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Buprenorphine for the Management of Intractable Pain in Skin Ulcers Associated With Calcific Uremic Arteriolopathy

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Background: Calcific uremic arteriolopathy, or calciphylaxis, is a rare and severe condition marked by calcification of small-to-medium blood vessels, causing tissue ischemia and necrosis. The pain is excruciating, emanating from tender lesions, severely impacting movement and touch. No approved treatment exists, making effective pain management vital for improving quality of life and outcomes.

Case Report: A woman with end-stage renal failure and calciphylaxis-related ulcers on the inferior pannus, left medial thigh, and right gluteus experienced refractory pain despite opioid therapy. Palliative care initiated adjustive buprenorphine, yielding remarkable and sustained pain relief.

Conclusions: This case emphasizes the urgent need for better treatment options for calciphylaxis, particularly in pain management. The success of adjunctive buprenorphine highlights the debilitating condition, ensuring comprehensive pain management.

Key words: Calciphylaxis, hemodialysis, pain, buprenorphine, palliative care

BACKGROUND

Calciphylaxis, also referred to as calcific uremic arteriolopathy, was initially identified in end-stage renal disease (ESRD) patients undergoing dialysis. In the United States, its annual incidence is approximately 35 cases per 10,000 patients (1). Previously reported, the one-year survival rate for all patients with calciphylaxis stands at 45.8%, with significantly poorer outcomes observed in those with ulceration, with an estimated mortality rate of 80% (2).

The condition manifests with the emergence of a painful purplish rash that progresses into ischemic necrotic ulcers due to arteriolar blockage (3). Pain originating from ischemic cutaneous lesions is a hallmark of calciphylaxis and can be exceedingly challenging to manage, often proving debilitating and refractory to opioid treatment. As the lesions advance, ulceration, necrosis, and infection may occur, typically affecting proximal areas with increased adipose tissue, such as the abdomen, thighs, and buttocks (4). The efficacy of available pharmacological and nonpharmacological interventions remains unclear, with individual responses varying among patients.

Current management strategies for calciphylaxis-associated pain involve aggressive opioid titration and the adjunctive use of neuropathic pain agents. Given the impaired renal function in calciphylaxis patients, pharmacotherapy necessitates consideration of renal dose adjustments and the risk of renal toxicity. However, due to the rarity and severity of the condition, limited high-quality trial evidence exists to guide pain management (5). The inclusion of adjunctive buprenorphine therapy, in this case report, underscores the exploration of novel approaches for relieving pain associated with calciphylaxis ulceration. This case presents a patient with calciphylaxis in the setting of ESRD with pain management proving challenging, necessitating exploration of adjunctive buprenorphine therapy.

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CASE PRESENTATION

A 56-year-old Caucasian woman with significant medical comorbidities, including chronic kidney disease (Stage V) secondary to oxalate nephropathy, a solitary kidney, medically complicated obesity (body mass index 53.7), pulmonary hypertension, and atrial fibrillation on chronic anticoagulation with warfarin, was admitted to the hospital for generalized weakness and failure to thrive in the setting of an acute lower urinary tract infection. The admission lasted 5 months, during which nephrology consultation revealed acute on chronic renal failure due to hypovolemia resulting from poor oral intake and gastrointestinal losses from nausea and vomiting. Despite considerations for dialysis in previous hospitalizations, it was not initiated due to her poor health status. The laboratory results displayed a creatinine of 7.03 mg/dL (0.59-1.04 mg/dL), blood urea nitrogen of 77 mg/dL (6-22 mg/dL), and bicarbonate of 12 mmol/L (22-29 mmol/L) that revealed acute kidney injury and acidemia.

Ten days into her hospitalization, the patient's condition deteriorated, necessitating transfer to the medical intensive care unit (MICU) due to refractory hypotension despite adequate fluid resuscitation. She was diagnosed with urosepsis and treated with vancomycin and piperacillin/tazobactam. Hemodialysis was scheduled 3 times weekly, reflecting the progression from chronic kidney disease (Stage V) to end-stage renal failure (ESRF).

During her MICU admission, the patient developed tender subcutaneous nodules on the inferior pannus, right gluteus, and left medial thigh, accompanied by localized pain. Ultrasound revealed small (< 2 cm) fluid-filled pockets with surrounding edema. Computed tomography scan confirmed multiple subcutaneous nodules of calcification (Fig. 1). Over the course of the patient's admission, she developed lesions that were violaceous and purple in color with a reticular pattern. The lesions continued to progress to more pronounced necrotic ulcers (Fig. 2). Dermatology consultation confirmed calciphylaxis. Wound care was prioritized, and warfarin was switched to apixaban due to its association with calciphylaxis. Sodium thiosulfate was initiated during hemodialysis to decrease calciphylaxis progression.

