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Case Report

Calciphylaxis associated with chronic kidney disease and low bone turnover: management with recombinant human PTH-(1–34)

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Introduction

In 1898 Bryant and White reported features of the condition that was later described as calciphylaxis by Selye in 1961 because of a pathophysiologic resemblance to anaphylaxis [1,2]. Calciphylaxis (or calcific uraemic arteriolopathy) is characterized by medial calcification of small arterioles, intimal proliferation, fibrosis and thrombosis resulting in ischaemia, necrosis and superinfection of the skin and subcutis. When renal function is normal, calciphylaxis has been reported infrequently, associated with conditions such as primary hyperparathyroidism [3]. However, amongst patients with chronic kidney disease (CKD) on dialysis, the annual incidence has been estimated at 1–4%, with an apparent increase over the past decades that may reflect the increased use of calcium-based phosphate binders [4,5]. For patients on dialysis, mortality rates are increased 8-fold if calciphylaxis develops [6]. The mortality of non-ulcerating types is ∼30% and ulcerating types around 80%, and most deaths occur within 6 months [7,8]. In this setting, calciphylaxis is usually associated with poorly controlled secondary hyperparathyroidism. However, cases have been reported in association with low bone turnover and following parathyroid surgery [9,10]. This entity has received little attention and no specific treatment has been suggested.

Case

A 49-year-old man with CKD due to chronic glomerulonephritis and a failing renal transplant was admitted to hospital in April 2005 for evaluation of a large, non-healing leg ulcer. He commenced haemodialysis in 1991 and a subtotal parathyroidectomy had been performed in 1994 for severe secondary hyperparathyroidism, with removal of $3^{1/2}$ glands. Because post-operative levels of intact-parathyroid hormone (iPTH) and serum calcium remained low, he was treated with oral calcitriol 0.75 mcg/day and calcium carbonate up to 5.4 g/day. Levels of serum phosphate were persistently elevated and aluminium hydroxide was added as a phosphate binder. In 1995 he received a cadaveric renal allograft. By 2003 the creatinine had risen to 400 mcmol/L and a biopsy showed chronic allograft nephropathy. In 2004 he experienced claudication due to arterial disease of the left femoropopliteal system. After a minor injury to the left ankle, he developed a 6 by 12 cm ulcer with irregular sloping edges and a necrotic base surrounded by indurated erythema, which failed to improve with antibiotic therapy and debridement. Biopsy of the ulcer edge showed typical changes of calciphylaxis. Calcium carbonate and calcitriol were continued due to hypocalcaemia, sevelamer hydrochloride 1600 mg three times a day was added for hyperphosphataemia and prednisolone 7.5 mg/day, mycophenolate mofetil and tacrolimus were continued. After drug committee approval and patient consent, subcutaneous recombinant human PTH-(1–34) [rhPTH-(1–34); teriparatide; Forteo®] was given by subcutaneous injection at a dose of 20 mcg/day. He reluctantly agreed to haemodialysis for 5 h twice a week with a measured Kt/V of 1.6. The ulcer improved and skin grafting was successful at 15 weeks.

Morning blood and urine samples were collected each week from the commencement of rhPTH-(1–3) therapy. iPTH was assayed using the Immulite system (Diagnostic Products Corporation, Los Angeles, CA). Two bone resorption markers were assessed: the osteoclast-derived active isoform 5b of tartrate-resistant acid phosphatase (TRACP 5b; medac GmbH for Suomen Bioanalytikka Oy, Oulu, Finland) and the deoxypyridinoline/creatinine ratio (Immulite 2000 Pyrilinks-D; Diagnostic Products Corporation, Los Angeles, CA). In addition to serum alkaline phosphatase (ALP), two osteoblast-derived bone turnover markers were assessed: bone-specific alkaline phosphatase (BALP; Access Ostase; Beckman Coulter, Fullerton, CA) and osteocalcin using a two-site immunometric assay recognizing the intact molecule (Nichols Advantage, San Juan Capistrano, CA). A bone biopsy with double tetracycline labelling was performed after 6 weeks of therapy.

