Calcific uraemic arteriolopathy: local treatment and hyperbaric oxygen therapy

Sir,

Calcific uraemic arteriolopathy (CUA) (‘calciphylaxis’) is a rare necrotizing cutaneous abnormality which is being increasingly recognized in the dialysis population [1]. It is usually associated with secondary hyperparathyroidism in the presence of advanced renal failure and high calcium/phosphate product [2]. Treatment is difficult and often unsuccessful and is associated with a high mortality (50–100%). We report a case of CUA developing 2 years post-parathyroidectomy, which was successfully treated with hyperbaric oxygen (HBO) as an adjunct to local surgical therapy.

Case. A 37-year-old female presented with end-stage renal failure in May 1994. Continuous ambulatory peritoneal dialysis was commenced. In November 1996, she underwent a parathyroidectomy for symptomatic secondary hyperparathyroidism. She had bone pain and proximal muscle weakness although there were no radiographic changes. Her serum parathyroid hormone (PTH) was 1052 pg/ml (5–45 pg/ml), calcium 2.78 mmol/l and phosphate 2.46 mmol/l.

In September 1998, she had peritonitis refractory to antimicrobial therapy. She was transferred to maintenance haemodialysis via a long-term venous catheter (a ‘permcath’). An arterio-venous fistula was created.

Over the next month the fistula thrombosed, as did the permcath, on three occasions necessitating a change. The patient was found to have a clot in the right atrium and severe, global impairment of cardiac function. A procoagulant screen, including lupus anticoagulant and anti-phospholipid antibody, was not revealing.

A left thigh arterio-venous graft (Thoratec, Pleasanton, CA, USA) was inserted and the patient was given warfarin as an anticoagulant. She lost 12 kg in weight over the next 10 months. Ten doses of i.v. iron (Ferrum H, Sigma Pharmaceuticals, Clayton, Victoria, Australia) were administered in April 1999. In June 1999, she had a fistulogram for increasing venous pressures; no significant stenosis was identified.

Six weeks after the fistulogram the patient noted burning dyseaesthesia in her left thigh 10 cm distal to the loop of the Thoratec graft in the region that hand pressure was applied post-fistulogram. This area became red and indurated, and progressed to an ulcer with a black eschar. The ulcer was painful and narcotic analgesia was required.

Examination revealed a 3 × 2 cm ulcerated area on the left thigh distal to the Thoratec graft. There was an additional, smaller area proximal to the graft and both areas were surrounded by erythema. There was marked livedo reticularis on the left calf. Peripheral pulses were palpable and of good volume. Blood pressure pre-dialysis was 130/80 mmHg, falling to 95/70 mmHg post-dialysis. She was in sinus rhythm. Medications at this time included warfarin, calcium carbonate, erythropoetin, folic acid and multivitamins. She was not on calcitriol. Plasma calcium was 2.6 mmol/l, phosphate 0.96 mmol/l, albumin 43 g/l, PTH 129 pg/ml (12–72 pg/ml) and haemoglobin 100 g/l. Plain X ray of the left leg did not reveal any calcification. Treatment was supportive with analgesia, antibiotics and local wound care, but the ulcer enlarged to 5 × 3 cm with a necrotic base and formal surgical débridement was performed. The vascular supply to the region was not compromised by the graft. Histology of resected tissue showed features of calcific uraemic arteriolopathy with circumferential calcification in the thickened walls of small arteries and arterioles. There was associated intimal fibrous proliferation that resulted in luminal occlusion of some vessels (Figure 1).

Treatment included oral antibiotics, daily saline dressings, cessation of warfarin and commencement of low molecular weight heparin (Fragmin, Pharmacia, Rydalmere, NSW, Australia), zinc and vitamin C supplements, and the substitution of aluminium hydroxide for calcium carbonate. There was extension of necrosis on the inferior aspect of the ulcer and further débridement was required. Due to the continued progression of the necrosis, adjunctive treatment with HBO was commenced (2.4 atm for 90 min, 6 days per week). There was no further necrosis and over the next week granulation tissue was evident in the ulcer base and a split skin graft (SSG) was performed. HBO was continued for a total of 23 sessions.