The patient reported constant burning sensation-like soreness focused in her abdominal area, bilateral hips, and bilateral lower extremities. Throughout the hospitalization, she experienced intense pain, rating 8/10 on the Visual Analog Scale (VAS). Specifically, she reported sharp, predictable incident pain upon leg movement or application of pressure to the areas affected by her calciphylaxis wounds, scoring 10/10 on the VAS.

Initially, her pain was managed with oral hydromorphone 2 mg every 4 hours as needed, along with acetaminophen 1,000 mg 4 times daily. Due to significant uncontrolled pain, she was transitioned to a hydromorphone patient-controlled analgesia pump with a 0.2 mg dose lockout at 10 minutes. Despite this, she continued to experience uncontrolled pain, leading to constant refusals of care related to wound management. Consequently, she was started on ketamine 20 mg as needed with dressing changes. However, she developed dissociation and psychosis thought to be secondary to ketamine use, prompting a transition back to hydromorphone. Despite this, her pain remained uncontrolled.

Given the persistent nature of her pain, a long-acting opioid compatible with renal function was considered, with methadone or buprenorphine at the forefront. Buprenorphine was favored due to its superior safety profile in a patient with baseline QT interval (QTc) prolongation and recent pain sedation mismatch with the use of a full opioid agonist. She was started on buccal buprenorphine 150 mcg twice daily, which was quickly titrated up to 300 mcg twice daily while continuing with 0.4 mg of intravenous hydromorphone for breakthrough pain. Following the increase in buprenorphine dose (300 mcg twice daily), her oral morphine equivalents (OME) use decreased to 13, representing an 81% reduction in OME usage after initiation of buprenorphine (Fig. 3). Her dressing changes became more tolerable, and her overall pain reduced to 4/10, remaining stable until her transition to terminal care. Informed consent was obtained from the patient for publication for the ethical principle of autonomy and transparency.

DISCUSSION

Currently, there is no standardized, evidence-based approach available to guide clinicians in addressing pain associated with calciphylaxis. The existing evidence indicates inconsistency in pain management practices for calciphylaxis (6). Chinnadurai et al (6) have developed clinical practice recommendations for managing calciphylaxis-related pain, drawing from literature on pain management in ESRF and expert consensus. They advise against the use of morphine, oxycodone, tramadol, and codeine for baseline analgesia due to the risk of opioid-induced neurotoxicity (e.g., confusion, drowsiness, seizures) in ESRF patients. Instead, they recommend employing fentanyl or fentanyl analogs,

