Clinical Note

Symptomatic Management of Calciphylaxis: A Case Series and Review of the Literature

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Abstract
Calciphylaxis, or calcific uremic arteriopathy, is a rare complication of end-stage renal impairment. It is characterized by the development of small vessel vasculopathy with subcutaneous necrosis and ulceration. Intense pain and cutaneous hyperesthesia are prominent features. Mortality rates are high, and the resulting morbidity is significant. While symptomatic management is the mainstay of treatment, it can be challenging. We describe the symptomatic management of a series of three patients with calciphylaxis. Particular emphasis is placed on the use of multimodal analgesia with high-dose opioids, ketamine, and benzodiazepines and on the use of preemptive analgesia. J Pain Symptom Manage 2006;32:186–190. © *2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Calciphylaxis, calcific uremic arteriopathy, vasculopathy, dialysis, ischemia, cutaneous ulceration, pain control, symptom management

Introduction

Calciphylaxis, or calcific uremic arteriopathy, is a rare complication of end-stage renal impairment, which is also occasionally encountered in other clinical settings.[1,2] The incidence in patients receiving dialysis may be as high as 4%;[3,4] female gender, younger age, obesity, diabetes, and suboptimal dialysis efficacy are all recognized risk factors.[5]

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The condition is characterized in its early stages by painful purpuric skin lesions and livido reticularis, and subsequently by the development of subcutaneous necrosis and ulceration.[6] The underlying pathology is a small vessel vasculopathy in the absence of vasculitis, where mural calcium deposition results in vascular fibrosis and thrombosis, leading to tissue ischemia. The initial precipitants of this process are not well understood, though hyperparathyroidism and an elevated calcium-phosphate product are thought to play a role.[7] Mortality rates are high, with death commonly resulting from sepsis within months. Significant morbidity also results, from cutaneous hyperesthesia and intense pain, infection, thromboembolism, and physical deconditioning.[8]

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Management of calciphylaxis remains primarily supportive. No disease-modifying treatment is supported by high-quality evidence, though case series have demonstrated good results in carefully selected patients with long-term hyperbaric oxygen therapy[9,10] and parathyroidectomy,[11,12] with some reports of complete resolution of ulceration. However, for the majority of patients these treatments are unsuitable or ineffective.

The challenges of providing symptomatic relief to patients with calciphylaxis are widely recognized. However, only a single case report has specifically addressed symptom control in this condition.[13] In this case series, we present the experience of this service in the management of the complex symptom issues of patients with calciphylaxis.

Case Series

Patient 1

The patient was a 54-year-old woman with multiple medical problems, including a 25-year history of renal failure secondary to analgesic nephropathy. A cadaveric renal transplant had failed 8 years previously, since which time she had been hemodialysis dependent. Her renal failure was complicated by recurrent fistula thromboses, persistently suboptimal dialysis efficacy, and the development of calciphylaxis. Other medical problems included obesity, hypertension, and anxiety.

Calciphylaxis had first manifested as a rapidly enlarging ulcer of the right thigh. Further ulcers developed over both legs, and a biopsy confirmed the diagnosis. Initial treatment with parathyroidectomy and high-dose immunosuppression was ineffective. Eighteen months after the initial diagnosis, she was admitted by her nephrologists with worsening symptoms. Frank ischemia had developed at the periphery of several ulcers and at two digits. The patient described severe somatic and neuropathic incident pain with both movement and dressing changes, as well as marked odor from the lesions. She was bedridden as a result of pain.

Her initial symptomatic management comprised intravenous tramadol 50 mg three times daily, morphine 2.5–5 mg intravenously for breakthrough pain, and amitriptyline 25 mg orally at night as a coanalgesic. This was not successful in reducing her distress. Hyperbaric oxygen therapy was introduced, also with limited success. A dressing regimen of charcoal and silver sulfadiazine dressings, chosen for antibacterial and antiodor properties, was applied daily.

Her course was then complicated by the development of a *Staphylococcus aureus* septicemia, which was treated with intravenous antibiotics. Her condition deteriorated, and her opioid requirements escalated. She developed significant opioid toxicity, with myoclonic jerks, worsening agitation, and a declining conscious state. At this point her vascular access failed again. In view of her poor quality of life, the decision was taken to cease dialysis and hyperbaric oxygen, and pursue a purely symptomatic approach to management. She was then transferred to the palliative care unit.

Her distress remained marked. The existing opioids were ceased, and her maintenance analgesic regimen was changed to sufentanil 600 μg over 24 hours by continuous subcutaneous infusion, with intermittent subcutaneous clonazepam 1 mg and chlorpromazine 25 mg for agitation. Sufentanil 100 μg sublingually as needed for breakthrough pain was augmented with preemptive subcutaneous ketamine 50 mg and midazolam 10 mg prior to movement and dressing changes. Inhaled nitrous oxide was also tried, but the patient was unable to cooperate.

This analgesic combination was only partially effective in reducing her pain. The day after admission, a subcutaneous infusion of ketamine 500 mg over 24 hours was commenced and the dose of sufentanil increased to 900 μg. These changes were largely effective, and the patient was able to tolerate both dressing changes and movement without distress. The symptoms of opioid toxicity also resolved, but her conscious state did not improve. She remained semiconscious until her death 3 days after transfer.

Patient 2

The patient was a 65-year-old woman, who resided in a nursing home. Her medical problems included bipolar affective disorder, Parkinson's disease, Type 2 diabetes, obesity, and ischemic heart disease. She was admitted with