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Teaching Point
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Hyperbaric oxygen as effective adjuvant therapy in the treatment of distal calcific uraemic arteriolopathy

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Introduction

Calcific uraemic arteriolopathy (CUA), calciphylaxis or uraemia of small-vessel disease is a rare life-threatening complication predominantly affecting patients with end-stage renal disease (ESRD) [1]. It typically occurs in those with secondary hyperparathyroidism and is associated with deranged calcium and phosphate metabolism. Other factors, such as malnutrition, obesity, diabetes mellitus, warfarin therapy and female gender, have been implicated as additional risk factors [2]. CUA presents as severely painful ulcers, usually occurring in the lower limbs. The mechanism of injury appears to be calcification of subcutaneous tissues and small arterioles. At a molecular level, derangement of vascular smooth muscle cell function leading to osteogenic differentiation in conjunction with endothelial cell dysfunction appears to be important [3]. The lesions are slow to heal, with superimposed bacterial infection leading to sepsis, the most common cause of death (in up to 80% of patients).

The first case series of CUA was published in 1976 [4]. Subsequently, the incidence of CUA in patients with ESRD has increased markedly [3]. Reports to the Australia and New Zealand Dialysis and Transplantation Registry (ANZDATA) demonstrate that CUA had been identified as a comorbidity or cause of death in 171 patients, from its first documentation in 1985 until March 2005 (Figure 1). Despite an increasing awareness of this disease and a better understanding of its aetiology, an effective form of treatment remains elusive. Most therapeutic regimens include aggressive wound care, ensuring adequate nutrition, improving calcium–phosphate balance and correcting secondary hyperparathyroidism. The use of bisphosphonates [5], low-molecular weight heparin [1] or sodium thiosulfate [6] has been met with success in a few patients.

Hyperbaric oxygen (HBO) involves breathing 100% oxygen within a pressurized environment. It is first-line therapy for a number of medical conditions, namely decompression sickness and carbon monoxide poisoning [7]. Most recently, HBO has been shown to be of benefit in advancing wound healing, including lesions due to CUA [8]. It is proposed to work by increasing oxygen tension in the ischaemic tissue, although the primary initiating factor of vascular calcification is not altered. We report our experience with the treatment of CUA with HBO, which appears to be well tolerated. We describe the largest, single-centre case series of patients with CUA successfully treated with a combination of therapies including HBO.

Methods

Twelve patients with ESRD were identified through the Royal Adelaide Hospital Hyperbaric Unit database, starting from 1997. The records were then confirmed with information available at the Queen Elizabeth Hospital and the Australia and New Zealand Dialysis and Transplantation (ANZDATA) registry. These cases were retrospectively studied and a systematic review of all medical records was undertaken. The data retrieved included patient characteristics (age, gender, duration and mode of dialysis), distribution of CUA lesions and biochemical parameters (serum calcium/phosphate, PTH, albumin, alkaline phosphatase) and response to the treatment.

Patients treated with HBO received a variable number of standardized sessions: breathing 100% oxygen at an equivalent depth of 10 m, three 25-min sessions separated by three 5-min breaks, followed by a 30-min ascent. Patients

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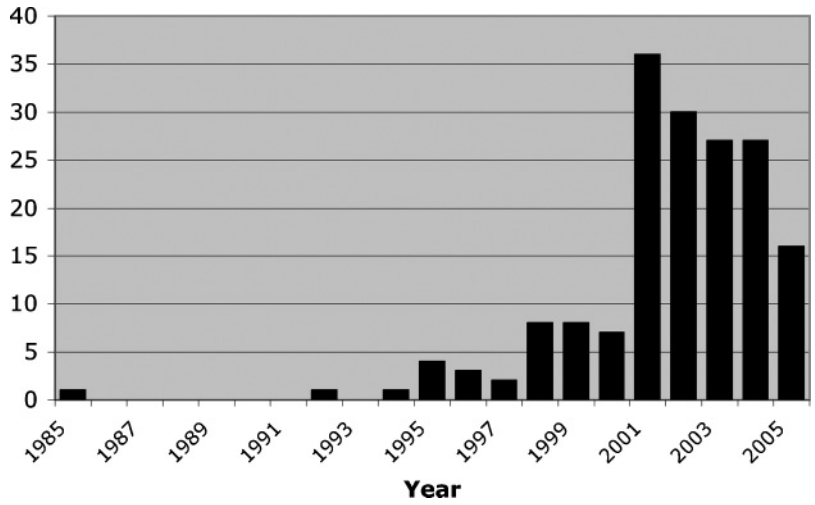

Fig. 1. The number of patients with ESRD and CUA as a comorbidity or cause of death reported to ANZDATA between 1985 and 2005.

were assessed for side effects at each appointment. Aggressive wound care, including debridement and antibiotics, was administered as required. Attempts were also made to correct abnormal biochemical parameters (such as elevated calcium/phosphate product), improve patient nutritional state and control secondary hyperparathyroidism. Wounds were considered healed if there was a resolution of the necrotic area.

