Cinacalcet as First-line Treatment for Calciphylaxis

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Sir,

Calciphylaxis is probably the most hazardous cutaneous complication of end-stage renal failure. Although its precise pathomechanism is still elusive, phosphates/calcium disturbances are likely to play a significant role, along with secondary hyperparathyroidism. Cinacalcet, a calcimimetic agent that directly decreases parathormone (PTH) concentration through an increase in sensitivity of calcium receptor present on parathyroid cells, is currently used to alleviate renal failure-related secondary hyperparathyroidism. Additionally, it was used successfully as a first-line treatment in two patients with calciphylaxis in whom surgical cure of hyperparathyroidism was not considered to be a valid option (1, 2). We report here on a new observation of this treatment in this rare but serious condition.

CASE REPORT

A 68-year-old woman with end-stage renal failure secondary to nephroangiosclerosis was referred for evaluation of a highly painful ulceration of her left forearm. She had received a renal graft in 1990, but haemodialysis had to be resumed in 1999 due to the occurrence of a late graft rejection with a schedule of three courses of dialysis of 5 h each per week. Her medical history also included past atrial fibrillation, ischaemic stroke and lower limb obliterating arteriopathy, leading to protracted treatment with warfarin. Four years before the current flare, she had already experienced livedoid and ulcerative lesions of the lower limbs that had been diagnosed as cutaneous manifestations of calciphylaxis and that had slowly resolved in months with local care.

The current 8×4 cm ulceration was superficial, fibrinous, surrounded with inflammatory and livedoid borders and had occurred 2 months before referral, with a progressively worsening course. Biological tests displayed normal calcium concentration (2.03 mmol/l), elevated phosphates concentration (2.40 mmol/l) and a normal calcium×phosphate product (4.87, normal <5.6). PTH was overtly elevated in the serum (269 pg/ml; normal range: 10–55 pg/ml). Immunological and coagulation investigations were all normal, including tests for antinuclear antibodies, anti-phospholipid and anti-cardiolipin antibodies, cryoglobulinaemia, and protein C and S deficiency. Standard X-rays of limbs showed diffuse calcifications of vessels, along with amorphous subcutaneous calcifications. A biopsy taken from the livedoid border of the left forearm ulceration revealed microthrombosis, parietal fibroblastic proliferation and media calcinosis, along with a limited inflammation in hypodermal vessels. Once again, cutaneous manifestations of calciphylaxis were considered, but parathyroidectomy was ruled out due to the relatively small size of the ulceration and to the limited increase in PTH rate. Instead, oral treatment with cinacalcet (Mimpara®, Amgen, Neuilly, France) was implemented at 30 mg/day, whereas the dialysis schedule was not modified. No phosphate binder was used. This procedure, associated with local care using hydrogel dressing, was followed by a quick improvement of ulceration, a significant decrease in local pain and a subsequent total healing within 2 months, whereas PTH concentration slightly decreased to 225 pg/ml. Conversely, no significant change in calcium or phosphates concentration was observed. After an 8-month follow-up, the ulceration did not recur.

DISCUSSION

Calciphylaxis is an unusual, but sometimes life-threatening, complication of end-stage renal failure, occurring in less than 4% of patients. Risk factors include dialysis, especially peritoneal, hyperphosphoraemia, hyperparathyroidism, warfarin treatment, female sex, diabetes mellitus and obesity. It is generally considered to be an acute micro-occlusive disorder involving mainly small- and middle-sized cutaneous, previously calcified vessels and leading to a rapidly extensive necrotizing livedo primarily located on the lower limbs, to abdominal fat necrosis or to digital necrosis. Vessels calcifications are very likely to be related to calcium/phosphates disturbances, but the exact triggering factors precipitating acute microthrombotic occlusions remain elusive and might be multiple, perhaps acting as a combination of events with an additive effect. Among these factors, secondary hyperparathyroidism is perhaps a major actor, either directly through vascular properties or indirectly by an increase in calcium×phosphates product (3). Accordingly, partial or subtotal parathyroidectomy may be considered as a first-line treatment of extensive disease, but no real consensus exists to date in this matter. However, in more limited cases as in our observation, attention has

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recently been drawn to the possible interest of cinacalcet, a calcimimetic drug that increases the sensitivity of PTH-secreting cells to extracellular calcium, resulting in a decrease of PTH production. This molecule is currently routinely used in end-stage renal failure-associated secondary hyperparathyroidism (4) and its efficiency in calciphylaxis has already been reported in two patients, in whom cutaneous lesions improved quickly after implementation of this treatment (1, 2). Similarly, a strikingly good and fast clinical result was observed in our observation. This favourable evolution is likely to be directly related to cinacalcet treatment, since the dialysis parameters remained unchanged, and the clinical efficiency was correlated with a decrease in PTH level, but not with changes in calcium or phosphates rates. Moreover, in these three patients, the efficacy and the rapidity of action of Cinacalcet appear to match the results obtained with parathyroid surgery. Accordingly, this molecule might be considered as a first-line option in patients with general contra-indication to surgery or when parathyroid surgery does not appear mandatory due to the mild nature of cutaneous lesions and/or to the limited PTH rate increase, as illustrated by our patient. Additionally, due to the risk of development of adynamic bone disease, this treatment should probably be restricted to patients with calciphylaxis and secondary hyperparathyroidism even though parathyroidectomy has been advocated in patients with low PTH levels.

Overall, this observation supports the concept of first-line treatment of end-stage renal failure-related calciphylaxis with cinacalcet in monotherapy in patients with secondary hyperparathyroidism.

Conflict of interest: None to declare.

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