ORIGINAL ARTICLE

Multi-intervention management of calcific uremic arteriolopathy in 24 patients

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ABSTRACT

Background. Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare but life-threatening condition predominately occurring in patients with end-stage renal disease on dialysis. In the absence of randomized clinical trials to guide management, clinicians must rely on observational data. We have previously reported the outcomes of our multi-intervention management in seven patients and now present a larger series of patients with extended follow-up.

Methods. We performed a retrospective analysis of all patients diagnosed with CUA at a single academic center between 2008 and 2017. We identified 24 patients including 13 hemodialysis, 8 peritoneal dialysis and 3 predialysis Stage 5 chronic kidney disease patients.

Results. Mean age at diagnosis was 60.5 years (range 35–83) and mean follow-up 30.5 months (range <1–99). Patients were predominantly female (71%) and Caucasian (83%) with diabetes mellitus diagnosed in 16 of 24 patients. Fifteen of 24 patients had ulcerating lesions suggestive of advanced disease and 20 of 24 had extensive involvement (bilateral disease or lesion size >5 cm). Treatment consisted of intensive hemodialysis (>20 h per week), sodium thiosulfate, wound care, analgesics and discontinuation of trigger medications including warfarin. Hyperbaric oxygen, cinacalcet, bisphosphonates and vitamin K were used in some cases. Overall 1 year mortality was 41% (9/22) and overall mortality at the end of follow-up was 64% (14/24). Cause of death was felt to be attributable to CUA in only four cases (16.7%). Complete or partial resolution of lesions occurred in 17 of 24 patients. One patient had recurrence of CUA 20 months after initial diagnosis.

Conclusions. Although mortality remains high in this group, direct CUA-attributable mortality is lower than historic reports. We conclude that a multi-intervention approach can be successful in treating a group of patients with severe CUA lesions.

Keywords: calcific uremic arteriolopathy, calciphylaxis, ESRD, sodium thiosulfate, vitamin K

INTRODUCTION

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare but life-threatening condition that is characterized by progressive cutaneous necrosis associated with small- and medium-sized vessel calcification, predominately occurring in patients with end-stage renal disease (ESRD) on renal replacement therapy [1]. Early clinical findings include the presence of livedo reticularis and painful subcutaneous nodules or plaques. Without adequate treatment these lesions progress to necrosis and ulceration, with the ischemic skin becoming secondarily infected in many cases [1]. CUA-attributable mortality rates in the literature range from 45 to 80% at 1 year, with cause of death most frequently due to sepsis [2, 3].

The true incidence of CUA is unclear and has been difficult to ascertain using administrative data due to the lack of a unique International Classification of Diseases 9th or 10th Revision code. The prevalence of this rare condition was previously reported as 4.1% in a study of 242 hemodialysis (HD) patients [4]. Data from a large nationwide registry in Germany estimated an annual incidence rate of 0.04% in German dialysis patients [5].

The pathogenesis of CUA has been elucidated by the current model of vascular calcification; however, it is thought that vascular calcification alone does not lead to CUA without the addition of other mediating factors such as local hypercoagulability and inflammatory cytokine excess [6, 7]. Nevertheless, the vascular calcification model explains that lesions begin with the transformation of vascular smooth muscle cells into osteoblast-like cells, which in a uremic milieu, increases reactive oxygen species, and decreases inhibitors of vascular calcification including Matrix Gla protein (MGP) and fetuin-A leading to calcification [6, 7]. A recent publication by Nigwekar et al. examined the role of MGP in the context of vitamin K deficiency [8]. Vitamin K is a cofactor for MGP carboxylation and the authors found that a reduction in the ratio of carboxylated MGP to uncarboxylated MGP was associated with an increased risk of CUA in both warfarin users and non-users compared with controls. Vitamin K deficiency is not restricted to warfarin use but is associated with malabsorption syndromes such as Crohn's disease or prior gastric bypass, both emerging risk factors for CUA.