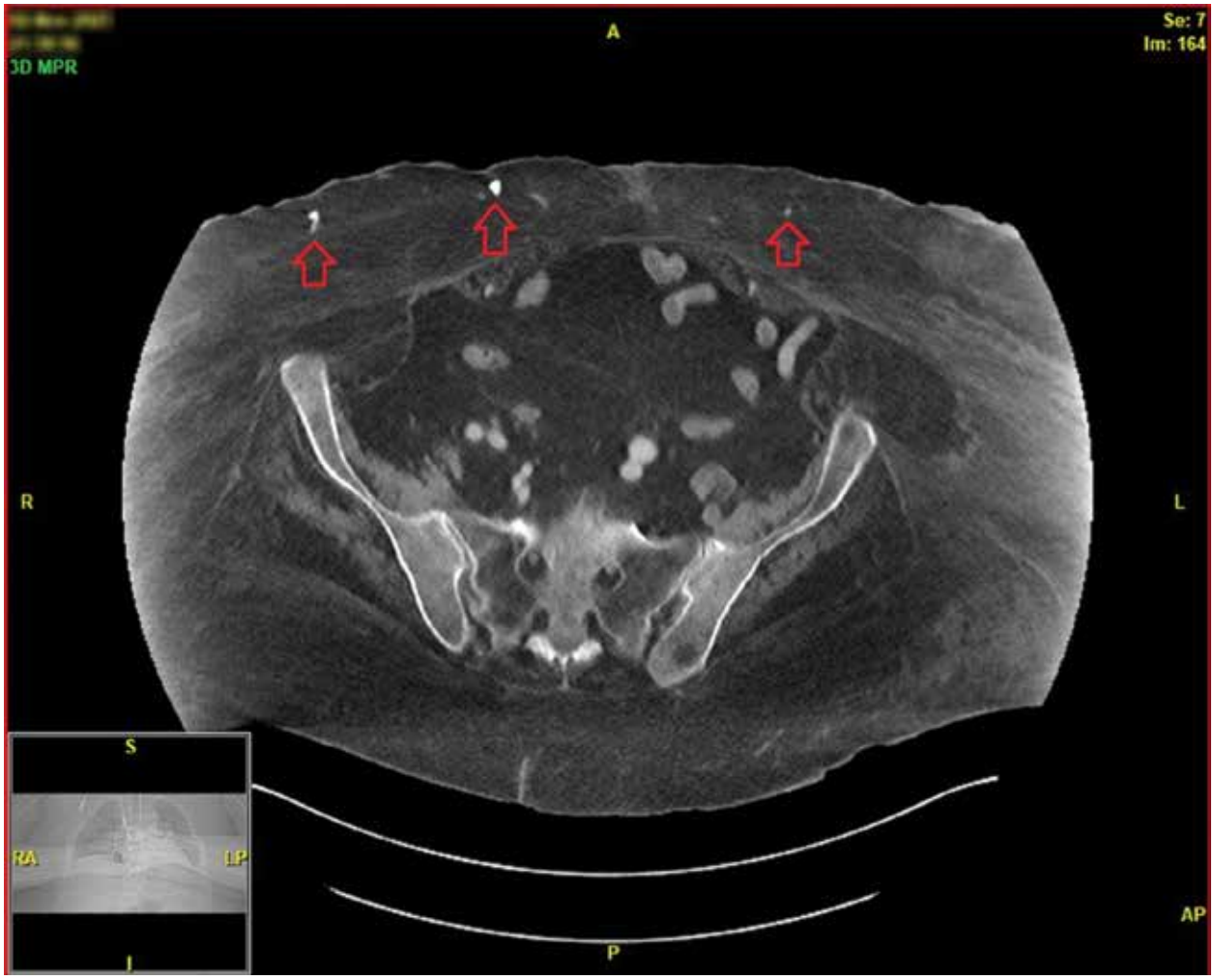

Fig. 1. Computed tomography findings of scattered subcutaneous calcified granulomas in a patient with calciphylaxis.

benzodiazepines, local anesthetics, neuropathic pain agents, buprenorphine, or ketamine (6).

When prescribing analgesics for patients with ESRF, meticulous attention must be paid to pharmacokinetic factors, particularly the extent to which the drug and its relevant active metabolites are eliminated renally, as well as whether dialysis removes the drug (7-8). Patients with ESRF face heightened susceptibility to adverse drug reactions, necessitating dose adjustments and avoidance of specific analgesics (7). Morphine, oxycodone, tramadol, and codeine are commonly avoided due to diminished elimination and heightened accumulation of active metabolites.

In the challenging clinical scenario of calciphylaxis, the use of buprenorphine offers the opportunity to utilize a long-acting (half-life of buccal film: 27.6 hours) and potent analgesic (25-100 times more potent than morphine) with a potentially better safety profile given its unique pharmacological properties (9). Buprenorphine functions as a partial mu-opioid receptor agonist, allowing it to provide analgesia without severe side effects compared to full opioid agonists. This would include less respiratory depression, neurotoxicity, and opioid-induced constipation. Buprenorphine undergoes extensive first-pass hepatic metabolism with little unchanged drug found in the urine. The 2 major metabolites, B3G and norbuprenorphine, are excreted fecally (9). Hemodialysis does not affect buprenorphine plasma levels, and the analgesic effect is stable during hemodialysis. These properties become fundamental when treating pain in patients with a high comorbidity burden, advanced renal dysfunction, and in frail older adults.