Patient survival after CUA diagnosis was examined using matched survival analysis. CUA cases were matched to controls by year of commencing renal replacement therapy (RRT), duration of RRT, race, age at start of RRT ($\pm$4 years) and RRT modality at diagnosis (or the corresponding time point from RRT start in controls). Ten cases were matched with up to five controls each and survival analysis was done by Cox regression stratified by groups adjusted for both age at commencement of RRT and gender.

Results

Twelve patients were treated for CUA during the 10-year period from May 1997. The demographic and biochemical characteristics are documented in Table 1. Mean age was 61 $\pm$ 10 years and time on dialysis was 46 $\pm$ 56 months at the time of diagnosis of CUA. Six patients had an unknown glomerulonephritis and the remaining had developed ESRD from a variety of causes (including diabetic nephropathy, interstitial nephritis, IgA nephropathy, focal segmental glomerulosclerosis, polycystic kidney disease and antiphospholipid antibody syndrome). Two patients had functioning renal transplants at the time of diagnosis (serum creatinine 1.5 and 2.3 mg/dL, respectively). Nine patients (75%) had hypertension, five had vascular disease (manifested as peripheral vascular disease, ischaemic heart disease or cerebrovascular disease) and four suffered type II diabetes mellitus. One patient had no comorbidities.

All patients were diagnosed with CUA based on characteristic clinical findings (a painful, necrotic eschar). Biopsies were only performed in six patients due to the associated risk of disease progression. These demonstrated histology consistent with CUA, with extensive calcification of walls of capillary-size vessels within the subcutis causing luminal narrowing, infarction of the epidermis and dermis, dermal capillaries containing fibrin thrombi and diffuse polymorphonuclear inflammatory cell infiltrate. All lesions were located on the lower legs (i.e. below knee). For those patients without diagnostic biopsies, vasculitic screens (including antinuclear, anti-neutrophil cytoplasmic, anticardiolipin and double-stranded DNA antibodies, cryoglobulin and complement levels) were negative.

In the 3 months preceding diagnosis, the average serum PTH was 710 $\pm$ 550 pg/mL (reference range 10–65 pg/mL). Two patients had required total parathyroidectomy with forearm autografting in the preceding months; histology of examined tissue was consistent with hyperplasia in both cases. Three months prior to the diagnosis of CUA, average haemoglobin was 10.5 $\pm$ 1.3 g/dL (reference range 11.5–15 g/dL), serum albumin was 3.0 $\pm$ 0.4 g/dL (reference range 3.1–4.0 g/dL) and total cholesterol was 15.8 $\pm$ 1.35 mg/dL (reference range <21 mg/dL). The average alkaline phosphatase was 177 $\pm$ 78 U/L (reference range 30–110 U/L), corrected (pre-diaysis) serum calcium 9.8 $\pm$ 0.8 mg/dL (reference range 8.5 $\pm$ 10.5 mg/dL) and (pre-dialysis) serum phosphate 6.6 $\pm$ 1.8 mg/dL (2.5 $\pm$ 4.5 mg/dL); significant derangement of calcium–phosphate balance (as defined by $Ca \times PO_4 > 17\ mg^2/dL^2$) was present in only three patients. In the 3 months subsequent to recovery, the only significantly improved haematological, biochemical or nutritional parameters were haemoglobin (11.3 $\pm$ 1.3 g/dL, $P < 0.001$) and serum phosphate (5.5 $\pm$ 1.7 mg/dL, $P < 0.05$). This may have impacted positively on wound healing.

Seven patients had significant microbial growths from wound swabs during the treatment period (two with methicillin-sensitive *Staphylococcus aureus*, two with multi-resistant *Staphylococcus aureus*, one with coagulase-negative staphylococcus, one with *Escherichia coli* and one with *Pseudomonas aeruginosa*). The remainder demonstrated mixed growths of skin flora.