Risk factors for CUA have been established from case report and observational data and include chronic kidney disease (CKD)-related bone mineral disease, age over the fifth decade, female sex, Caucasian race, diabetes, obesity, autoimmune or hypercoagulable disorders, long dialysis vintage, hypoalbuminemia and medications including calcium-based phosphate binders, activated vitamin D, iron, vitamin K antagonists (warfarin), corticosteroids and subcutaneous injections for insulin or heparin [5, 9]. The interaction between calcium, phosphate and parathyroid hormone (PTH) levels and CUA is complex, with both high and low levels of calcium and PTH associated with CUA in observational studies [5, 9]. In one recent study, warfarin users had a CUA incidence rate of 6.24 per 1000 patient years compared with 3.41 per 1000 patient years in non-users [9]. Peritoneal dialysis (PD) was identified as a risk factor for CUA in one prior study but this result may be confounded by higher calcium-based binder use in PD patients at the time of the initial study [3, 10].

There are no consensus guidelines on the treatment of CUA. Evidence for treatment comes from case reports and case series, with no randomized controlled trials published in the literature. Treatment is generally multi-interventional and multidisciplinary. Reported treatments include wound care and pain management, sodium thiosulfate (STS), management of CKD-bone mineral disease (non-calcium phosphate binders, cinacalcet and bisphosphonates), optimization of dialysis, hyperbaric oxygen therapy (HBOT) and discontinuation of offending medications. A clinical trial of vitamin K administration for patients with CUA is currently underway by Nigwekar et al. and expected to be completed by December 2017 (ClinicalTrials.gov identifier: NCT02278692). The use of vitamin K has already been reported as part of multi-interventional treatment in 18% of a German registry of CUA patients [5].

MATERIALS AND METHODS

We performed a retrospective analysis of all patients diagnosed with CUA at a single tertiary care hospital in Vancouver, Canada between 2008 and 2017. We identified a total of 24 cases diagnosed with CUA including extended follow-up on the seven patients previously reported by our center [11]. Hospital charts, electronic records and medication records from the 24 patients were reviewed for extraction of relevant data including pathology reports, laboratory and outcome data.

Statistical analyses for categorical variables were analyzed by the Chi-squared and Fisher's exact tests. Ethics approval for this study was obtained from the institutional Clinical Research Ethics Board.

RESULTS

Patient demographics are listed in Table 1. The mean age of patients at diagnosis was 60.5 years and patients were predominately female (70.8%) and Caucasian (83.3%). Contrary to our previous report, the most common dialysis modality at diagnosis was HD with 13 patients on HD (12 conventional HD, 1 home HD, 4 h, 3 times per week), 8 patients on PD and 3 patients who had predialysis Stage 5 CKD. One patient had no prior history of CKD but had initiated dialysis 3 months prior to diagnosis for acute kidney injury (AKI) presumed secondary to acute tubular necrosis (ATN). All patients had multiple comorbidities with diabetes mellitus diagnosed in 16/24 of patients (66.7%). Concurrent with the literature, obesity was a pervasive risk factor in our population with 87.5% of our patients meeting body mass index (BMI) criteria for overweight (5/24) or obese (16/24) with a mean BMI of 33.4 kg/m^2 by the Du Bois equation. Fifty per cent of patients (12/24) were on vitamin K antagonist therapy prior to diagnosis with high use of other trigger medications including activated vitamin D (11/24), calcium (22/24) and iron (15/24). Mean calcium, phosphate and intact PTH (iPTH) values at diagnosis were 2.26 mmol/L, 1.83 mmol/L and 56.88 pmol/L, respectively. Mean serum albumin at diagnosis was 32.7 g/L. Time averaged values of calcium, phosphate and iPTH were obtained from patients in the 6 months prior to diagnosis and yielded similar values with a mean calcium, phosphate and iPTH of 2.17 mmol/L, 1.90 mmol/L and 59.47 pmol/L, respectively. The mean dialysis vintage was 27 months with range of <1–169 months. The main cause of ESRD was diabetes but interestingly, 3/24 patients had oxalate nephropathy, higher than would be expected in the general ESRD population and an evolving risk factor for CUA.

The clinical diagnosis of CUA was confirmed by skin biopsy in 19 of 23 cases. In one case, skin biopsy was not performed as the diagnosis was felt to be clinically consistent with CUA along with concern about wound healing. In the four cases whose pathology was not typical for CUA, the experienced dermatologists and nephrologists involved felt the diagnosis remained CUA with no alternate diagnosis. Interestingly, two of four of these cases involved lesions on the abdomen. The majority of cases had involvement of the legs (23 of 24). Fifteen of 24 patients had ulcerating lesions suggestive of advanced disease and 20 of 24 had extensive involvement defined as bilateral disease or lesion size >5 cm.

