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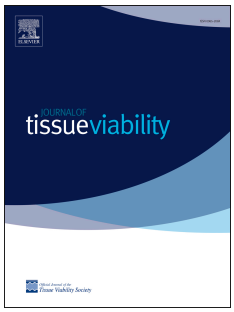


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**Title**

Calciphylaxis – a case study in a patient with Maori heritage

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**Abstract**

This case history describes a rare complaint - Calciphylaxis, seen in a New Zealand Maori patient undergoing renal dialysis. This condition causes non-healing tissue ulceration, typically with sepsis and is associated with a very high mortality rate. The need for vigilance among health professionals is highlighted, including the risk factors that may faciliate an early diagnosis; together with the value associated with a multi-disciplinary team approach to management.

**Keywords**

Calciphylaxis

Calcific uremic arteriolopathy

Ulceration

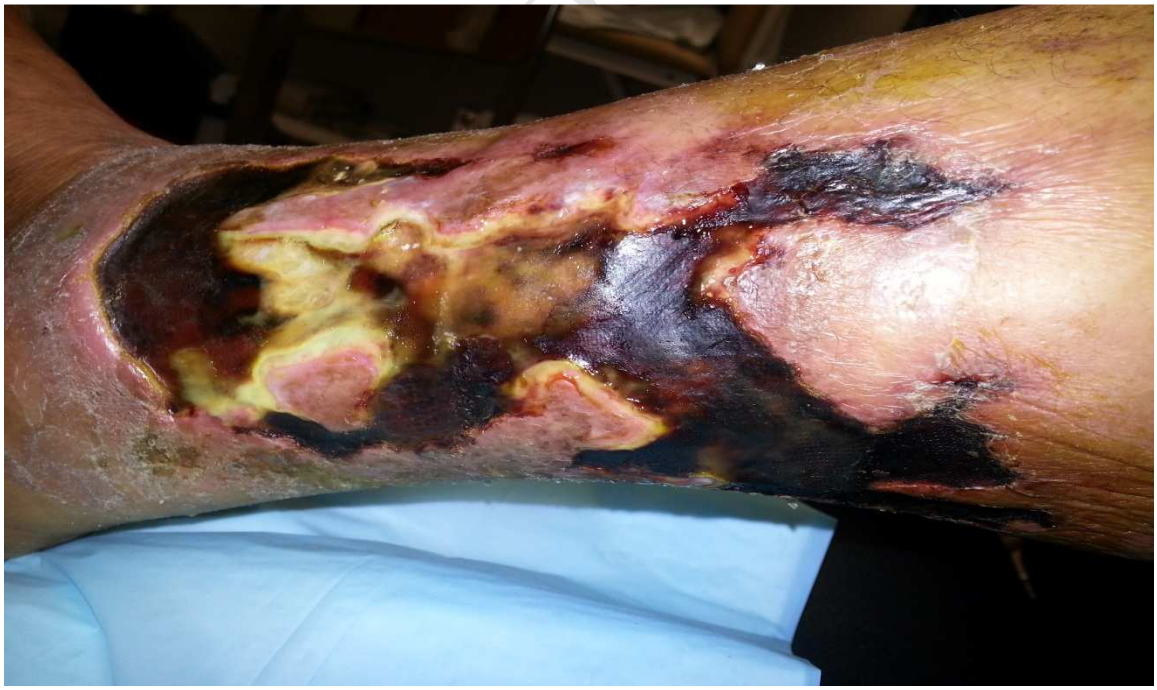
## 1 Introduction

Calciphylaxis or calcific uremic arteriolopathy (CUA) is a rare, but potentially devastating complication that almost exclusively affects patients undergoing dialysis for renal failure (stage 5 chronic kidney disease or CKD-5). [1] We report a case of calciphyaxis in a New Zealand Maori patient with CKD-5.

## 2 Case history

A 66 year-old female patient of New Zealand Maori ethnicity with CKD-5 secondary to complicated type-two diabetes mellitus was seen at the multidisciplinary clinic for assessment of recent leg ulceration. She was undergoing haemodialysis (3x/week) and had a background of Peripheral Vascular Disease with right below knee amputation and stenting of the the left superficial femoral artery in the preceding 12 months. A small black eschar was first noted over the lateral aspect of the leg. This lesion rapidly progressed to an irregular shaped, necrotic spreading ulceration with black eschar formation and violaceous peri-wound tissue (Livedo Reticularis) over 2-3 weeks. The lesion was mildly malodourous, very painful and wound depth was difficult to determine (Figure 1).

