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Exceptional Cases

Hypercalcaemia as a prodromal feature of indolent Pneumocystis jivorecii after renal transplantation

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Abstract

Following renal transplantation, hypercalcaemia is frequently caused by persisting hyperparathyroidism. Unregulated extrarenal 1,25-dihydroxyvitamin D $(1,25(OH)_2D)$ synthesis, which is well recognized as a cause of hypercalcaemia in granulomatous diseases, may also occur after kidney transplantation. This mechanism is also likely to be responsible for hypercalcaemia reported during treatment of cytomegalovirus and associated with acute symptomatic pneumocystis jivorecii pneumonia (PCP). Hypercalcaemia as a prodromal feature of indolent PCP has not been described. We report a renal transplant recipient who developed hypercalcaemia 30 months post-transplant due to extrarenal production of $1,25(OH)_2D$. Two months later, PCP was diagnosed and hypercalcaemia resolved after initiation of treatment.

Keywords: 1,25-dihydroxyvitamin D; hypercalcaemia; kidney transplantation; pneumocystis jivorecii pneumonia (PCP)

Background

Pneumocystis jivorecii pneumonia (PCP) is a potentially life-threatening opportunistic infection, occurring most frequently in the first 6–12 months after transplantation. The onset of symptoms is generally fulminant, with fever, cough, dyspnoea and hypoxia. However, PCP may develop some years after transplantation following increased immunosuppression, with less specific symptoms such as sweating, weight loss, cachexia and a more indolent course [1].

Case report

The patient was a 55-year-old cadaveric kidney transplant recipient with a background of polycystic kidney disease. Two years post-transplant, he was diagnosed with polyoma (BK) virus infection and acute cellular rejection (ACR) and was treated with methylprednisolone, cidofovir, ciprofloxacin and conversion of mycophenolate mofetil to leflunomide. Six months later, the creatinine was 370 μmol/L (estimated GFR 17 mL/min/1.73 m^2) and repeat biopsy showed ACR and BK virus nephropathy. He was treated with methylprednisolone 500 mg daily for 3 days and changed from tacrolimus to cyclosporine.

Between Weeks 5 and 6, following this change in therapy, his serum calcium rose from 2.45 mmol/L to 2.97 mmol/L. Supplementation with cholecalciferol and calcium carbonate was immediately ceased, as was alendronate treatment. As shown in Table 1, the intact-parathyroid hormone (iPTH) level was suppressed to 1.8 pmol/L, having been elevated at 14.6 pmol/L post-transplant. The serum $1,25(OH)_2D$ level was elevated and levels of 25(OH)D fell. Serum phosphate rose and ALP levels remained in the low normal range. PTH-related peptide, angiotensin-converting enzyme and serum and urine immunoelectrophoresis were normal and bone marrow examination showed no evidence of tuberculosis, granulomatous or lymphoproliferative disease. Computerized tomography (CT) of the chest, abdomen and pelvis and a bone scan disclosed no cause for hypercalcaemia. Elevated calcium levels were unresponsive to two 60 mg doses of pamidronate over 2 weeks or to one 4 mg dose of zoledronate given 2 weeks later. Hypercalcaemia was also unresponsive to an increase in oral prednisolone to 20 mg/day and to dietary calcium restriction.

Seventy days after detection of hypercalcaemia, a repeat chest CT showed bilateral, upper lobe 'ground glass' opacities in a bronchiolar distribution and bronchoalveolar lavage was positive for pneumocystis jivorecii. Treatment was commenced with co-trimoxazole, which was changed to atovaquone due to pancytopaenia, and haemodialysis was required for 1 week due to graft dysfunction. Over the following 28 days, hypercalcaemia and hyperphosphataemia resolved, $1,25(OH)_2 D$ levels normalized and the creatinine returned to 358 μmol/L.

Discussion

The renal conversion of 25(OH)D to $1,25(OH)_2D$ is tightly controlled under normal physiological conditions. PTH is

Table 1. Laboratory investigations (normal range)[a]

	Day 8 prior	Baseline	Day 9	Day 21	Day 62	Day 70	Day 76	Day 82	Day 98
Calcium (2.13–2.63 mmol/L)	2.45	2.97	3.16	3.23	3.16	3.15	2.56	2.03	2.4
Phosphate (0.81–1.45 mmol/L)	0.87	1.41	1.43	1.47	2.01	1.38	1.71	1.95	0.6
ALP (30–115 U/L)	63	55	51	61	100	81	74	85	113
1,25(OH)$_2$D (36–120 pmol/L)		191					190	110	
25(OH)D (>50 nmol/L)[a]		100	46			46	41		
Intact-PTH (1–6.8 pmol/L)		1.8							
Creatinine (55–105 µmol/L)	341	365	374	345	465	418	533[b]	536	362

Time period in days is shown prior to and after detection of hypercalcaemia (Baseline). Treatment of PCP was commenced on Day 71.
[a]Vitamin D adequacy.
[b]Haemodialysis for 1 week.

a major regulator of this process, with increased levels stimulating 1α-hydroxylase activity and 1,25(OH)$_2$D synthesis. Increased levels of calcium, phosphate, 1,25(OH)$_2$D and fibroblast growth factor 23 (FGF-23) directly suppress 1α-hydroxylase activity and reduce 1,25(OH)$_2$D synthesis, in addition to modulating the activity of PTH. Both 1,25 (OH)$_2$D and FGF-23 increase 24-hydroxylase messenger RNA levels and activity, which is responsible for 25(OH) D and 1,25(OH)$_2$D catabolism [2].

