Denosumab-related hypocalcaemia in chronic kidney disease

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CASE

A man aged 81 years presented to hospital with a two-day history of confusion. His medical history included vitamin D deficiency, for which he was on regular supplementation, and stage 5 chronic kidney disease (CKD) secondary to diabetic nephropathy (baseline serum creatinine 330–350 μmol/L and estimated glomerular filtration rate [eGFR] 13 mL/min/1.73m²), for which he was on a conservative (non-dialysis) pathway. Complications from his CKD included chronic kidney disease mineral and bone disorder (CKD-MBD) with secondary hyperparathyroidism and low bone density, for which he received a denosumab 60 mg subcutaneous injection two weeks earlier. Observations on admission, including blood pressure and temperature, were within normal limits. He was alert but disorientated to time and place, with no focal neurological deficit or features of hyperexcitability on examination.

Initial investigations revealed new hypocalcaemia with corrected calcium of 1.40 mmol/L (2.33 mmol/L three weeks earlier). His creatinine was elevated to 399 μmol/L. Other laboratory values included sodium of 142 mmol/L, potassium of 5 mmol/L, phosphate of 1.55 mmol/L, parathyroid hormone (PTH) of 33.3 pmol/L (range 0.8–5.5 pmol/L) and a normal white cell count. An electrocardiogram showed a prolonged corrected QT (QTc) interval of 505 ms. Septic screening was negative and computed tomography (CT) of the head was unremarkable.

Question 1

What is the most likely cause of his delirium?

Answer 1

Given his negative septic screen and unremarkable neuroimaging, new-onset hypocalcaemia, supported by the prolonged QTc interval, is the most likely cause of delirium. Tetany, ranging from paresthesia to carpopedal spasm and seizures, is the classic presentation of acute hypocalcaemia. Altered PTH production due to autoimmune or postsurgical causes can lead to hypocalcaemia with low PTH. Meanwhile, a high PTH level can be due to hypocalcaemia in patients with vitamin D deficiency, CKD and extravascular deposition, which is seen in hyperphosphataemia and osteoblastic metastases.

In this case, investigations revealed acute worsening in renal function, elevated PTH, hyperphosphataemia and recent denosumab administration. Thus, hypocalcaemia was thought to be secondary to acute worsening of CKD and denosumab administration.

CASE CONTINUED

The patient received intravenous and oral calcium replacement to good effect. The corrected calcium level improved to 2.05 mmol/L and his delirium resolved. He was subsequently discharged home on oral calcium replacement.

Question 2

What is the mechanism of action of denosumab?

Answer 2

Denosumab is a monoclonal antibody directed against the receptor activator of nuclear factor kappa-B ligand (RANKL). It is used to prevent osteoporotic fractures by decreasing activation of osteoclasts.

Question 3

How is hypocalcaemia managed?

Answer 3

The metabolism of denosumab does not depend on renal function; however, denosumab is associated with hypocalcaemia, especially in patients with CKD (usually within one month post-injection). Pretreatment assessment of serum calcium and vitamin D levels with appropriate supplementation to correct any deficiencies can reduce the risk of denosumab-induced hypocalcaemia. It is equally important to monitor serum calcium 8–14 days post-injection to facilitate early detection of hypocalcaemia. Treatment of hypocalcaemia requires large doses of oral calcium (up to 5000 mg daily) and calcitriol (up to 1.5 μg daily). This corrects the hypocalcaemia over a median of 71 days.

Question 4

What is the difference between CKD-MBD and osteoporosis?

Answer 4

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Both CKD-MBD and osteoporosis increase the risk of bone fractures and share overlapping features such as low bone mineral density (BMD). CKD-MBD is a systemic disorder characterised by biochemical abnormalities involving calcium, phosphorus, PTH or vitamin D; abnormalities in bone turnover, mineralisation or strength; and/or extraskeletal calcification. Osteoporosis is characterised by skeletal fragility and high fracture risk due to low BMD.

Answer 5
In patients with stage 1–3 CKD, fulfilment of the World Health Organization criteria for osteoporosis without biochemical abnormalities may be used to diagnose osteoporosis. In stage 4–5 CKD, diagnosis of osteoporosis is made after excluding CKD-MBD as the cause of fragility fracture or low BMD. Specialist input to consider bone biopsy is reasonable if knowledge of the type of renal osteodystrophy will affect treatment decisions.

Answer 6
Management of CKD-MBD focuses on addressing the underlying metabolic abnormality by treating hyperphosphataemia and abnormal serum PTH levels while maintaining normal serum calcium. Management of osteoporosis in stage 1–3 CKD without CKD-MBD is similar to management of patients without renal disease and focuses on addressing lifestyle measures along with calcium and vitamin D supplementation. Managing patients with stage 4–5 CKD with fragility fracture is challenging. For patients without CKD-MBD, denosumab is an option, while bisphosphonate use is contraindicated in patients with an eGFR <30 mL/min/1.73 m².

Key points
- Hypocalcaemia is a well-recognised complication of denosumab therapy, especially in CKD, requiring large doses of calcium replacement and a prolonged period of monitoring owing to the long half-life of denosumab.
- Pretreatment assessment of serum calcium and vitamin D levels, and correction where necessary, can reduce the risk of denosumab-related hypocalcaemia.
- Serum calcium level needs to be monitored 8–14 days post-denosumab.
- Diagnosis of osteoporosis in patients with CKD can only be made after excluding CKD-MBD.

References