Figure 1 – Presentation of ulceration



Surgical debridement and biopsy was undertaken and intra-venous (IV) antibiotics instigated (Gentamicin) to combat any super-added infection. Calciphylaxis was suspected on the basis of patient profile and clinical features. Histology of specimens indicated *"underlying granulation tissue, fibrosis, chronic inflammation and scattered calcifications within the superficial and deep dermis"* were consistent with Calciphylaxis. Unusually calcium and phosphate levels remained normal, where increased levels might normally be expected. A summary of additonal tests are presented in Table 1.

Table 1 – Clinical characterisitcs

| **Characterisitic** | **Value** | **Range** |
|---|---|---|
| Sodium | 139 mmol/L | 135-145 |
| **Potassium** | **3.1** mmol/L | **3.5-5.2** |
| Chloride | 96 mmol/L | 95-110 |
| Glucose | 6.1 mmol/L | 3.0-11.0 |
| **Urea** | **10.2** mmol/L | **3.2-7.7** |
| **Creatinine** | **440** mmol/L | **45-90** |
| Urate | 0.22 mmol/L | 0.14-0.36 |
| Phosphate | 0.91 mmol/L | 0.70-1.50 |
| Calcium (ablumin adjusted) | 2.50 mmol/L | 2.1-2.6 |
| **Albumin** | **28 g/L** | **38-52** |
| Magnesium | 0.77 mmol/L | 0.70-1.00 |
| CRP | 154 | <5 |
| **Haemoglobin** | **84 g/L** | **115-155** |
| **RBC** | **2.99 xE12/L** | **3.6-5.6** |
| **Haematocrit** | **0.27** | **0.35-0.46** |
| Mean cell volume | 90 fL | 80-99 |
| Mean cell haemoglobin | 28.1 pg | 27-33 |
| RDW | 14.7 | 11.5-15.0 |
| Platelets | 383 xE9/L | 150-400 |
| MPV | 9.2 fL | 9.0-12.2 |
| **WBC** | **17.2 xE9/L** | **4.0-11.0** |
| **Neutrophils** | **17.2 xE9/L** | **1.9-7.5** |
| **Eosinophils** | **17.2 xE9/L** | **0-0.5** |
| **Monocytes** | **17.2 xE9/L** | **0.2-1.0** |
| Lymphocytes | 1.5 xE9/L | 1.0-4.0 |

Our patient's foot pulses were not palpable and monophasic on Doppler capture. Duplex scan confirmed the recently stented artery remained patent, although there was extensive untreatable arterial disease in the arteries further down the leg, with no vessel reaching the foot uninterrupted. Despite the latter, there was no clinical evidence of critical limb ischaemia. However, with little sign of improvement, further surgical debridement was undertaken three weeks later together with continued IV antibiotics. Tissue culture isolated heavy growths of gram negative bacilli and Pseudomonas Aeruginosa and Enterobacter Clocae complex. Given the range of bactera isolated, the ultra broad spectrum antibiotic

Metropenem IV was added to Gentamicin, to give broader cover. Additionally, Sodium Thiosulphate infusions were undertaken to manage the severe metabolic acidosis that can accompany Calciphylaxis.

In spite of surgical debridements, IV antibiotics and sodium thiosulphate over the following two weeks, the patient developed extensive spreading necrosis and sepsis requiring a left above knee amputation. After a prolonged period of rehabilitation (12 weeks) she recovered enough to return home and remains surprisingly positive and well.

## 3 Discussion

Calciphylaxis is a rare complication seen in patients with CKD-5 undergoing Haemodialysis with a reported prevalence of 1-4% [1]. Lesions are most commonly noted on the legs, but may occur on upper limbs or trunk [2,3]. While the precise aetiology of Calciphylaxis remains unknown, the pathology is caused by calcium deposits in the microvascular network causing vascular obstruction [2,4]. The subsequent ischeamia causes necrosis of skin and fatty tissue with associated vascular calcifications and thrombosis [2,3]. These changes lead to non-healing tissue ulceration and sepsis with very high mortality rate (60-80%); overwhelming sepsis being the main cause of death [5].

