Case Report

Proximal calciphylaxis treated with calcimimetic ‘cinacalcet’

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Abstract
Calciphylaxis is a rare condition affecting patients suffering from end-stage renal failure, characterised by cutaneous ischaemia and necrosis. The management of calciphylaxis is challenging owing to the lack of optimal medical therapy, although parathyroidectomy has shown some benefit. We present a case of severe proximal calciphylaxis treated with a small dose of the calcimimetic ‘Cinacalcet’.

Keywords: calciphylaxis; end stage renal failure; haemodialysis; hyperparathyroidism; cinacalcet; metastatic calcification

Introduction
Calciphylaxis is a rare but potentially fatal condition, characterized by painful purpuric skin lesions, subcutaneous nodules and necrotic ulceration. The disorder occurs mostly in patients with end-stage renal failure on dialysis or after kidney transplantation associated with secondary or tertiary hyperparathyroidism [1–4]. The correct treatment of calciphylaxis is controversial but most authorities recommend parathyroidectomy for patients with high parathyroid hormone (PTH) levels. Parathyroidectomy improves wound-healing and increases survival rate [3–5]. However, parathyroidectomy is not without its complications in addition to anaesthetic risk, which often preclude surgery in a subgroup of patients. In this group of patients, medical treatment with Cinacalcet represents a potential alternative. Clinical trial results have proven that Cinacalcet reduces PTH as well as calcium and phosphate in haemodialysis patients with secondary hyperparathyroidism [6,7]. Nonetheless, evidence for Cinacalcet efficacy in treatment of calciphylaxis is sparse and anecdotal.

Here we report a case of proximal calciphylaxis in a 76-year-old lady who was successfully treated with the calcimimetic ‘Cinacalcet’.

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Case report
A 76-year-old Caucasian lady with end-stage renal failure secondary to diabetic nephropathy, treated with thrice weekly haemodialysis presented in June 2005 with multiple painful lumps and ulceration over the lower abdomen and thighs. A few months prior to presentation, she noted a 6 kg loss in body weight and complained of a constant dull aching pain over the left hip region. The patient had a long-standing history of type 2 diabetes mellitus, secondary hyperparathyroidism, ischaemic heart disease, and previous uterine neoplasia, but no history of arthritis or skin rash.

On presentation, her medication included atenolol 25 mg once daily, alfalcaldiol 0.5 mcg daily, sevelamer hydrochloride 800 mg thrice daily, calcichew 1.25 g twice daily, omeprazole 20 mg once daily, insulin and aspirin 75 mg once daily; she was not treated with warfarin or heparin.

Physical examination revealed an obese lady (BMI 31.5), with multiple violaceous lesions over the abdomen and thighs which were extremely tender on palpation. There was a painful 5 cm × 3 cm necrotic ulcerated area surrounded by erythema on the right lower abdomen (Figure 1). A similar ulcer of 3 cm × 2 cm was also noted on the left thigh. The peripheral pulses were normally felt on the lower limbs. A tender hard swelling could easily be felt on the left hip. The rest of her systemic examination was unremarkable.

Laboratory data revealed normal haematocrit, haemoglobin, white blood count, and platelets. Her blood chemistry was consistent with a patient with established renal failure on haemodialysis. Corrected plasma calcium was 2.47 mmol/l, phosphate: 1.97 mmol/l, alkaline phosphatase: 167 IU/l (reference range: 25–110 IU/l), albumin: 30 g/l, intact PTH: 997 pg/ml (reference range: 15–65 pg/ml) and CRP: 62 mg/l. Cryoglobulin, antinuclear antibodies and antineutrophil cytoplasmic antibodies were all negative. Multiple blood and wound swab cultures were also negative.

