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 parathyroidectomy5-8 or cinacalcet,9-11 decreasing serum calcium and phosphate levels through the use of low-calcium dialysis12 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 oxygen20-25 and ozone therapy.26 Tissue plasminogen activator27 and prostacyclin28 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.

**CASE REPORTS**

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

From the 1Department of Medicine, University of British Columbia; and 2Department of Medicine, Division of Nephrology, St Paul’s Hospital, University of British Columbia, Vancouver, British Columbia, Canada.

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Address correspondence to Adeera Levin, MD, FRCPC, St Paul’s Hospital, 6010A Providence Bldg, 1160 Burrard St, Vancouver, British Columbia, V6Z 2E8, Canada. E-mail: alevin@providencehealth.bc.ca

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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 $\geq 2.0$. 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 ($\geq 369.2$ pg/mL, $\geq 369.2$ 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 nonadherence.

Table 1. Patient Demographics and Laboratory Values

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)/Sex</th>
<th>ESRD Cause</th>
<th>Dialysis Modality/ Vintage (mo)</th>
<th>Comorbid Conditions</th>
<th>Intact PTH (pg/mL)</th>
<th>Serum PO4/Ca2⁺ (mg/dL)</th>
<th>Trigger Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83/F</td>
<td>Unknown</td>
<td>HD/57</td>
<td>CAD, atrial fibrillation, CHF, seizures</td>
<td>90.5</td>
<td>5.1/9.2</td>
<td>Warfarin</td>
</tr>
<tr>
<td>2</td>
<td>42/M</td>
<td>Diabetes</td>
<td>PD/30</td>
<td>Type 1 DM, PVD, BKA, CAD/CABG, dyslipidemia, HTN, CVA, hip fracture</td>
<td>533.5</td>
<td>6.4/8.7</td>
<td>Ferrous sulfate</td>
</tr>
<tr>
<td>3</td>
<td>64/F</td>
<td>Oxalosis</td>
<td>PD/41</td>
<td>Ileal bypass, recurrent DVT</td>
<td>155.1</td>
<td>4.3/6.3</td>
<td>Warfarin, ferrous sulfate</td>
</tr>
<tr>
<td>4</td>
<td>68/F</td>
<td>HTN ≥ oxalosis</td>
<td>None</td>
<td>Gastric bypass, DVT, hypothyroid</td>
<td>75.7</td>
<td>1.7/8.6</td>
<td>Alphacalcidol, calcium carbonate, warfarin</td>
</tr>
<tr>
<td>5</td>
<td>63/F</td>
<td>Diabetes</td>
<td>PD/29</td>
<td>Type 2 DM, HTN, dyslipidemia</td>
<td>776.4</td>
<td>6.5/10.1</td>
<td>Iron, alphacalcidol</td>
</tr>
<tr>
<td>6</td>
<td>69/F</td>
<td>Reflux</td>
<td>PD/48</td>
<td>Type 2 DM, HTN, dyslipidemia, colon/uterine cancer (treated)</td>
<td>746.8</td>
<td>6.8/9.8</td>
<td>Calcium acetate, alphacalcidol, iron</td>
</tr>
<tr>
<td>7</td>
<td>67/F</td>
<td>Diabetes</td>
<td>PD/48</td>
<td>Type 2 DM, HTN, dyslipidemia, eczema</td>
<td>886.2</td>
<td>6.1/10.1</td>
<td>Alphacalcidol</td>
</tr>
</tbody>
</table>

Note: All patients were white. Conversion factors for units: phosphate in mg/dL to mmol/L, $\times 0.3229$; calcium in mg/dL to mmol/L, $\times 0.2495$; no conversion necessary for PTH in pg/mL and ng/L. Abbreviations: BKA, below knee amputation; Ca2⁺, 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; PO4, phosphate; PTH, parathyroid hormone; PVD, peripheral vascular disease.

Table 2. Patient Treatment Regimens and Outcomes

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

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.
of CUA lesions but died 1 year later of stroke.

DISCUSSION

We present the outcomes of patients treated with a prespecified multi-interventional approach to CUA. We systematically introduced the regimen into clinical practice and evaluated outcomes objectively. Results presented here are substantially better (86%) than those in the literature (<20%).2,3 The only patient who did not recover had several confounding issues related to her premorbid condition. The remaining 6 recovered completely and continued on HD therapy without recurrence. The mainstays of therapy included the removal of potential trigger agents, wound care, and antibiotics supplemented with intensified HD, use of chelating agents (sodium thiosulfate, 6 patients, and deferoxamine, 1 patient), and treatment of hyperparathyroidism and hyperphosphatemia with cinacalcet and nonphosphate calcium binders, respectively. Given the association of warfarin with CUA and current controversies with respect to the use of warfarin in HD patients, warfarin therapy was not resumed after resolution of CUA. Antiplatelet agents and heparin on dialysis therapy were believed to be adequate treatment for these individuals given the risk.

The sample size is small but typical of the literature in this area, as are the characteristics of the cohort: mostly women and on PD therapy. The multipronged intervention was based on a set of principles, which in practice were implemented with some variability. Individual circumstances accounted for that variability. Chelation therapy was well tolerated by most. One patient had improved initially with sodium thiosulfate therapy but experienced severe nausea and thus converted to deferoxamine therapy based on the potential importance of chelation and our recent observations of the deposition of iron in lesions of CUA.29 Oxygen therapy implementation was inconsistent due to patient tolerance issues, but may be the least important of the strategies. Because recovery rates were not different between those who did and did not receive oxygen in any form, its benefit remains questionable. Hyperbaric oxygen therapy may be an important adjunct therapy, but given that most did not receive it, we cannot comment on its utility.

Which of the specific components in this regimen are responsible for these results? Recent reports of sodium thiosulfate have described similarly positive effects, but also were combined with other strategies. However, these were variable and not articulated within a consistent protocol described here.16-18 We propose that the multi-interventional protocol and perhaps the synergistic effect of each aspect of the strategy is responsible for the positive outcomes for this complex condition.

The improved outcomes reported here provide encouragement for this condition. A pragmatic trial using a multi-interventional treatment protocol consistently applied to all cases would further validate this approach.

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REFERENCES


