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Clinical Report

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Denosumab for treatment of immobilization-related hypercalcaemia in a patient with advanced renal failure

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Abstract
We describe the case of a young adult with immobilization-related hypercalcaemia and advanced renal insufficiency. Because of the uncertain safety profile of bisphosphonates in such patients, only a low dose of pamidronate was administered twice. This did not result in a sufficient decrease in the serum calcium concentration nor was the decrease sustained. We decided to administer a single dose of denosumab, a monoclonal antibody against the receptor activator of nuclear factor-κB ligand, a new antiresorptive agent registered for use in osteoporosis. This resulted in rapid and sustained decrease in the serum calcium concentration. Transient hypocalcaemia ensued with normalization after vitamin D supplementation. Furthermore, we summarize what is known about hypercalcaemia caused by immobilization.

Keywords: denosumab; hypercalcaemia; immobilization; renal calcium excretion

Background

Severe hypercalcaemia requires a thorough analysis of the underlying cause and immediate treatment. Immobilization is a rare cause of hypercalcaemia that occurs particularly in children and adolescents because of their high bone turnover [1, 2]. Bisphosphonates are commonly used in the treatment of this condition [1, 3]. However, in patients with advanced renal insufficiency [glomerular filtration rate (GFR) <30 mL/min], there is a possibility of renal toxicity [4]. Denosumab is a novel agent registered for the treatment of osteoporosis. It is a human monoclonal antibody directed against receptor activator of nuclear factor-κB ligand (RANKL) that decreases osteoclast activity and bone resorption. As such, it could be an alternative for treatment of resorption-related hypercalcaemia particularly in patients with renal insufficiency.

Case report

A 19-year-old male was admitted to the intensive care unit of our hospital for meningococcal meningitis complicated by multi-organ failure including acute renal insufficiency. Amputation of the right lower leg had to be performed and there were significant neurological sequelae resulting in prolonged immobilization. During this admission, hypercalcaemia developed after 2 months with a maximum corrected serum calcium concentration of 3.4 mmol/L. The serum parathyroid hormone (PTH) concentration was below the detection limit (for laboratory values, see Table 1). The tentative diagnosis was immobilization-related hypercalcaemia. Despite renal impairment [estimated GFR (eGFR) of 18 mL/min/1.73 m^2], a reduced dose of pamidronate (30 mg) was administered intravenously with near normalization of the serum calcium concentration (see Figure 1). Three months later, the serum calcium concentration had increased again (to 2.96 mmol/L) and the same dose of pamidronate was administered. The serum calcium concentration again decreased to a near-normal level (2.70 mmol/L). Renal function remained stable. The serum phosphate level was high, which is attributed to both impaired renal excretion and increased efflux from the bones. After a prolonged admission, the patient was discharged to a rehabilitation centre. Mobilization was limited to spending 4 h in a chair per day. He had a persistent renal insufficiency with an eGFR of 24 mL/min/1.73 m^2. Unfortunately, 2 months later, the serum calcium concentration increased again to a corrected level of 3.9 mmol/L and the patient suffered from nausea and vomiting. He was readmitted to the hospital and hyper hydration was performed in combination with oral furosemide (dose 125 mg twice daily), and calcitonin was administered subcutaneously (dose 400 IU twice daily). The serum calcium concentration decreased to 2.74 mmol/L. At this time, further analysis showed that both the serum 25-OH-vitamin D and 1,25-di-OH-vitamin D concentrations were low. No PTH-related peptide was present. Urinary calcium excretion was high (9.4 mmol/24 h with a fractional calcium excretion of 9.8%). Other rare causes of hypercalcaemia were excluded: urinary metanephrines and the serum thyroid stimulating hormone, cortisol and aluminium concentrations and the free light chain kappa/lambda ratio were all normal. A