### 3.1 Clinical presentation and diagnosis

The initial presentation, as noted in this case, is typically painful mottling of skin, sometimes precipitated by minor trauma, occasionally with haematoma. Underlying necrosis can be deep, even in early stages. A variety of risk factors are reported (Box 1). Our patient was female, in whom Calciphylaxis is more common [6], but notably not of Caucasian ethnicity. Calciphlyaxis has rarely been reported in Maori populations, diabetes and CKD-5 were other key risk factors. Recognising these risk factors together with vilgilance associated with new lesion formation represents the best chance for early diagnosis. [6]

Box 1 – Risk factors for Calciphylaxis [3,7]

| |
|---|
| Female gender |
| Caucasian ethnicity |
| Diabetes |
| End Stage Renal Failure |
| Increasing time on renal dialysis |
| Hyperparathyroidism |
| Hyperphosphatemia |
| Hypercalcamia |
| Calcium supplementation |
| History of protein C or S deficiency |
| Liver disease |
| Warfarin or corticosteroid therapy |
| Obesity |

An increase in Calciphylaxis is reported over recent years, which may represent a true increase in prevalence due to greater levels of chronic kidney disease with a range of underpinning aetiology (e.g. obesity, diabetes and aging population in western societies) and/or an increased clinical recognition [8]. People with Maori and Pacific island heritage have a greater incidence of CKD-5 in comparison to the rest of the population – particularly in relation to diabetes; typically these groups also suffer from poorer outcomes [9-11]. As Calciphylaxis is almost exclusively seen in CKD-5, consequently a higher index of suspicion is required by clinicians managing these populations; particularly in respect of early recognition and management. Blood tests did not reveal any apparent dysregulation in calcium or potassium levels. Recent reviews [6] indicate other isolated case reports with similar findings suggesting a need for further investigation in larger observation studies.

Diagnosis is initally based on clinical appearance and history [5]. Tests for elevated calcium/phosphate and parathyroid hormone levels may aid the clinical picture, but remained normal in this case [5,8]. However, particularly in dialysed patients calciphylaxis can occur when calcium and phosphate levels are normal [12]. Wong et al. [10] found deep tissue biopsy more helpful than punch biopsy, histological examination remaining the gold standard for diagnosis [3]. However, biopsy may also lead to new lesion formation [6,14]. Drawing these aspects together, Hayashi et al.[5] proposed a diagnostic criteria. Key differential diagnosis (owing to their similar clinical appearance) include warfarin-induced skin necrosis, cholesterol embolisation, pyoderma gangrenosum and primary vasculitis [15-17]. The history in this case did not indicate these alternatives. Where Calciphylaxis is suspected in the absence of renal disease other co-morbidities (e.g. primary hyperparathyroidism, liver disease, and inflammatory arthritis) can lead to a higher index for suspicion [7,10,18].

**3.2 Management**

There appears little consensus in the literature regarding management although a multi-disciplinary approach that can incorporate wound and pain management, improved biochemical paraemters and pharmacological management are thought to be key [2,19,20]. Controlling infection, with a low threshold for broad spectrum antibiotic therapy and managing pain are primary considerations, together with improving arterial supply where necessary, often in conjunction with surgical debridement [4,6]. However, surgical debribement is controversial owing to vasculopathy [2,15]. Debridement reportedly increases one-year survival rates [21], but requires experienced teams owing to the complexity of these wounds [6,22]. If only a dry black eschar and no ulcer or infection are present, it may be better to not debride as this could worsen the condition. Typically aggressive wound care is required, which may include hyperbaric oxygen where vascular perfusion is poor and re-

vascularisation not possible [2]. Additionally, opioid-based analgesia may be required to facilitate optimal wound care as these wounds are often very painful [3]. In our case Sodium Thiosulphate infusion (previously used for cyanide poisoning) was instituted to manage the toxicity associated with spreading infection. Nigwekar and colleagues reported considerable clinical benefit from Sodium Thiosulphate infusion in a cohort of 172 patients with Calciphylaxis [23]. Alternatviely, Bisphosphonates (e.g. Pamidronate infusion) have reportedly been used with some success in decreasing mineralisation and reducing pro-inflammatory cytokines [3].

Where indicated, the normalisation of calcium/phosphate and parathyroid hormone levels where indicated is helpful. A range of options are available to faciliate this, including increasing the number of dialysis sessions and/or parathyroidectomy [3,7], but was not required in this example. More recently, success with Cinacalet (a calcimimetic agent) as a first line treatment have been reported [24].

However, the uncommon nature of calciphylaxis coupled with an incomplete understanding of the pathogenesis have limited the options for high quality controlled trials, with most of the available knowledge derived from case series.

## 4 Conclusion

Calciphylaxis is a rare, but potentially devastating complication associated with a high mortality rate, most commonly seen in renal failure. We highlight the need for vigulence among health professionals who treat patients at risk of calciphylaxis to facilitate early diagnosis and mullti-disciplinary management, which incorporates wound care, pain management, surgical debridement, and dialysis as well as mimising risk factors as Calciphylaxis often has an unfavourable prognosis.

**Conflicts of interest**

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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**Highlights**

- Calciphylaxis is a rare complication with high mortality seen in renal failure
- Vigulence is needed to facilitate early diagnosis
- Mullti-disciplinary management is key to reducing morbidity and mortality