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Table 1. Bone turnover markers and biochemistry assessed at commencement of therapy with rhPTH-(1–34) and after 8 weeks of treatment

Laboratory investigations	Normal range	Start of therapy	8 weeks
Alkaline phosphatase	30–115 U/L	25	92
BALP	3.7–20.9 mcg/L	8.3	17.2
Osteocalcin	1.1–7.2 ng/ml	1.2	4.7
TRACP 5b	1.3–4.8 U/L	<1	1.2
Deoxypyridinoline/creatinine	2.3–5.4 nmol/mmol Cr	2.2	3.2
Corrected serum calcium	2.13–2.63 mmol/L	1.80	1.86
Serum phosphate	0.81–1.45 mmol/L	1.54	1.88

The TRACP 5b range is that expected for healthy men aged 22–54 and the osteocalcin range is that expected for subjects with normal renal function.

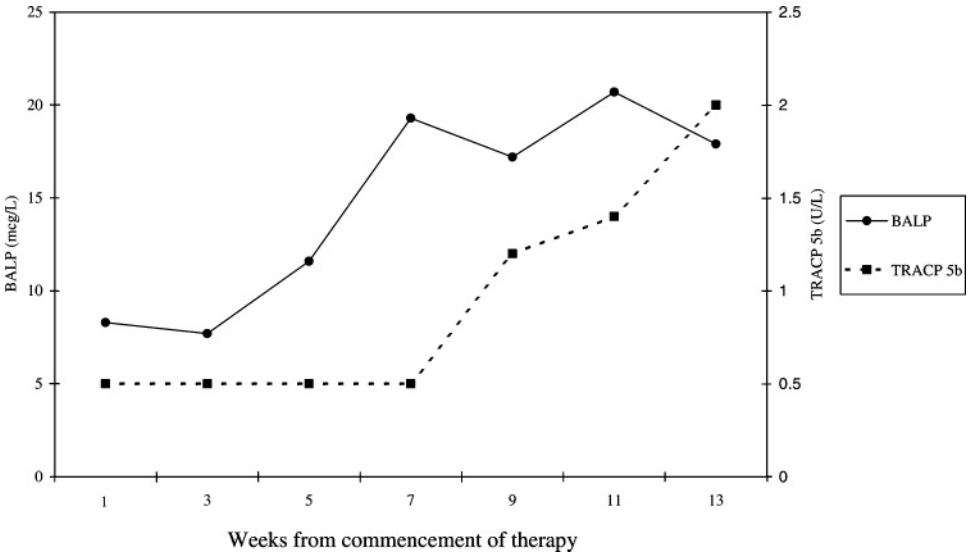

Fig. 1. BALP and TRACP 5b responses to treatment with rhPTH-(1–34). BALP normal range: 3.7–20.9 mcg/L. TRACP 5b normal range: 1.3–4.8 U/L.

At the start of therapy with rhPTH-(1–34), the level of serum iPTH was 1.3 pmol/L (normal range 1–7 pmol/L) despite a corrected serum calcium of 1.8 mmol/L (normal range 2.1–2.6 mmol/L). Bone formation and resorption markers were consistent with low bone turnover at the start of therapy and improved towards the normal range by 8 weeks (Table 1). By Weeks 11 to 13, levels of BALP were slightly elevated and TRACP 5b levels were normal (Figure 1). Phosphate levels rose from 1.54 mmol/L at the start of therapy and remained within the range 1.83–1.88 mmol/L from Weeks 3 to 13, while calcium levels did not vary from the start of therapy to Week 8 but then rose to 2.09 and 2.58 mmol/L at 11 and 13 weeks respectively. Bone biopsy after 6 weeks of rhPTH-(1–34) therapy showed an increased mineral apposition rate of 1.6 mm/day (normal range 0.60–0.80 mm/day) with a reduced mineralization lag time of 9.7 days (12.1–19.9 days) and reduced osteoid area, surface and seam width. The resorption surface and osteoclast number were normal and the trabecular bone area was increased at 32.6% (21–29%). Aluminium staining was absent. The bone histomorphometry was reported to be consistent with increased bone activation due to rhPTH-(1–34) therapy on a background of osteosclerosis, likely to be due to CKD and hypoparathyroidism.

