ORIGINAL ARTICLE

Multimodal treatment of calcific uraemic arteriolopathy (calciphylaxis): a case series

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Abstract

Background: This is an incident series of five dialysis patients with late-diagnosed calcific uraemic arteriolaphathy (CUA), severe uncontrolled hyperparathyroidism and infected skin ulcerations.

Methods: A multimodal intervention was based on wound care, antibiotics, surgical debridement, sodium thiosulphate and cinacalcet and associated with regression of skin disease in four cases after varying treatment time periods ranging from 4 to 33 months.

Results: Multimodal treatment including sodium thiosulphate and cinacalcet was associated with very favourable local outcomes and survival. This series further confirms that the diagnosis of CUA is rarely made at the nodular, non-ulcerative phase of the disease.

Conclusions: This series contributes to the build-up of case series reporting on the treatment of CUA, and will hopefully serve as a basis of well-conceived comparative effectiveness studies investigating the value of the combined interventions applied so far in this severe condition.

Key words: calcific uraemic arteriolopathy, cinacalcet, CUA, parathyroid hormone, skin ulcers

Introduction

Calcific uraemic arteriolopathy (CUA) is a severe systemic disease with short survival characterized by progressive calcification of arterioles leading to local ischaemia and thrombosis [1]. The clinical phenotype of this arteriolopathy in part overlaps with that of other diseases and this condition is often diagnosed only at the advanced, ulcerative stage rather than at the more precocious nodular phase characterized by the presence of non-ulcerated calcified skin plaques [2]. CUA is multifactorial in nature and hyperparathyroidism, excessive vitamin D administration, hyperphosphataemia, inflammation and deficiency of inhibitors of vascular calcification are held as major factors responsible for this devastating disease [3]. Female gender, diabetes, obesity, a pro-coagulant state, the use of warfarin and hypoalbuminaemia...
are considered as important predisposing risk factors and/or as disease accelerators [2, 4] in dialysis patients. Owing to the multifactorial nature of this calcific disease, experts’ recommendations in the most accessed electronic source of evidence-based information [4] suggest a combined therapeutic approach including intensive wound care and avoidance of skin trauma, correction of hyperphosphataemia, sodium thiosulphate, low calcium dialysate, oxygen therapy and adequate treatment of hyperparathyroidism, with surgery in the most severe, refractory cases or with cinacalcet in less severe cases responsive to this drug. However, given the rarity of CUA, there are no randomized trials underpinning these recommendations. As commonly occurs in rare diseases [5], the building of knowledge on this condition rests on well-conceived registries [6] and on careful interpretation of case series. Recent post hoc analyses in the frame-work of the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOlve) trial [7] suggest that cinacalcet may reduce the incidence rate of CUA in the dialysis population. Information on clinical outcomes in patients treated by the currently recommended combined approach including cinacalcet [4] remains mainly based on single case reports [8–22] or on small clusters of three to seven patients [23–26], the largest series published so far being composed of 27 patients collected in a national effort by Austrian nephrologists [24]. Early studies were mainly centred on cinacalcet [8–12, 14, 16], while subsequent studies focused on combined treatment including thiosulphate [10, 12, 18–21, 23–26]. Furthermore, variable policies were applied in these studies for the use of non-calcium-based phosphate binders, low calcium dialysate, active forms of vitamin D [17] and oxygen therapy [21, 23, 25]. Accruing information on carefully designed multimodal therapies including cinacalcet in studies at single institutions is of relevance to gain further non-experimental insights on the efficacy of these approaches and to enlarge the collection of treated cases for future systematic reviews and comparative effectiveness studies. In this perspective, we report a series of five patients where the disease was diagnosed at an advanced phase. All these patients were treated according to a multimodal therapy, including sodium thiosulphate and cinacalcet, as well as with the full series of interventions (avoidance of calcium binders and vitamin D, stopping warfarin, low calcium dialysate; intensive dialysis; careful wound care and broad-spectrum antibiotics) that current literature indicates as possibly useful for the management of this disease [4]. Owing to logistic reasons, our approach excluded oxygen therapy.

Materials and methods

Case 1

A 33-year-old obese female was admitted to our department for renal graft failure 13 years after transplantation. She had a history of long-term treatment with warfarin because of inferior cava hypoplasia, hyperparathyroidism [parathyroid hormone (PTH) ≥1000 pg/mL on multiple testing], hyperphosphataemia and hypocalcaemia. On admission, large skin ulcers were present on both legs. She presented multiple painful subcutaneous nodules, which had been interpreted as a sign of polyarteritis nodosa, and she had received a short course of prednisone and cyclophosphamide. A skin biopsy made at admission documented CUA.