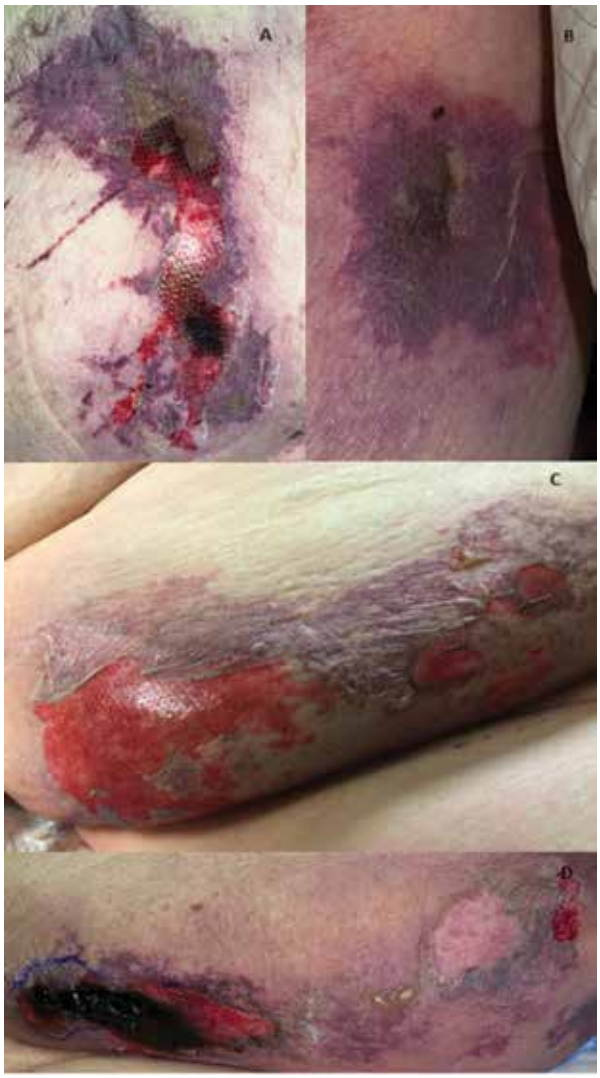

Fig. 2. Calciphylaxis lesions: Clinical presentation on the patient. A) Right gluteus. B) Left medial thigh. C & D) Inferior pannus.

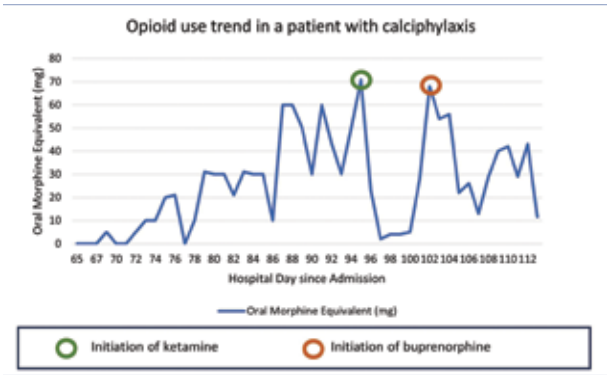

Fig. 3. Illustration of the trend of opioid utilization in a patient diagnosed with calciphylaxis. The horizontal axis represents the days spent in the MICU, while the vertical axis displays the daily opioid requirements measured in OME (mg). A condensed trajectory is depicted in the graph, highlighting the period surrounding the commencement of buprenorphine therapy (highlighted by the orange circle). Notably, a pronounced decrease in OME was observed and sustained following the initiation of buprenorphine. MICU, medical intensive care unit; OME, oral morphine equivalents.

Other potential opioids to use in ESRF include hydromorphone, fentanyl, and methadone. The patient was already on high doses of hydromorphone and experiencing a pain-sedation mismatch. Intravenous fentanyl has a shorter duration of action and would need to be dosed more frequently. Methadone was considered, but given the prolonged QTc, it would be contraindicated in this patient. Therefore, buprenorphine was the best option for pain management.

The decision to utilize buprenorphine to achieve analgesia in a patient with calciphylaxis ulcer lesions was based on previous evidence showing its effectiveness as an adjunctive analgesic (6). The duration and dose of buprenorphine used in this case were based on derivative evidence for moderate-to-severe chronic pain (10). One day after the initiation of buprenorphine, OME requirements had decreased. By day 5, the patient experienced an 80% reduction in OME with an improvement in her pain scores from 8/10 to 4/10. The initiation of buprenorphine both decreased pain and reduced the use of hydromorphone.

This case stresses the importance of managing patients with poorly understood and under-researched conditions. Effective pain management for calciphylaxis is vital to mitigate the intense pain associated with ischemic cutaneous lesions, improve the patient's quality of life, and prevent complications arising from uncontrolled pain. Finally, although this case demonstrated buprenorphine's efficacy as a substitute analgesic for patients with ESRF and calciphylaxis, buprenorphine is not without risk, and further research is warranted.

CONCLUSIONS

The case presented underscores the formidable challenge of managing calciphylaxis-associated pain, a condition characterized by intense suffering and high mortality rates. Traditional pain management strategies

often fall short in addressing the excruciating pain and debilitating nature of calciphylaxis lesions. In this context, the use of buprenorphine emerged as a promising option, offering a balance between a potent analgesia and a favorable safety profile, particularly in patients with ESRF.

The case highlights the importance of tailoring pain management approaches to the unique needs of patients with complex comorbidities, such as those with calciphylaxis and ESRD. Nonetheless, this case underscores the importance of exploring solutions to address the profound pain burden associated with calciphylaxis, ultimately aiming to improve patient outcomes and enhance their overall well-being.

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