At the time of diagnosis of CUA, one patient was anticoagulated with warfarin and this was changed to unfractionated heparin. Six dialysis-dependent patients were being treated with vitamin D3, which was ceased. Eight

Table 1. Demographic characteristics, comorbid conditions, biochemical parameters (in the preceding 3 months prior to diagnosis), renal replacement therapy type and duration, site of CUA, total number of HBO treatments and result of treatment of 12 patients diagnosed with CUA

Patient no., gender/age at diagnosis; renal disease	Comorbid conditions	Duration RRT (months)/type	Wound site	HBO sessions	Outcome	Survival (months)
1. M/38 IgA nephropathy	Nil	85/HD 74/Tx	L lower leg	29	Healed	12
2. F/55 Unknown GN	Dmm HT	27/HD 240/Tx	L lower leg	7	Failed	3
3. F/65 PCKD	CVA HT	182/HD	R lower leg	28	Healed	44.7
4. F/67 Interstitial nephritis	Dmm COAD HT	0.7/HD	Bilateral lower legs	20	Healed	3.7
5. F/63 Diabetic nephropathy	Dmm HT PVD	0.5/HD	Bilateral lower legs	26	Healed	1.5
6. M/46 Unknown GN	Smoker HT	96/HD 11/PD 75/Tx	R lower leg	31	Healed	Alive
7. M/79 Unknown GN	Smoker Dmm HT IHD PVD	2.2/PD	Bilateral lower legs	28	Healed	20.3
8. M/77 Unknown GN	Smoker IHD PVD COAD	1/HD	Bilateral lower legs	30	Healed	56.8
9. M/68 Unknown GN	HT	69/HD 404/Tx	L lower leg	31	Healed	16
10. M/60 FSGS	IHD PVD	13/HD 208/Tx	R lower leg	41	Healed	Alive
11. F/55 APD syndrome	CVA HT MVD warfarin	38/HD	R lower leg; biopsy proven	31	Healed	9.6
12. M/68 Unknown GN	HT Smoker	24/HD 120/Tx	L lower leg	30	Healed	Alive

M, male; F, female; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; APD, antiphospholipid; DM, diabetes mellitus; HT, hypertension; CVA, cerebrovascular accident; PVD, peripheral vascular disease; IHD, ischaemic heart disease; COAD, chronic obstructive pulmonary disease; MVD, mitral valve disease; HD, hemodialysis; PD, peritoneal dialysis; Tx, transplant; L, left; R, right.

patients (one transplant recipient, seven dialysis-dependent patients) were treated with calcium-containing salts; these were ceased or changed to aluminium-containing phosphate binders as appropriate. Detailed information regarding nutritional support and changes to dialysis prescriptions was not available.

Eleven out of twelve patients demonstrated healing of wounds over an average of 6 weeks' treatment. Representative photographs demonstrating wound healing of patient 10 are shown in Figure 2. One patient had progression of lesions and died due to secondary infection after only seven treatments. The average duration of survival following successful treatment for CUA was 25.5 months (range 1.5–82); three patients remained alive at the time of writing, one having suffered a late relapse. Overall, survival is poor with $<50\%$ of patients still alive at 2 years following a diagnosis of CUA. When compared with matched controls, survival was significantly worse such that the HR for death was 2.9 (95% CI 1.2–6.9, $P = 0.017$) (Figure 3).

The number of HBO sessions varied between patients; the average was 27 ± 8 (range 7–41). Documented changes in tissue oxygen tension were not available for all patients. Three patients experienced ear barotrauma and an additional patient needed grommet tubes to be placed prior to treatment. One patient experienced claustrophobia. Despite these side effects, only five sessions of HBO were missed. More serious complications, such as visual changes (myopia), pulmonary toxicity or seizures, were not observed.

Discussion

CUA is an illness predominantly, but not exclusively, associated with ESRD [1]. It is increasingly recognized as either a comorbidity or an independent disease entity in these patients [3]. Mortality remains high due to superimposed infection of the lesions leading to fulminant sepsis. The pathogenesis continues to remain speculative, although the presence of renal disease and disordered calcium and phosphate metabolism are required for its development.