Case 2

A 68-year-old male on continuous ambulatory peritoneal dialysis exhibited bilateral skin ulcers and painful nodules on both legs and an ulcer on glans penis which had been interpreted as a neoplastic lesion. On histology, the glans lesion showed extensive calcium deposits in the lumen of a small-sized vessel which were pathognomonic of CUA. This patient had a history of very poor compliance to therapeutic prescriptions and severe, uncontrolled hyperparathyroidism.

Case 3

A 67-year-old diabetic female on haemodialysis presented with a painful ulcerated nodule, which was initially interpreted as a consequence of peripheral artery disease. New ulcers appeared on contralateral calf in the subsequent weeks. She had been treated with warfarin for many years because of atrial fibrillation. She had uncontrolled hyperparathyroidism (PTH persistently ≥1000 pg/mL), hyperphosphataemia and hypocalcaemia.

Case 4

A 65-year-old female had initiated haemodialysis 5 years earlier. She was admitted to our department because of the presence of large symmetrical infected ulcers on lower limbs. Ulcers had been considered as an expression of peripheral artery disease. The patient had a history of scarce compliance to treatments applied to control bone mineral disorders with severe, uncontrolled hyperparathyroidism and was on long-term treatment with warfarin for atrial fibrillation.

Case 5

A 68-year-old diabetic female who had been on haemodialysis for 4 years was hospitalized for painful subcutaneous inductions in the thighs and infected ulcers on both calves which had been attributed to diabetes and peripheral artery disease. During the year preceding the appearance of these ulcers, the patient had decided to stop all medications. The diagnosis of CUA was made on clinical grounds because of uncontrolled hyperparathyroidism.

Multimodal treatment of CUA

In all cases, we applied a standard multimodal treatment protocol contemplating immediate treatment with cinacalcet. This drug was initiated at starting dose of 30 mg/day and the dosage was increased every other day up to the maximal tolerated dose and under strict monitoring of serum calcium concentration. Intravenous sodium thiosulphate infusion was initiated 4–8 weeks after cinacalcet; this gap was due to delivery time from manufacturer. Sodium thiosulphate was administered intravenously at an initial test dose of 12.5 g. The drug was then continued with a standard dose (25 g administered during the last 30 min of each haemodialysis session). Sodium thiosulphate treatment was prolonged until ulcer healing plus an additional 2 months. Furthermore, along with current recommendations [4], our multimodal approach contemplated: withdrawal of calcium-containing phosphate binders and vitamin D compounds; replacement of warfarin with subcutaneous heparin; reduction of dialysate calcium concentration (1.25 mmol/L); increased number and/or duration of dialysis sessions; and wound management withatraumatic resection of necrotic skin and administration of broad-spectrum antibiotics.

All patients gave informed consent concerning off-label use of sodium thiosulphate. Procedures were conducted in adherence to the Declaration of Helsinki.
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Follow-up of 19.2 ± 3.8 months (range: 15–33 months). During this observation period, no skin ulceration relapses were registered. In all cases of this series, the diagnosis of CUA had been missed before referral to our unit (Table 1) and none of these patients had been treated with cinacalcet or sodium thiosulphate.

A favourable response to the multimodality treatment was registered after various periods of treatment in all but one patient (Case 2). In this patient, the multimodal therapy was stopped after 30 months because after an initial, brief period of compliance, the patient refused thiosulphate treatment and continued to show poor adherence to cinacalcet, phosphate binders and to the prescribed dialysis schedule as well as to suggested parathyroidectomy, so that his hyperparathyroidism remained uncontrolled. In the other four patients, skin ulcerations healed after an average period of 18.7 ± 11.9 months (range: 4–33 months). After the healing of skin lesions, these patients had an additional follow-up of 19.2 ± 3.8 months (range: 15–24 months). During this observation period, no skin ulceration relapses were registered. All patients, including the one with unabated hyperparathyroidism, poor therapeutic compliance and persisting skin ulcers, are still alive and on dialysis treatment. At last follow-up visit (Table 2), hyperparathyroidism was well controlled in the four patients with healed skin ulcerations.

**Discussion**

In the present series of five dialysis patients with advanced, late-diagnosed CUA, a multimodal intervention, including wound care, antibiotics, sodium thiosulphate and cinacalcet, was associated with full regression of skin lesions in four cases after variable treatment periods ranging from 4 to 33 months. This favourable clinical course paralleled with almost full regression of hyperparathyroidism. The patient unresponsive to this multimodal therapy was overtly non-compliant and presented unabated hyperparathyroidism across a 30-month follow-up. All patients survived over global follow-up periods ranging from 24 to 48 months.