Table 1. Laboratory data

Variable	Reference range	February 2011	February 2011	March 2011	May 2011	May 2011	June 2011	July 2011	August 2011	September 2011	October 2011	November 2011	November 2011	December 2011	January 2012	January 2012	February 2012	March 2012	March 2012
Calcium (mmol/L)	2.20–2.60	2.99	2.31	2.26	2.72	2.86	2.58	3.26	3.81	2.59	3.02	1.89	1.97	2.24	2.19	2.39	2.68	2.48	2.44
Albumin (g/L)	35.0–50.0	20.3	19.4	16	28	40	34	41	36.2	32.5	40	40	36	36	35	38	41	37	35
Corrected calcium (mmol/L)	2.20–2.60	3.38	2.72	2.74	2.96	2.86	2.7	3.24	3.89	2.74	3.02	1.89	2.05	2.32	2.29	2.43	2.66	2.54	2.54
Ionized calcium (mmol/L)	1.15–1.32	1.56	1.27						2.15										
Phosphate (mmol/L)	0.80–1.50	1.75	1.19	1.3	2.5	1.73	1.1	1.64	1.66	1.01	1.16	0.58	0.64	0.85					
Creatinin (μmol/L)	74–120	393	387	406	378	376	310	337	388	348	286		231	245	240	260	266	311	337
eGFR MDRD (mL/min/ 1.73 m²)	>60	18	19	18			24		19	21	26		34	31	32	29	28	24	22
Alkalic phosphatase (U/L)	0–120	143				226			188					106					
25-OH vitamin D (nmol/L)	50–100	71							26										
1,25-di-OH-vitamin D (pmol/L)	50–170	<20							<20										
PTH (pmol/L)	1.0–7.0	<0.6			0.4	0.99			1.4				47.8				0.6		
PTH-related peptide (pmol/L)	<0.6								<0.3										

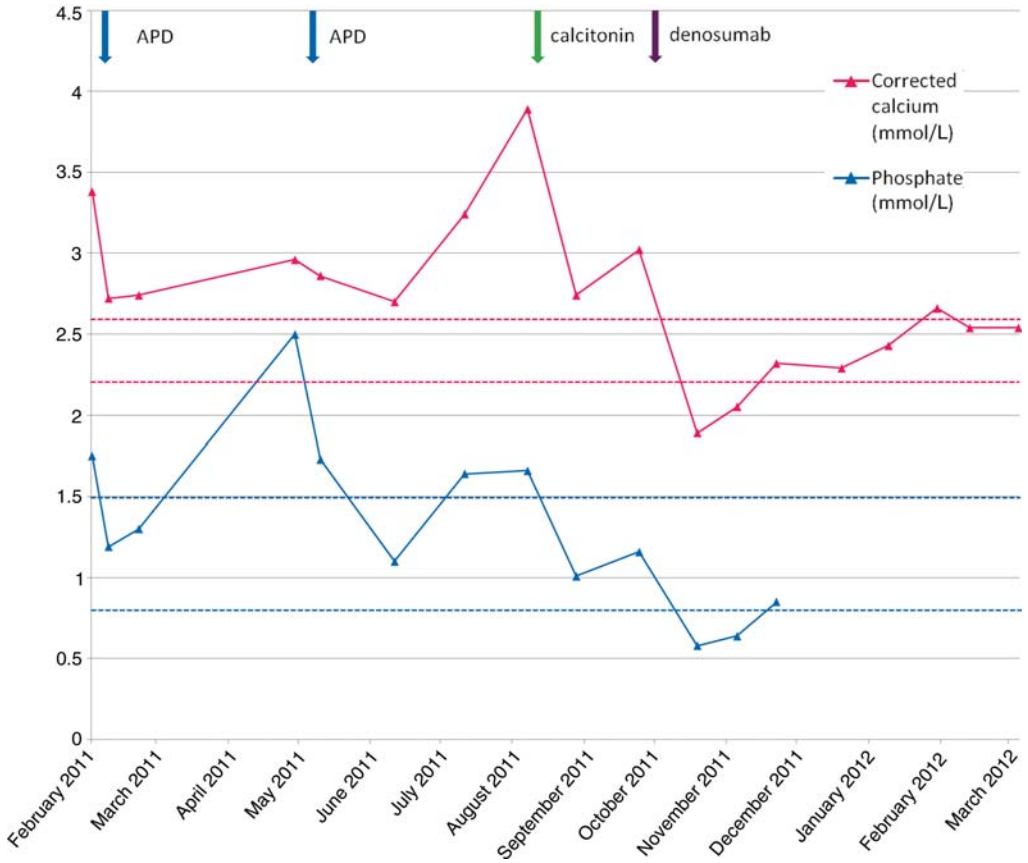

Fig. 1. Time course of serum corrected calcium and phosphate level and administered medication.

