents and ketamine. It is best that the patients be managed by pain medicine and palliative teams because of the severity and complexity of pain in this population.

Managing the wound requires expertise from specialists dealing with complex wounds. The goals of wound care are to control exudate, prevent infection, facilitate wound healing, and keep the wound bed free of necrosed devitalized tissue.²⁰ The role of surgical debridement is controversial.^{23,24} The decision to debride should be based on the patient's total condition, as patients with calci-phylaxis have impaired wound healing. Weenig et al²⁵ demonstrated that surgical debridement was significantly associated with survival. Infected wounds may need surgical debridement and placement of negative pressure vacuum system to facilitate healthy granulation over which split skin graft could be applied. Large necrotic eschars may require intervention if conservative management fails. Treatment with hyperbaric oxygen²⁶ and sterile maggot therapy²⁷ has been described as second-line therapies.

The role of parathyroidectomy has been established in the treatment of calci-phylaxis;²⁸ however, some recommend it only in the presence of hyperparathyroidism.²⁹ The theory is that by removing the parathyroid glands, the drive of parathyroid hormone as a tissue sensitizer and a cause of hypercalcemia improves calci-phylaxis and limits the progression of wounds and complications.³⁰ Therefore, patients who undergo parathyroidectomy have been shown to have improved wound healing^{28,31} and increased survival.² Patients should undergo total parathyroidectomy rather than subtotal parathyroidectomy.

Calci-phylaxis is a condition associated with significant morbidity and mortality. Most cases of mortality result from sepsis and severe infections, ranging from 33 to 87%.^{2,33} A multivariate analysis on 26 patients showed that female gender, obesity, and need for vascular procedures are significant factors associated with poorer survival.³⁴ Similarly, extensive lesions, prior renal transplant, and leukocytosis are also associated with adverse outcomes.³²

CONCLUSION

Calci-phylaxis is a serious condition with high morbidity and mortality and should be managed by a multidisciplinary team. The aim of treatment should be to decrease the serum calcium-phosphate product. Patients are at increased risk of infection and severe sepsis. Wound

care objectives should include pain control, avoidance of trauma, and the prevention of infection. Emerging evidence indicates that intravenous sodium thiosulfate should be strongly considered as well.

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