Discussion

Patients with CKD are prone to developing soft tissue calcification due to disturbed mineral metabolism and an imbalance between factors that promote and inhibit calcification. An important mechanism for vascular calcification is the induction of vascular type III sodium-dependent phosphate cotransporters, which occurs in response to increased levels of serum calcium and phosphate. Secondary hyperparathyroidism predisposes to increased release of calcium and phosphate from bone due to uncoupling of bone resorption from formation, but abnormal calcium and phosphate homeostasis also occurs when bone turnover is low or adynamic because of a reduced capacity of bone to incorporate or 'buffer' calcium and phosphate. Increased activity of the sodium-dependent phosphate cotransporters and an increase of intracellular phosphate induces the master osteoblast regulator Cbfa-1. In turn this can result in transdifferentiation of vascular smooth muscle cells to cells with an osteoblast phenotype, capable of producing ALP, osteocalcin, osteopontin, collagen rich extracellular matrix and matrix vesicles that initiate hydroxyapatite crystallization. As renal function worsens, the effectiveness of natural inhibitors of this process that include matrix Gla

protein, fetuin-A, osteoprotegerin, (beta-glucosidase, BMP7, PTHrP and pyrophosphate, declines.

In this case report, the patient's risk factors for calciphylaxis included hypoparathyroidism causing low bone turnover, worsening post-transplant CKD and hyperphosphataemia, which was likely to have been exacerbated by calcitriol therapy. High-dose calcium-based phosphate binders may also have played a role. As this case illustrates, after 6 weeks of rhPTH-(1–34) treatment, bone biopsy demonstrated a mineral apposition rate twice the normal upper range, and serum and urine markers were consistent with improved bone turnover. Low or low normal levels of TRACP 5b and high normal to elevated levels of BALP (Figure 1) were consistent with an overall anabolic effect of this treatment, and reflected the bone biopsy findings. These influences may have contributed to the resolution of calciphylaxis. Animal experiments suggest that another potential action of intermittent injection of rhPTH-(1–34) is a direct inhibition of vascular ossification and proliferation through actions on vascular PTH receptors [11,12].

In addition to the effects of rhPTH-(1–34), we cannot exclude a contribution of concomitant treatments, particularly the commencement of haemodialysis, to this outcome. However, dialysis was limited to 10 h/week, levels of serum phosphate increased despite haemodialysis and sevelamer therapy, doses of calcium and calcitriol were unchanged and earlier antibiotic and surgical management had not prevented progressive deterioration of his condition.

Parathyroidectomy, bisphosphonates, sodium thiosulfate and cinacalcet are amongst the therapies that have been used with varying success when calciphylaxis is associated with hyperparathyroidism and high bone turnover. However, no specific management directed towards the pathogenesis of calciphylaxis has been suggested when bone turnover is low or adynamic as in this case. The use of rhPTH-(1–34) has not previously been reported and is worthy of further assessment.

This case also highlights the potential utility of ALP and its bone isoenzyme BALP as bone formation markers and TRACP 5b as a bone resorption marker in patients with renal impairment, in whom the utility of markers influenced by renal function is limited. BALP and TRACP 5b are not influenced by renal function and, as this case demonstrates, responded rapidly to therapy that increased bone turnover. Further histomorphometric correlation is warranted to determine whether their use might improve the non-invasive assessment of bone in CKD.

Conflict of interest statement. None declared.

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