chest X-ray showed no lymphadenopathy and there were no signs of skeletal metastasis on magnetic resonance imaging of the vertebrae and the left leg that was performed earlier. This analysis confirmed that immobilization was the cause of the hypercalcaemia. A few weeks later, the serum calcium concentration had increased again to 3.02 mmol/L. Because of the recurrent hypercalcaemia and lack of success of treatment with low-dose biphosphonate, we decided to treat the patient with a single subcutaneous dose of denosumab (60 mg). One week later, the serum calcium concentration had decreased from 3.02 to 1.9 mmol/L. The serum phosphate level had decreased in parallel (to 0.58 mmol/L) suggesting effective inhibition of bone resorption. Supplementation with both calciumcarbonate/colecalciferol and active vitamin D (alfacalcidol) was started after which the serum calcium concentration normalized. During the episode of hypocalcaemia, serum PTH concentration increased to 47.8 pmol/L. After 2 months, the serum calcium level rose to 2.66 mmol/L. At that time, all vitamin D and calcium-supplementation was stopped. During a 2-month follow-up since then, the patient's serum calcium concentration has remained within the normal range without further administration of denosumab.

Discussion

After exclusion of other causes of hypercalcaemia, our patient was diagnosed with immobilization-induced hypercalcaemia. Prolonged immobilization, e.g. after acute spinal cord injury, has long been known to result in hypercalciuria and hypercalcaemia combined with accelerated bone resorption and nephrolithiasis [5–7]. Immobilization-related hypercalcaemia has been described in several clinical situations (see Table 2). In this condition, an imbalance occurs in the bone-remodelling process with excessive osteoclastic bone resorption exceeding the rate of osteoblastic bone formation [8]. Increased bone resorption results in hypercalciuria within days and hypercalcaemia after a few weeks if the capacity of the kidneys to excrete calcium is exceeded [9]. Therefore, renal insufficiency increases the risk of immobilization-related hypercalcaemia [10, 11]. Children and adolescents are particularly vulnerable because of their high bone turnover [1, 2]. According to a recent

Table 2. Clinical situations associated with immobilization-related hypercalcaemia

Acute spinal cord injury [3, 5, 7, 9, 26–30]
Acute anterior poliomyelitis [31]
Guillain–Barré syndrome [32–34]
Haemiplegia after stroke [35–38]
Polyneuropathy (critical illness [1], alcoholic [39] and acute intermittent porphyria [40])
Extensive burns [10, 41–43]
Multiple fractures [44–48]
Single limb fracture in children and adolescents [47, 49–54]
Sepsis [2, 55–57]
Liver transplantation [58]
Polyarticular gout [59]
Parkinson's disease [60]
Haemodialysis patients immobilized for fractures or coma [11, 61, 62]

review, the exact pathogenesis of immobilization-related bone loss at the cellular level has not yet been resolved [12], although the RANKL/RANK/OPG system is likely to be involved [13]. The diagnosis is made in an appropriate clinical situation after exclusion of other causes of hypercalcaemia [9]. Immobilization is a rare cause of hypercalcaemia [1]. Limited data suggest that this type of hypercalcaemia can be treated successfully with bisphosphonates [1, 3, 14].

In agreement with this, the hypercalcaemia in our patient responded twice to administration of pamidronate, but the response was incomplete and of relatively short duration on both occasions. This may have been due to the fact that only a low dose of pamidronate was administered because of concerns about potential renal adverse effects.

Bisphosphonates are excreted by the kidneys. Treatment with iv bisphosphonates has been associated with renal toxicity probably due to direct tubular injury [4]. High peak levels seem to be a risk factor and consequently the dose of bisphosphonates should be decreased and the infusion time prolonged in patients with diminished renal function. If the eGFR is above 30 mL/min/1.73 m², renal risk is low. Very little is known about the safety of intravenous bisphosphonates in patients with Stage 4 and 5 chronic kidney disease (CKD) (eGFR <15–30 mL/min) [4, 15]. We therefore decided not to use a higher dose of pamidronate. Administration of calcitonin also effectively decreased the serum calcium concentration in our patient but its effect is known to be limited to a few days because of development of tachyphylaxis [16].