Since the first report of HBO to treat CUA was published in 1994 [9] there have been 46 cases treated with HBO including the present series. Previously, its use has been demonstrated in 9 case series, with a total of 34 patients receiving HBO and 23 (67%) recovering [3]. The present study, one of the largest patient cohorts reported providing follow-up, further confirms the utility of HBO in treating

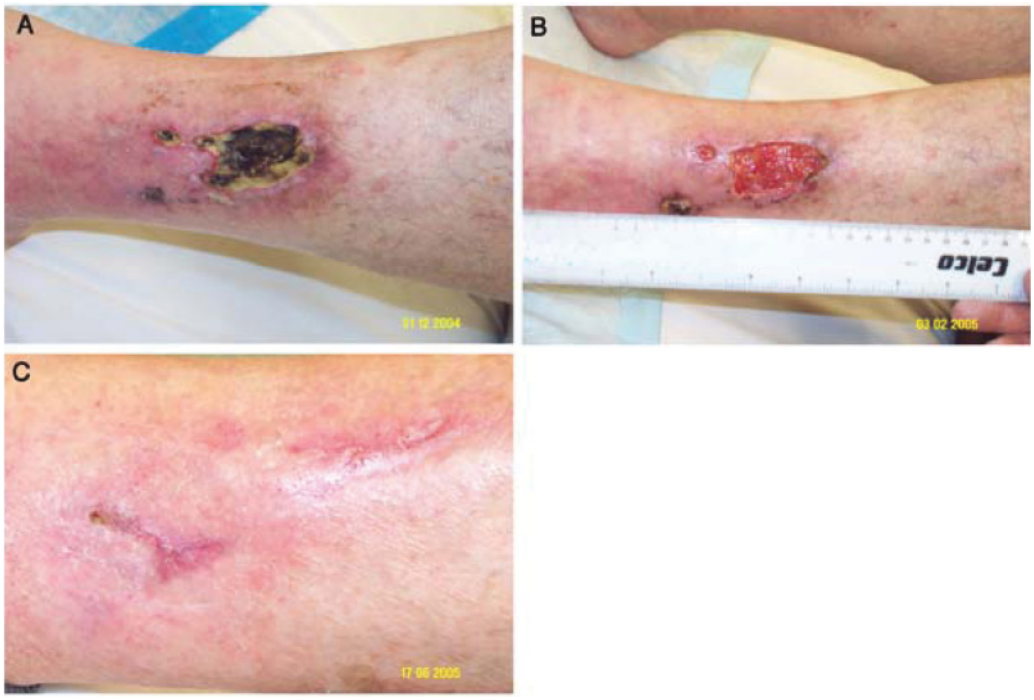

Fig. 2. Improvement of CUA in a patient (patient 10) treated with HBO demonstrating reduction and subsequent healing of dermal necrotic lesions over a total of 41 treatments. Long-term follow-up of the leg lesion revealed stable healed skin.

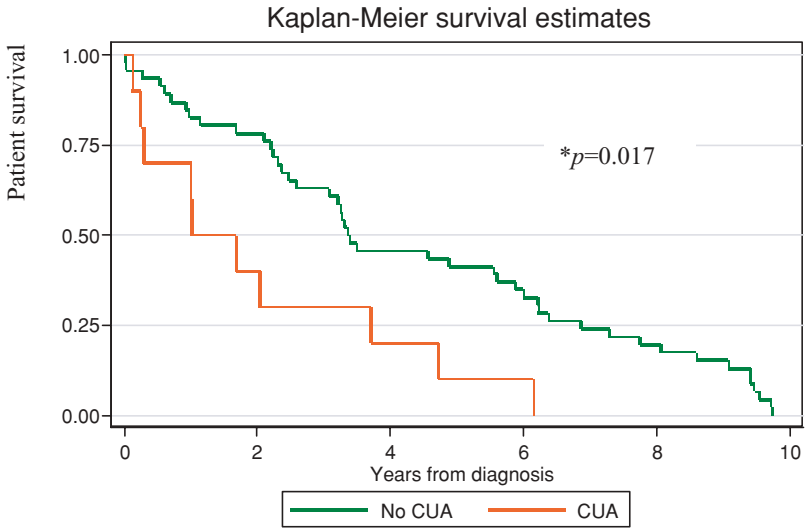

Fig. 3. A Kaplan–Meier estimate of patient survival following a diagnosis of CUA compared to control cases matched for age, modality, duration and year of commencing renal replacement therapy. Survival was significantly worse in patients diagnosed with CUA (HR for death 2.9, 95% CI 1.2–6.9, $P = 0.017$).

this disease. In our series of patients with distal CUA treated with HBO, 11 out of 12 (92%) healed, which is consistent with the reported literature of total pooled distal CUA cases treated with HBO where 14 out of 16 lesions were reported to have healed [8,10–12]. The only reported cases of proximal CUA have all responded to HBO [12,13,14] and this may be due to publication bias.