Hypercalcaemia in association with granulomatous disease was initially suspected to be caused by increased renal 1,25(OH)$_2$D production. However, 'extrarenal' 1,25(OH)$_2$D production was strongly suggested by a 1981 report of hypercalcaemia and elevated levels of 1,25(OH)$_2$D, which were found to be present in a patient with sarcoidosis both before and after bilateral nephrectomy [3]. Subsequent studies have shown that normal peripheral blood monocytes and pulmonary alveolar macrophages are capable of 1,25(OH)$_2$D production, although these cells are also responsive to 1,25(OH)$_2$D feedback [4]. On the other hand, extrarenal 1,25(OH)$_2$D production by disease-activated tissue macrophages is poorly regulated and correlates to levels of the 25(OH)D substrate, as well as to levels of inflammatory cytokines such as gamma-interferon. These cytokines antagonize the feedback of 1,25(OH)$_2$D that would normally suppress 1α-hydroxylase and induce 24-hydroxylase activity, with the consequence that hypercalcaemia may develop [4]. Pulmonary alveolar macrophages mediate pneumocystis clearance from the lung and interactions between alveolar epithelial cells, alveolar macrophages and the pneumocystis organisms initiate cascades of cellular responses in both the organism and these cells [5]. Characteristic features of PCP lung histopathology include inflammation, oedema, exudates, interstitial fibrosis and alveolar epithelial erosions [6]. While uncommon, granulomatous pneumonia may also occur, and organisms have been identified within single or multiple necrotizing and non-necrotizing granulomas that range in diameter from 0.1 to 2.5 cm [7]. Whether hypercalcaemia is more often associated with PCP granulomatous pneumonia has not been reported.

Following transplantation, hypercalcaemia is most frequently caused by persisting hyperparathyroidism, but other causes should be kept in mind. Hypercalcaemia has been reported during the treatment of cytomegalovirus infection [8], at the onset of symptomatic acute PCP in the 12 months after transplantation and following PCP treatment [9–12]. Hypercalcaemia has also been reported in the late post-transplant period associated with lymphoproliferative disease [13] but to our knowledge has not been reported as a prodromal feature of indolent PCP.

In this case, hypercalcaemia was clearly caused by unregulated extrarenal 1,25(OH)$_2$D production. Despite the reduced eGFR of 17 mL/min/1.73 m^2, levels of 1,25 (OH)$_2$D were >50% above the assay upper range and due to increased substrate utilization, levels of 25(OH)D fell. Increased calcium and 1,25(OH)$_2$D levels caused suppression of PTH. The lack of response of hypercalcaemia to intravenous bisphosphonates and the early reduction in ALP levels indicated that gastrointestinal calcium uptake rather than an increase in bone turnover was responsible for the hypercalcaemia. The immediate rise in serum phosphate levels while renal function remained stable is also likely to reflect increased 1,25(OH)$_2$D-mediated gastrointestinal phosphate absorption.

In a recent report, five renal transplant patients with acute PCP were found to have hypercalcaemia [12]. This represented 20% of all patients with PCP in that transplant cohort and suggested that hypercalcaemia may be a more frequent accompaniment of PCP than previously recognized. Those data, together with the present case, indicate that a diagnosis of PCP should be considered whenever post-transplant hypercalcaemia is accompanied by suppressed or relatively suppressed levels of iPTH. This case also demonstrates that PCP may occur some years after transplantation and that hypercalcaemia may be a prodromal feature of indolent PCP, occurring many weeks before the infection can be diagnosed.

Conflict of interest statement. None declared.

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Crescentic glomerulonephritis associated with vascular endothelial growth factor (VEGF) inhibitor and bisphosphonate administration

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Abstract

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, has been widely used in a variety of malignancies offering substantial clinical benefit. Hypertension and proteinuria are the most commonly reported manifestations of bevacizumab-related nephrotoxicity with the risk increasing along with the dose and with the concomitant use of bisphosphonates.

We describe the first case of a patient with small-cell lung cancer who developed diffuse extracapillary necrotizing crescentic glomerulonephritis, temporarily necessitating haemodialysis, following administration of bevacizumab and zolendronate. Renal function improved without any specific treatment and the patient remained off dialysis after withdrawal of bevacizumab–zolendronate.

Special caution is required when VEGF inhibitors are combined with bisphosphonates. Such a combination can cause crescentic necrotizing glomerular lesions. Withdrawal of the offending medications may be adequate for the alleviation of this severe glomerulonephritis.

Introduction

Neoangiogenesis is a mechanism of critical importance in the development and expansion of malignant tumours. Vascular endothelial growth factor (VEGF) is the major representative of molecules mediating the process of angiogenesis [1]. Bevacizumab, a VEGF inhibitor, has been used in a variety of malignancies offering substantial clinical benefit when combined with standard chemotherapy [2]. Overall, the use of bevacizumab appears well tolerated; most of the reported adverse events range from mild to moderate [2]. Occasionally, it has been associated with severe adverse events such as thromboembolic episodes, gastrointestinal perforation, congestive heart failure and haemorrhage [2]. Hypertension and proteinuria are the most frequent manifestations of bevacizumab-related nephrotoxicity displaying a dose-dependent risk [3–5]. Bevacizumab-induced hypertension