Details of treatment regimens are summarized in Table 2. All patients received intensified HD (at minimum 20 h per week), which involved a permanent modality change to HD for the eight patients on PD at diagnosis. The details of the HD prescriptions are provided in the Supplementary data (Item S1) with our current protocol consisting of daily dialysis for 2 weeks followed by five times per week (4 h) for 6 weeks with tapering down of frequency depending on clinical response thereafter. Mean duration of intensified HD was 40.3 weeks (range 1–240)

Table 1. Patient demographics and laboratory values

Patient No.	Age (years)/ sex	ESRD cause	Dialysis modality/ vintage (months)	iPTH (pmol/L)	PO_4/Ca^{2+} (mmol/L)	BMI (kg/m^2) (Du Bois)	Trigger agents
1	62/M	DM	PD/10	6.9	1.49/2.44	28.6	VKA, alfacalcidol, calcium, iron
2	63/F	GN	HD/53	145	1.38/2.4	37.3	VKA, alfacalcidol, calcium, iron
3	72/F	Renovascular disease	Predialysis/0	20.2	2.23/2.16	29.1	VKA, calcium, iron
4	48/F	DM	HD/18	6.4	1.78/2.38	46.8	Calcium, iron
5	39/F	GN, previous transplant	HD/9	69.4	2.22/2.1	37.0	VKA, alfacalcidol, calcium, iron
6	40/M	DM/HTN	HD/0	35.8	1.9/2.06	39.2	Alfacalcidol, calcium, iron
7	35/F	Secondary FSGS	PD/64	10	2.24/2.47	18.8	Calcium
8	75/F	DM and IgM nephropathy	HD/17	19.4	1.25/2.15	37.7	VKA, calcium, vitamin D
9	75/M	DM	HD/1	25.6	1.57/2.5	32.2	VKA
10	67/F	DM	PD/48	96	1.98/2.52	35.7	Alfacalcidol, calcium
11	62/F	DM	PD/30	84.2	2.1/2.51	37.9	Alfacalcidol, iron
12	64/F	Oxalate nephropathy	PD/40	16.8	1.16/1.5	20.4	VKA, calcium
13	67/F	Reflux nephropathy	PD/35	80.9	2.2/2.43	27.4	Calcium, iron
14	83/F	Unknown	HD/56	18.8	2.05/2.28	17.7	VKA, calcium, iron
15	42/M	DM	PD/31	35.1	2.01/2.38	29.2	Calcium, iron
16	81/M	HTN	Predialysis/0	28.2	1.44/2.26	33.6	VKA, alfacalcidol, calcium
17	68/F	HTN +/− oxalate nephropathy	HD/0	8.2	0.89/2.28	31.3	VKA, calcitriol, calcium
18	56/F	DM	PD/41	15.3	1.98/2.21	37.4	Calcium, iron
19	64/F	DM	HD/15	11.8	1.86/2.47	36.9	Calcium, iron, prednisone
20	62/F	DM/HTN	HD/7	13.2	1.67/2.19	26.0	Calcium, iron
21	77/F	Oxalate nephropathy	Predialysis/0	30.9	2.73/1.63	23.0	Alfacalcidol, calcium
22	39/F	AKI secondary to ATN	HD/3	12.7	2.39/2.34	66.1	VKA, calcium
23	46/M	DM	HD/169	393.1	1.14/2.4	30.7	VKA, calcitriol, calcium, iron
24	64/M	DM/HTN	HD/5	181.3	2.34/2.2	40.6	Alfacalcidol, calcium, iron

Ca^{2+}, calcium; DM, diabetes mellitus; F, female; GN, glomerulonephritis; HTN, hypertension; IgM, mmunoglobulin M; M, male; No., number; PO_4, phosphate; VKA, vitamin K antagonist.