The SSG remained viable and the smaller, proximal lesion settled. Fragmin (Pharmacia) was continued indefinitely as the recommencement of warfarin was considered unsafe.

Comment. CUA is a rare condition which typically affects women with significant renal impairment [1,2]. Our patient developed cutaneous lesions associated with a prodrome of dysaesthesia. Her lesions and skin biopsy were classic examples of those previously described.

The pathogenesis of CUA is not well defined. Janigan et al. [3] describe two stages of the process: the primary lesion being the calcification in the subcutaneous vessels, and the secondary lesion being the infarction of adjacent tissue and skin. It is unknown how long primary lesions take to

Fig. 1. Several small vessels within the subcutis showed circumferential calcification (arrows). In addition there was associated intimal fibrous proliferation and this caused occlusion of the lumen of the vessel at the top left (*). Stained with haematoxylin and eosin. Original magnification × 100.
develop since they are asymptomatic. The first symptoms correlate only with the development of the secondary lesion. Dysregulation of calcium/phosphate was not apparent in our patient at presentation suggesting that it is not the only factor contributing to the development of CUA. She had evidence of a thrombotic tendency and was on maintenance warfarin. She had experienced recent weight loss and had documented poor cardiac function. She had recently received a course of i.v. iron, and there was a temporal relationship between the pressure applied post-fistulogram and the development of the cutaneous manifestations. These are all risk factors for the development of CUA. Relatively low blood pressure has been noted in affected patients. Hypotension may exacerbate the lesion by inducing ischaemia; this may be systemic, such as in shock, or local as in compression of the skin [3].

Parathyroidectomy, dietary control of the calcium/phosphate product, low calcium dialysate, aluminium-based phosphate binders, débridement of necrotic tissue, broad spectrum antibiotics and skin grafting are the mainstays of treatment [2,3]. Maintenance of good tissue oxygenation is believed to be important to aid in bacterial killing and wound healing [4]. Oxygen tension in ischaemic tissue is lower than in healthy tissue. HBO increases oxygen tension in the arterial blood and tissues, and the cellular oxygen supply is improved by raising the tissue-cellular diffusion gradient [4]. HBO therapy can increase the tissue oxygen tension to 400 mmHg (eight times that achieved with room air) resulting in a substantially increased gradient from healthy tissue to the wound centre. The high arterial oxygen pressure achieved with HBO results in demonstrable increases in wound oxygen tension in previously hypoxic wounds. Wounds with severely compromised microcirculation show marked improvement with HBO as compared with oxygen inhalation at normal atmospheric pressure [5,6]. The primary lesion of vascular calcification is not altered with this therapy.

The cellular and biochemical benefits of HBO include promotion of angiogenesis and wound healing, killing of anaerobic organisms, improvement of phagocytosis by neutrophils and stimulation of collagen synthesis [4–6]. The side effects of HBO are minimal if pressures are kept below 300 atm and the duration of treatment less than 2 h. The most common side effect is reversible myopia due to oxygen toxicity on the lens of the eye, but others include headaches, seizures, reversible barotrauma and pulmonary symptoms [5]. Our patient did not experience any side effects.

CUA is a rare condition with a high mortality and morbidity. The treatment is still unsatisfactory. Our patient had a number of risk factors but had good control of serum calcium and phosphate, and PTH, having had a parathyroidectomy 2 years prior. The process may have been precipitated by i.v. iron or by the pressure applied post fistulogram, and then exacerbated by the ischaemia and volume depletion consequent to dialysis and cardiomyopathy. We employed the use of HBO as an adjunct to aggressive local therapy with a favourable outcome.

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