Radiology of the left hip showed huge tumour-like calcification on the left hip area, as well as calcified left femoral artery (Figure 1). There was also extensive calcification affecting the splenic, mesenteric, external iliac, profunda femoris and brachial arteries.
A diagnosis of proximal calciphylaxis was made on clinical grounds, and treatment commenced with analgesia, antibiotics, local wound care and phosphate binders (sevelamer hydrochloride and calcichew). The patient was assessed for parathyroidectomy but was considered unsuitable, owing to her co-morbidities. Instead, in August 2005, she was commenced on Cinacalcet 30 mg/day orally. Over the following 2 months, her parathyroid levels reduced to 264 pg/ml, serum phosphate normalized, corrected calcium fell to 2.02 mmol/l and ulcers began healing with granulation. By the end of the 4th month, her PTH value fell to 98 pg/ml (Figure 2) with complete healing of both abdominal and thigh ulcers (Figure 3). Interestingly, the patient’s anginal pain seemed to have stabilized, with less frequent attacks and need for medication. She was maintained on Cinacalcet 30 mg/day. A year later, while on Cinacalcet 30 mg/day, a follow-up X-ray showed remarkable regression in the size of the left hip region calcification (Figure 3). She remained in good health until March 2007, when she died from a cerebrovascular accident.

Discussion

Calciphylaxis is the ischaemic ulceration of the skin due to metastatic calcification of the subcutaneous tissue and small arteries in patients with end-stage renal failure. Hyperparathyroidism has been suggested to be a risk factor but some cases of calciphylaxis with normal or even low PTH levels have been reported [8]. The incidence of calciphylaxis in dialysis patients is estimated at 1%/year, with a reported prevalence of 4% [9]. Calciphylaxis is a potentially lethal disease, with a high mortality rate (60–80%) principally due to ischaemic events and sepsis complicating secondary infection of the ulcers [10]. Diagnosis of calciphylaxis require high index of suspicion in a patient with end-stage renal failure with typical skin lesions, as there are no specific laboratory tests. Skin biopsy is specific and can establish the diagnosis, but is not pathognomonic.

Proximal calciphylaxis with lesions affecting the abdomen, thighs and buttocks carries a poor prognosis (63% mortality rate) compared to distal lesions (23% mortality rate) [4]. White race, female gender, recent loss of weight, morbid obesity and poor nutrition are reported risk factors associated with proximal calciphylaxis [11]. Our patient’s lesions appeared proximally with similar characteristics, including female sex, low serum albumin, recent weight loss and Caucasian ethnicity. In this case, diagnosis of calciphylaxis was suggested by the characteristic skin lesions without performing a skin biopsy.

Therapeutic options for calciphylaxis are limited, unsatisfactory and essentially supportive, involving calcium and phosphate control, parathyroidectomy and local wound care [12]. Vassa et al. recommend treatment of calciphylaxis ulcers with hyperbaric oxygen [13,14]. Experience with calcimimetics in the treatment of calciphylaxis is sparse and limited to a few case reports. Velasco et al. reported a case of distal calciphylaxis successfully treated with Cinacalcet as an alternative to parathyroidectomy [15]. In his report, treatment with Cinacalcet 60–120 mg/day for a period of 9 months reduced PTH levels with resolution of the distal leg ulcers. In our patient however, a small dose of Cinacalcet (30 mg/day) normalized PTH values with complete healing of abdominal and thigh ulcer within a relatively short period.
of 20 weeks. Furthermore, following a one-year treatment with Cinacalcet, we noticed a regression in the size of tumour calcification at the left hip region (Figure 3). Although parathyroidectomy reduces the intact PTH level to zero or close to zero, we do not know what degree of suppression by Cinacalcet is required to be similarly successful. On one hand, it is not sensible to reduce PTH to zero, but on the other hand, we know that inadequate suppression would probably not halt the skin necrosis. Therefore, we opted to treat to a PTH of approximately 100 pg/ml (98 pg/ml). While low PTH levels are associated with adynamic bone, in our patient’s case we thought it was safer to over-rather than under-suppress. Furthermore, it is well recognised that even with PTH levels in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) range of 150–300 pg/ml, many patients may have adynamic bone [16].

In conclusion, our case demonstrates the beneficial therapeutic effect of Cinacalcet in the treatment of proximal calciphylaxis with secondary hyperparathyroidism. Apart from mild asymptomatic hypocalcaemia, there were no reported side effects. The drug appears to be safe and well-tolerated over a treatment period of 18 months. We recommend using Cinacalcet to treat calciphylaxis in high-risk surgical patients, or in those who do not wish surgery; however, further clinical trials are needed to confirm this effect.

Conflict of interest. No part of this manuscript has been published before either in part or whole by any of the authors.

References