Table 2. Patient treatment regimens and outcomes

Patient No.	STS (week)	Intensive HD (weeks)	HBOT (No. treatments)	Cinacalcet (*on pre-dx)	Outcome	Mortality (*attributable to CUA)	Cause of death	Time to death from diagnosis (months)
1	9	8	N	N	PR	Deceased	CVA	2
2	18	14	Y (40)	Y	CR	Deceased	Cardiac	37
3	8	9	Y (14)	Y*	PR	Deceased	Traumatic SAH	3
4	11	94	N	N	CR	Living		
5	67	240	Y (41)	Y	CR	Deceased	Cause unknown	59
6	17	160	Y (40)	Y	CR	Living		
7	5	5	N	N	CR	Living		
8	2	2	N	N	NR	Deceased	SBO/aspiration pneumonia	<1
9	4	4	N	N	NR	Deceased*	Withdrawal of dialysis secondary to CUA	1
10	14	19	N	Y	CR	Living		
11	6	7	N	Y	CR	Living		
12	10	6	N	N	CR	Deceased	Loss of vascular access	47
13	6	17	Y (11)	Y	NR	Deceased*	Sepsis secondary to CUA	7
14	9	3	N	N	CR	Deceased	Unable to tolerate hemodialysis due to BP	13
15	11	10	Y (20)	N	CR	Deceased	Cardiac arrest	38
16	4	1	N	N	NR	Deceased	Gastrointestinal bleed	1
17	4	5	N	N	CR	Living		
18	13	91	Y (44)	N	PR → recurrence	Living		
19	1	1	N	N	NR	Deceased	Biliary sepsis	<1
20	7	55	N	N	CR	Living		
21	3	5	N	N	CR	Living		
22	4	55	N	N	NR	Deceased*	Withdrawal of dialysis secondary to CUA	<1
23	7	7	N	N	NR	Deceased*	Sepsis secondary to CUA	1
24	16	20	N	N	PR	Living		

BP, blood pressure; CR, complete response; CVA, cerebrovascular accident; dx, diagnosis; No., number; N, No; NR, no response; PR, partial response; SAH, subarachnoid hemorrhage; SBO, small bowel obstruction; Y, yes.

given that we encouraged ongoing intensified dialysis regimens even after resolution of lesions such as long-term nocturnal dialysis. All medications associated with an increased risk of CUA were discontinued including vitamin K antagonists, activated vitamin D, calcium and iron. Low-molecular weight heparin was used if anticoagulation was felt to be essential and non-calcium-based binders were substituted. Seven patients received cinacalcet for treatment of hyperparathyroidism, one of which was on cinacalcet at the time of CUA diagnosis. Patients were treated with cinacalcet if their iPTH was >60 pmol/L as per our treatment protocol (Supplementary data, Item S1). Two additional patients met this criterion, but were not treated with cinacalcet due to chronic medication nonadherence. Bisphosphonates were used in two patients with hypercalcemia (Intravenous (IV) palmidronate).

STS was used in all patients three times per week (mean duration 11 weeks) and was generally well tolerated. The majority of patients received 25 g IV thrice weekly after dialysis. Two of the 24 patients required dose lowering to 12.5 g and 6 patients were treated with 12.5 g thrice weekly throughout the treatment course as was the standard dose in the literature at the time of their treatment. The main dose-limiting side effects were gastrointestinal, in particular nausea and vomiting. Increase in dialysate bicarbonate was required in some cases to combat metabolic acidosis from STS. Three patients were treated with deferoxamine (DFO), an iron chelator. One of these patients had evidence of iron overload with a ferritin of 1868 ng/mL, while the other two were treated with DFO after completing a course of STS due to persistence of CUA lesions. All of these patients had complete resolution of CUA lesions at the end of follow-up.

Seven patients received HBOT and six received vitamin K (10 mg thrice weekly after HD). Patients received antibiotics at the nephrologist's discretion and all patients received specialized wound care. Pain control was provided with both opioid and non-opioid analgesics with consultation of palliative care physicians in complex cases. Seventeen of 24 patients were inpatients for a portion of their treatment course.

Mean patient follow-up after diagnosis was 30.5 months (range <1–99). Fourteen patients died during follow-up, nine within the first year, yielding an overall 1 year mortality of 40.9% (9 of 22). In only 4 of the 24 patients (16.7%), cause of death was felt to be directly attributable to CUA. In these cases, with cause of death secondary to sepsis from wounds or withdrawal of dialysis due to pain and worsening wounds. Mean time to death was 15 months in all patients and 2.3 months in CUA-attributable cases. Other causes of death are listed in Table 2.

All surviving patients had complete or partial resolution of their wounds at time of follow-up. Complete resolution of CUA lesions occurred in 13 of 24 patients, with partial resolution in 4/24. The remaining seven patients died shortly after diagnosis with no improvement in wounds documented prior to death even in the cases where death was not felt to be attributable to CUA. Complete resolution was defined as the absence of any identifiable lesions on physical examination. If CUA lesions were significantly improving on physical examination but some lesions were still evident, this was defined as a partial resolution. One patient required an above-knee amputation for severe infection secondary to CUA lesions in addition to peripheral vascular disease and later died due to ongoing infection and withdrawal of dialysis. Another patient has had a recurrence of lesions 20 months after initial diagnosis with partial response and is undergoing treatment. Three patients with complete resolution of their lesions went on to undergo renal transplantation.

