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Case Report

Multi-intervention Management of Calciphylaxis: A Report of 7 Cases

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Calcific uremic arteriolopathy (calciphylaxis) is a devastating but rare complication seen predominantly in dialysis patients that often is fatal. Because of the rarity of the disease and the multifactorial nature of its cause, no clinical trials have been conducted to date to determine the best therapy for the condition. We report a case series of 7 patients at a single institution in whom a systematic multi-interventional treatment strategy was implemented, consisting of trigger-agent cessation (calcium-based phosphate binders, alphacalcidol, and warfarin), wound management, and antibiotic therapy, supplemented by intensified hemodialysis (4 hours daily for 7 days followed by 5-6 times weekly), intravenous sodium thiosulfate (12.5-25 g intravenously 3 times a week), and attempted oxygen therapy (given through a face mask or hyperbaric chamber as tolerated by patient circumstance). Treatments selected were based on literature review, consensus discussion, and attempts to address the physiologic disturbances that underlie the condition. All 7 patients identified with biopsy-proven calcific uremic arteriolopathy were treated with this regimen in 2007-2010, with 6 of 7 showing complete recovery. We suggest that consistent implementation of a multi-interventional approach may alter the course of this devastating disease. Further studies are needed to confirm and extend these findings.
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INDEX WORDS: Calciphylaxis; improved outcomes.

Calcific uremic arteriolopathy (CUA; calciphylaxis) is a rare but devastating complication of end-stage renal disease occurring in 1%-4% of dialysis patients annually.[1,2] CUA is characterized by the deposition of calcium-phosphate products in small-vessel media, leading to subsequent fibrosis, stenosis, and ultimately, thrombosis.[2] Clinically, patients present with subcutaneous nodules or plaques, typically in proximal areas composed of adipose tissue, such as thighs and abdomen, that progress to violaceous lesions. If untreated, these lesions necrose and ulcerate due to local tissue hypoxia. The clinical course often is complicated by secondary infection and sepsis, with mortality rates as high as 80%.[2,3] Traditionally quoted risk factors for CUA include secondary hyperparathyroidism, hyperphosphatemia, hypercalcemia, calcium-based phosphate binders, female sex, obesity, diabetes, protein C deficiency, and warfarin use.[4] Nonetheless, the pathogenesis of CUA remains poorly understood and thus there is a lack of consensus about the optimal treatment.

Successful recovery from CUA has been reported with treatments aimed at decreasing parathyroid hormone levels through parathyroidectomy[5-8] or cinacalcet,[9-11] decreasing serum calcium and phosphate levels through the use of low-calcium dialysis[12] and bisphosphonates,[13,14] and reversing calcium-phosphate deposition through the use of sodium thiosulfate.[15-19] Similarly, good outcomes have been reported with treatments aimed at improving local tissue oxygenation through hyperbaric oxygen[20-25] and ozone therapy.[26] Tissue plasminogen activator[27] and prostacyclin[28] also have been reported to reverse the disease process.

Given the relative absence of a unified recommended treatment approach in the current literature and practice, we aimed to systematically implement a specific multi-interventional treatment protocol and evaluate the results of this application at a single institution. The protocol addressed key symptoms and risk factors and was based on literature review and input from pharmacists, nephrologists, and nurses. We report the success of this approach in a consecutive case series of 7 patients during the last 3 years.

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St Paul's Hospital is a tertiary-care teaching hospital in Vancouver, Canada. The nephrology group cares for 450 hemodialysis (HD) and 150 peritoneal dialysis (PD) patients and a large group of

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Table 1. Patient Demographics and Laboratory Values

Patient No.	Age (y)/Sex	ESRD Cause	Dialysis Modality/ Vintage (mo)	Comorbid Conditions	Intact PTH (pg/mL)	Serum Po_4/Ca^{2+} (mg/dL)	Trigger Agents
1	83/F	Unknown	HD/57	CAD, atrial fibrillation, CHF, seizures	90.5	5.1/9.2	Warfarin
2	42/M	Diabetes	PD/30	Type 1 DM, PVD, BKA, CAD/CABG, dyslipidemia, HTN, CVA, hip fracture	533.5	6.4/8.7	Ferrous sulfate
3	64/F	Oxalosis	PD/41	Ileal bypass, recurrent DVT	155.1	4.3/6.3	Warfarin, ferrous sulfate
4	68/F	HTN ± oxalosis	None	Gastric bypass, DVT, hypothyroid	75.7	1.7/8.6	Alphacalcidol, calcium carbonate, warfarin
5	63/F	Diabetes	PD/29	Type 2 DM, HTN, dyslipidemia	776.4	6.5/10.1	Iron, alphacalcidol
6	69/F	Reflux	PD/48	Type 2 DM, HTN, dyslipidemia, colon/uterine cancer (treated)	746.8	6.8/9.8	Calcium acetate, alphacalcidol, iron
7	67/F	Diabetes	PD/48	Type 2 DM, HTN, dyslipidemia, eczema	886.2	6.1/10.1	Alphacalcidol