Fortunately, another treatment option for hypercalcaemia now exists. Denosumab is a fully human antibody against RANKL that inhibits binding of RANKL to its receptor RANK on osteoclasts. In adult bone remodelling, osteocytes are now known to be the primary RANKL-producing cells, in contrast to the older paradigm that osteoblasts were the most important source of RANKL [17]. Several other cell types, including endothelial cells, activated T lymphocytes and tumour cells, have been shown to express RANKL. After binding to its receptor RANK on osteoclasts and osteoclast precursors, RANKL stimulates osteoclast formation, activation and survival, thus leading to increased bone resorption [18]. After subcutaneous injection of denosumab, bone turnover decreases within 24 h as reflected by decreases in urinary and serum bone turnover markers, such as the urinary N-telopeptide/creatinin ratio and the serum N-telopeptide concentration. The maximum effect of denosumab is achieved after 2–4 weeks and lasts for several months depending on the dose [19].

Denosumab is registered both for treatment of postmenopausal osteoporosis and for prevention of skeletal-related events in bone metastasis in breast and prostate cancer. Side effects are limited to sporadic cases of osteonecrosis of the jaw and mild hypocalcaemia in a small percentage of patients [18]. Denosumab is not excreted by the kidneys and dosing therefore does not have to be adjusted in patients with renal insufficiency. *Post hoc* analysis of the FREEDOM trial, which showed that denosumab reduces the risk of fractures in patients with osteoporosis, did not report a difference in side effects with increasing levels of renal insufficiency. However, no Stage 5 CKD patients (eGFR <15 mL/min) were included in this study [20].

Interestingly, the renal excretion of calcium greatly increased in response to hypercalcaemia in our patient despite advanced renal insufficiency. This is in contrast to the situation in patients with CKD in general, in whom the calcium excretion is low [21] and does not readily increase when dietary calcium intake is increased [22]. Since the filtered load of calcium was greatly diminished in our patient despite the hypercalcaemia, hypercalciuria must have been caused by a reduced fractional tubular reabsorption of calcium. Several factors may have contributed to this. Firstly, hypercalcaemia reduces the paracellular reabsorption of calcium in the thick ascending limb of Henle's loop (TALH) by activating the basolateral calcium sensing receptor in this nephron segment [23]. In this respect, our patient differs from CKD patients who usually develop hypocalcaemia as renal insufficiency progresses [21]. Secondly, PTH secretion was appropriately suppressed in the presence of hypercalcaemia in our patient, whereas it usually increases in patients with advanced CKD [21]. Suppression of PTH secretion will facilitate renal calcium excretion, since a function of this hormone is to stimulate calcium reabsorption in the TALH and distal tubules [23]. Thirdly, the concentration of active vitamin D was low in our patient, which is relevant because active vitamin D increases calcium reabsorption in the distal tubules [23]. In this respect, our patient may also differ from CKD patients, because most of them will receive active vitamin D supplements. Volume expansion (which suppresses calcium reabsorption in the proximal tubules) and treatment with a loop diuretic (which suppresses calcium reabsorption in the TALH) [23] may have facilitated calcium excretion even further at the time of severe hypercalcaemia.

This case of a patient with immobilization-related hypercalcaemia successfully treated with denosumab helps to remind us that immobilization is a cause of hypercalcaemia that should not be overlooked. The literature on the use of denosumab for hypercalcaemia is scarce and limited to malignancy-induced hypercalcaemia [24, 25]. Unlike bisphosphonates, the drug is not contraindicated in patients with renal insufficiency, and the effect is much more prolonged than that of calcitonin. However, clinicians should be aware that considerable hypocalcaemia may develop rapidly after administration of denosumab, and perhaps the initial dose of denosumab should be lower than the dose used for other indications.

Conflict of interest statement. None declared.

(See related Editorial comment by F. Malberti. Treatment of immobilization-related hypercalcaemia with denosumab. *Clin Kidney J* 2012; 5: 491–495)

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