There was no statistically significant difference in clinical response of lesions when patients were divided into those with extensive lesions (defined as bilateral disease or >5 cm in size) versus those with limited disease (P = 0.8). There was no significant difference in outcomes (clinical response or death at 1 year) between those patients with ulcerating versus non-ulcerating disease (P = 0.9). The 1 year mortality in our patients with ulcerating lesions was 46% (7 of 15). Those patients with non-ulcerating lesions all survived to 1 year (zero of six); however, the difference between two groups did not meet statistically significance (P = 0.06). There were no differences in outcomes between those who received or did not receive HBOT (P = 0.3).

DISCUSSION

We present the outcomes of 24 patients with CUA treated with a multi-interventional approach. Our 1 year mortality rate was 40.9% (9 of 22) with only four deaths found directly attributable to CUA (16.7%). This result heralds more significance given that the majority of the patients had ulcerated lesions, which has been associated with mortality rates of 80% in one prior case series of 36 patients compared with 46% in our group with ulcerated lesions [3]. These authors postulated that the high-mortality rate in this group was a demonstration of ulceration representing a late clinical finding in the course of CUA.

In contrast, Russo et al. recently published a case series of five patients with ulcerating CUA lesions and complete response in four of five patients with multimodal treatment [12]. However, in this series, a histologic diagnosis was made in only two of five cases and all patients had uncontrolled hyperparathyroidism treated with cinacalcet, distinct to our case series population. Thus, while we agree that ulcerating lesions represent a late clinical manifestation, we are encouraged that the survival with multimodal treatment in our cases series and Russo et al.'s has improved from historical reports [3, 12].

Our experience is that intensive dialysis is helpful for wound healing in patients with CUA and our practice is to reintensify dialysis if lesions worsen at any time after initial improvement. The literature on intensive dialysis for the treatment of CUA is limited but of theoretical benefit. The aim of intensive HD in conjunction with low dialysate calcium is to reduce the calcium phosphate product and improve the uremic milieu that contributes to vascular calcification. Conversion from PD to HD is controversial in the literature but is supported by one case series that included 54 PD patients, 13 of which were switched to HD, with improvement in 11 of 13 of cases [10]. In the absence of clinical evidence to the contrary and given the high mortality of this condition, our group's opinion is that intensive HD should be performed.

STS is one of the backbones for CUA therapy and has been used for >10 years for this indication, although its use remains off-label. There are no prospective trials to report its efficacy but many retrospective reviews of its use and case reports have been published with encouraging results. Nigwekar et al. performed a retrospective review published in 2013 of 53 patients with a treatment response of >70% seen (resolution or improvement) [13]. However, as data were collected via survey questionnaires sent to treating physicians regarding 172 patients with CUA, there may have been selection bias in this group. Peng et al. have recently performed a systematic review of the literature and found similar results with clinical response in 70.1% of patients and death 37.6% of patients treated with

STS [14]. Of course, it is difficult to draw definitive conclusions regarding the effectiveness of STS given that it is almost always part of a multimodal therapy. Intralesional use of STS has also been reported [15, 16].

DFO was used by some clinicians in our case series in refractory cases. Our group has previously reported on the potential role of iron in the pathogenesis of CUA evidenced by the presence of iron deposition in areas of microvascular calcification on skin biopsy [17]. Thus DFO could be considered in cases with concomitant iron overload or those refractory to usual first-line therapies, but more evidence is required in this area.

Three of the 24 patients had a history of oxalate nephropathy following remote intestinal bypass procedures. Deficiencies in fat soluble vitamins A, D, E and K are known complications of intestinal bypass surgery due to fat malabsorption. Given the emerging role of vitamin K in the pathophysiology of CUA, this may have been a contributing risk factor for CUA in these patients. Deficiencies in vitamin D following gastric bypass and associated hypocalcemia may also result in the ingestion of large doses of vitamin D and calcium to maintain normal electrolyte balance, potentially contributing to vascular calcification as well. A case of fatal non-uremic CUA was reported by Allegretti *et al.* in a patient following gastric bypass [18].