Note: All patients were white. Conversion factors for units: phosphate in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495; no conversion necessary for PTH in pg/mL and ng/L.

Abbreviations: BKA, below knee amputation; Ca^{2+}, calcium; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; DVT, deep vein thrombosis; ESRD, end-stage renal disease; HD, hemodialysis; HTN, hypertension; PD, peritoneal dialysis; Po_4, phosphate; PTH, parathyroid hormone; PVD, peripheral vascular disease.

patients with chronic kidney disease and transplant patients. All HD patients receive at least thrice-weekly 4-hour dialysis sessions, and all PD patients have Kt/V values >2.0. Suspected cases of CUA undergo biopsy on site, read by a trained dermatopathologist. Patients with biopsy-proven CUA in 2007-2010 represent the cases of interest.

Patient demographics, including cause of end-stage renal disease and laboratory values, are listed in Table 1. Mean age of patients was 65.1 years, all were white, most were women, 4 were obese, and all had multiple comorbid conditions. One patient (patient 1) had been treated previously for hyperparathyroidism with parathyroidectomy. Four patients were on vitamin D therapy with alphacalcidol (patients 4, 5, 6, and 7). Five of 7 patients were on PD therapy at presentation. Lesions involved the extremities (distal and proximal) in all patients and the abdomen in 1; ulceration was present in 3 patients.

Specific details of treatment regimens are listed in Table 2. The multi-interventional treatment protocol is described in detail in Item S1 (provided as online supplemental material) and consisted of conventional treatment with trigger-agent cessation, wound management, and antibiotic therapy supplemented with intensified HD, intravenous sodium thiosulfate, and oxygen therapy. For sodium thiosulfate intolerance (due to nausea), substitution with deferoxamine was implemented (patient 7). Cinacalcet was administered to 4 patients (patients 2, 5, 6, and 7) for elevated intact parathyroid hormone levels >369.2 pg/mL (>369.2 ng/L). Similarly, noncalcium phosphate binders were administered for phosphate control (patients 2, 3, 5, 6, and 7). Dialysate calcium concentrations ranged from 2.0-4.0 mg/dL (1.0-1.5 mmol/L). All patients who converted to intensified HD therapy continued on HD therapy after resolution of CUA, except for 1 patient who received a kidney transplant 12 months after her presentation with CUA (patient 5).

Delivery of oxygen therapy was variable across the case series. Reasons include inability to tolerate or receive the hyperbaric oxygen therapy (transportation or logistic issues) or patient nonad-

Table 2. Patient Treatment Regimens and Outcomes

Patient No.	Intensified HD (wk)	Sodium Thiosulfate (wk)	Oxygen Therapy (wk)	Cinacalcet	Sevelamer	Therapy (wk)	Outcome	Follow up (mo)	Mortality
1	2.5	8	0	No	No	8	Resolved	12	Dead
2	12	10	0	Yes	Yes	12	Resolved	32	Living
3	7	10	13	No	Yes	13	Resolved	24	Living
4	2.5	3	2	No	No	3	Resolved	26.8	Living
5	8	6	4	Yes	Yes	8	Resolved	18.5	Living
6	14	5	Unknown	Yes	Yes	14	Unresolved	NA	Dead
7	18	14	0	Yes	Yes	18	Resolved	7.5	Living

Note: Patients received 3-18 (mean, 10.9) weeks of therapy and were followed up for 7.5-32 months (mean, 21.1 months; patients 1-5 and 7) after resolution of lesions. All patients remained on HD therapy except for patient 5, who received a kidney transplant 12 months after presentation.

Abbreviations: HD, hemodialysis; NA, not applicable.