CUA is a complex, multifactorial disease. Hyperparathyroidism is held as a major causal component of this deadly condition [27] and severe hyperparathyroidism was a hallmark in our series. Several factors may either trigger or exacerbate this disease, and in line with previous studies [1, 2] obesity, diabetes and warfarin exposure were possible inciting factors or disease accelerators in our series.

Early diagnosis and timely treatment of risk factors may, in theory, limit the aggressiveness of CUA. However, the diagnosis of this disease is frequently overlooked and, in most cases, the diagnosis is made at the advanced, ulcerative stage only [2], which dictates a very short survival. In all cases, we describe here that the correct diagnosis was omitted and skin lesions were initially attributed to peripheral artery disease, panniculitis or cancer.

Even though no historical series exist to support the contention that survival and clinical outcomes have improved over the last decade, it is the prevailing view that greater focus on wound care, aggressive treatment of hyperparathyroidism, the use of thiosulphate and perhaps oxygen therapy [4] improved the outlook of patients with this disabling disease characterized by an ominous prognosis.

In general, the contribution of single components of multimodal therapies to clinical outcomes is difficult to dissect. This is particularly true in small series like ours. Sodium thiosulphate is held as a major disease-modifying agent in CUA [24, 28]. Its favourable action is generally attributed to calcium chelation and possibly to inhibition of vascular calcification in injured blood vessels [28]. However, sodium thiosulphate treatment has no effect on hyperparathyroidism, which is a relevant underlying causal factor in CUA. In the largest cases series published so far [23, 24], the combined use of thiosulphate and cinacalcet associated with complete regression of skin lesions in six of seven cases in the series of Canadian patients by Baldwin et al. [23] and with a 52% (complete) and 19% (partial) regression rate of the same lesions in the Austrian series by Zitt et al. [24]. In this second series,
the largest study reporting on the treatment of calciphylaxis, the use of antibiotics and cinacalcet were relevant predictors of a favourable clinical response. Nevertheless, the death rate in Austrian patients was as high as 52% over an average 3-month follow-up, which is substantially higher than in Canadian patients where the death rate was 25% during an average follow-up of ~20 months. In these studies, the use of cinacalcet was apparently related in an inverse fashion with the death risk, because this drug was used in 30% of patients in the Austrian study [24] and in 57% of patients [23] in the Canadian study. Along with this hypothesis, in our study, the effect on skin lesions of the multimodality approach contemplating cinacalcet as a fixed component was very good, with an 80% remission rate (four of five patients) and all patients surviving over follow-up periods extended up to 48 months. However, survival data in small studies are per se hardly interpretable. In this respect, the quite long survival (censoring period 30 months) in the patient uncompliant to the multimodal treatment in our study indicates that survival may be unexpectedly long also in patients with unremitting hyperparathyroidism.

Our study has limitations and strengths. The fact that the disease was diagnosed at an advanced stage (negative selection) might have in theory hindered the response to therapy. However, the remission rate of skin lesions and the survival rate of our patients were remarkably high. Another important limitation is the fact that we corroborated the diagnosis of calciphylaxis with histology in just two cases. For the risk posed by severe ulcer infection, the diagnosis in remaining cases was made just on clinical criteria. Indeed, definitive diagnosis of calciphylaxis requires a skin biopsy to exclude other conditions that can mimic CUA; skin biopsy, however, may expose patients to possible risks such as ulceration, superimposed infection, propagation of new lesions, bleeding and induction of necrosis [29]; these risks may be reduced by performing punch biopsy rather than an incisional biopsy [29] and, when possible, in a non-ulcerative phase of the disease, in our opinion.

The strengths of our study are the fact that it is based on a single institution and on a pre-established multimodal therapeutic approach which was uniformly applied to all cases. Overall, our observations are compatible with the hypothesis that a multimodal regimen including a drug, which effectively counters hyperparathyroidism, may prompt a very favourable response in patients with CUA, a hypothesis in line with the recent observation that long-term cinacalcet treatment substantially prevents the occurrence of CUA in dialysis patients [7].

In conclusion, the present case series further confirms that the diagnosis of CUA in dialysis patients is rarely made at the nodular, non-ulcerative phase [2] of the disease. The multimodal treatment applied in the present study was associated with very favourable local outcomes and survival. This series adds to previous observations and contributes to the information build-up that will hopefully serve as a basis for well-conceived comparative effectiveness studies investigating the value of the combined interventions applied so far.

**Conflict of interest statement**

None declared.

**References**