Our patient group is comparable to other cohorts reported in the literature, particularly in terms of co-morbidities. The average age was slightly greater in our study (61 ± 11 versus 55 ± 11 years); however, not all ages in other series had been reported. The approximate duration of each HBO treatment, the elevation in atmospheric pressure and total number of sessions was also consistent with previous reports. The number of sessions required to heal CUA lesions is also similar to the number required for other wounds (such as diabetic and radiation-induced), with the eventual number determined by progression of wound healing.

Treatment options for CUA are limited and essentially supportive, involving expert wound care and correction of hyperphosphataemia. Other factors such as cessation of calcium-containing phosphate binders and vitamin D3 analogues, use of low-calcium dialysate baths and improving nutritional state also form part of the treatment protocol. Parathyroidectomy for significant secondary hyperparathyroidism can lead to rapid correction of calcium–phosphate balance and a survival benefit is found for those who achieve this surgically rather than medically [15]. A number of case reports describe the use of unfractionated heparin, bisphosphonates [16,17] or sodium thiosulfate [18] as important components of treatment mainly in an attempt to control thrombosis and calcium–phosphate deposition within arterioles.

The pathophysiology of CUA is complex. The final pathway is the development of ischaemic eschars in the subcutaneous tissues. Ischaemic panniculitis in the subdermis produces painful but superficial serpiginous lesions. Characteristically, pain precedes necrosis and likely represents ischaemic necrosis of fat. In obese patients, diminished blood flow at the abdomen, buttocks and upper thighs is proposed to enhance ischaemia [19]. The situation is compounded by vascular calcification and small-vessel thrombotic occlusion. Local tissue hypoxia remains a potent stimulus for the expression of osteogenic genes in vascular smooth muscle cells and also inhibits collagen matrix formation. In this context, HBO represents a logical treatment by increasing the amount of dissolved oxygen in plasma [7]. Hence, a greater oxygen supply is available even without considering the contribution from oxygen bound to haemoglobin. By augmenting tissue oxygen tension, HBO reverses the progression of devitalised tissue that occurs despite surgical debridement and appropriate wound care.

HBO is administered within a monoplace chamber that increases atmospheric pressure up to 2.5 atmospheres (250–280 kPa). The oxygen is administered via a tight-fitting hood, mask or endotracheal tube. At such increased pressures, the amount of oxygen dissolved in plasma alone is sufficient for normal cellular metabolism of most resting tissues. The wound-healing process may be helped by raising the blood-to-tissue oxygen gradient in circumstances of compromised perfusion. Hyperoxia provides additional benefits such as angiogenesis and killing of certain bacterial species (such as anaerobes and *Pseudomonas* sp.), restoring neutrophil-mediated killing and reducing leukocyte-mediated release of proteases and free radicals that characterize reperfusion injury [13].

HBO treatment is not without risk. The side-effect profile ranges from general features such as claustrophobia and fatigue, to barotrauma affecting sinuses or middle ear, to oxygen toxicity causing convulsions or pulmonary oedema. A decompression illness (pneumothorax or gas embolization) is also a potential hazard if the atmospheric pressure is lowered too rapidly. The reported adverse effects are typically mild, although possibly under-reported in clinical trials. It is estimated that 20% of patients will experience reversible myopia, symptomatic barotrauma will be seen in 15–20% and severe central nervous system effects in up to 2% [7]. The side-effect profile in this case series appeared to be limited and mild.

There is an increasing number of case reports where CUA has been successfully treated with HBO [3]. However, this relatively good survival of a typically fatal condition may be a reflection of better recognition of CUA, faster initiation of treatment, improvements in dialysis techniques and the emergence of non-calcium-containing phosphate binders in addition to other medications available to successfully treat CUA (such as bisphosphonates). Due to the relatively rare occurrence of this disease, it is unlikely that a single-centre randomized controlled trial could be initiated to establish the best treatment modality, although the increasing frequency of patients identified with this condition (see Figure 1) could potentially allow multicentre studies to be performed. Whilst control of calcium–phosphate balance remains fundamental to biochemically controlling vascular calcification, aggressive wound care is vital to preventing secondary infection. The survival analysis presented in this report controlled for a number of variables, but not for calcium–phosphate product or PTH as these variables were not recorded at that time in the ANZDATA registry. By matching with up to five cases per index case across Australia and New Zealand, it is presumed that these matched cases were reflective of comparable patients' biochemistry for that specific modality at that time. The present single-centre experience supports the addition of HBO as a therapeutic option for the treatment of CUA.

Conflict of interest statement. None declared.

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