Whether vitamin K supplementation is effective in ameliorating established CUA is still under investigation with a randomized controlled trial by Nigwekar *et al*. Given the possible benefit of supplementation, we have elected to use vitamin K supplementation (both oral and IV routes) in six of our recent cases. The risk of vitamin K supplementation is primarily driven by the risk of hypersensitivity reaction with the IV route (anaphylactoid type) [19]. There is also concern regarding reversal of anticoagulation and subsequent risk of thrombosis in those patients on vitamin K antagonist therapy. We did not observe any adverse reactions to vitamin K. Patients on warfarin therapy who were felt to have high risk of thrombosis were placed on therapeutic doses of low-molecular weight heparin therapy with monitoring of anti-Xa levels.

As the majority of patients in our case series were normocalcemic at presentation, bisphosphonate therapy was only used in two patients. However, bisphosphonates have been promising in the treatment of CUA lesions in both hypercalcemic and normocalcemic patients and can be considered as an adjunct therapy, albeit more evidence is required [20, 21]. None of our patients had surgical parathyroidectomy during the active treatment period and seven received cinacalcet. Cinacalcet remains our choice of therapy for secondary hyperparathyroidism in CUA patients in the absence of a survival benefit for surgical parathyroidectomy demonstrated in the literature [22].

The literature supports a possible protective role of cinacalcet against the development of CUA. Adverse event reports from the 'Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events' (EVOLVE) trial revealed a lower incidence of CUA in the group of patients that received cinacalcet compared with placebo [23]. However, the ability to draw conclusions from this study is limited by the low event rate. Interestingly, the reduced incidence of CUA in the cinacalcet group appeared to be independent of iPTH level. As both adynamic bone disease and uncontrolled hyperparathyroidism are risk factors for CUA, further exploration of an optimal iPTH to mitigate CUA risk is needed. Although our mean iPTH was 56.88 pmol/L, our median iPTH was 22.9, indicating possible relative oversuppression of PTH in some patients. This is in keeping with a high use of calcium-containing binders and vitamin D analogs in our cohort.

Controversy still exists regarding the use of HBOT. Although there was no association between HBOT therapy and clinical response in our group, only a small group of patients received this therapy both due to contraindications and changes in the clinical practice of our hyperbaric oxygen unit. Evidence for HBOT is supported by several observational studies and case report data, the largest of which included 46 patients, with improvement in lesions in 58% of patients [24]. Those patients who are not candidates for hyperbaric therapy can be treated with standard oxygen therapy but there is no evidence for this apart from the encouraging results from our previous report [11].

Although wound care is emphasized in the literature as a crucial aspect of CUA treatment, controversy still remains regarding how wounds are best cared for and whether surgical debridement should be part of routine CUA care [25]. This controversy stems from the concern that aggressive debridement could cause local injury that could worsen CUA lesions. Negative-pressure therapy (NPT) including vacuum assisted closure (VAC®) has a potential application in CUA as it is non-traumatic and allows for less frequent dressing changes [25]. Other theoretical benefits of NPT include the acceleration of granulation, improvement in blood flow, reduction in wound edema and potential anti-inflammatory effects [26, 27]. NPT has been used in CUA with successful wound healing in case reports; however, the decision to use NPT must be made on an individual basis by experienced wound clinicians [25, 28]. With respect to surgical approaches, surgical debridement improved the 1 year survival rate in a retrospective analysis of 63 patients with CUA compared with unmatched controls who did not receive surgical debridement (61.6% survival versus 27.4%), but this result has not been consistent across the literature and likely relies on the surgeon's expertise with this complex wound type [22]. A case series of seven CUA patients treated with deep ulcer shaving and split thickness skin graft showed complete healing in six of seven patients and death in only one patient, unrelated to CUA [29].

In summary, the treatment of CUA remains challenging with a persistence of high mortality rates. These high mortality rates should be viewed in the context of the already high mortality rates of patients with ESRD on dialysis with multiple comorbidities. Ongoing clinical trials are needed to validate which components of the multi-intervention treatment strategy are effective in improving clinical response. Further information on the pathophysiology of CUA will be helpful to guide future clinical trials.

AUTHORS' CONTRIBUTIONS

M.F., M.K., W.L. and C.H. were responsible for the research idea and study design. W.L. and C.H. performed the literature review and data acquisition. C.H. carried out statistical analysis. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work.

CONFLICT OF INTEREST STATEMENT

None declared.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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