CASE REPORT

Denosumab causing severe, refractory hypocalcaemia in a patient with chronic kidney disease

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SUMMARY

Denosumab is a fully human monoclonal antibody that is being increasingly used for the treatment of osteoporosis and prevention of skeletal-related events (SREs) in bone metastases from primary tumours. It has improved efficacy, better tolerability and convenient administration via subcutaneous route, in comparison with bisphosphonates; however, it has been reported to cause severe hypocalcaemia in certain high-risk individuals. We report the case of a 71-year-old man with a history of haemodialysis-dependent end-stage renal disease who developed severe hypocalcaemia with electrocardiographic changes after being started on denosumab for prevention of SREs from a recently diagnosed metastatic prostate cancer. He was admitted to the hospital for close monitoring and received multiple doses of intravenous calcium gluconate, along with haemodialysis with high calcium bath. We aim to highlight the risk of severe, life-threatening hypocalcaemia associated with denosumab and to recognise patients at risk of developing this serious adverse effect, so that prompt treatment and preventive strategies can be implemented.

BACKGROUND

Denosumab is a RANKL (receptor activator of nuclear factor-kappa B ligand) binding human monoclonal antibody used in the treatment of osteoporosis and prevention of skeletal-related events (SREs) in bone metastases from solid tumours.^{1 2} However, it can potentially cause severe, symptomatic and life-threatening hypocalcaemia in patients at risk.³ We present a case of severe and difficult-to-correct hypocalcaemia causing abnormal electrocardiographic findings in

a patient with metastatic prostate cancer and dialysis-dependent end-stage renal disease (ESRD).

CASE PRESENTATION

A 71-year-old man with a history of hypertension, diabetes mellitus and haemodialysis-dependent ESRD was seen in oncology clinic for a recently diagnosed metastatic prostate cancer. He was started on abiraterone and prednisone a month back with addition of leuprolide a week later. He was also given 120 mg of subcutaneously administered denosumab 3 weeks prior to the current presentation. He complained of fatigue and muscle cramps for the past week but denied circumoral numbness or paresthesias of the hands and feet. Vital signs were stable. Physical exam was unremarkable, with negative Chvostek's and Trousseau's signs. Laboratory work-up showed the following: serum calcium: 5.2 mg/dL; albumin: 3.1 g/dL; corrected calcium: 5.92 mg/dL (1.49 mmol/L); ionised calcium: 0.68 mmol/L; creatinine: 4.42 mg/dL; potassium: 3.9 mmol/L; magnesium: 1.7 mg/dL; phosphate: 4 mg/dL; alkaline phosphatase: 155 IU/L; parathyroid hormone (PTH): 758.2 pg/mL; 25-hydroxy vitamin D: 31.9 ng/mL; and prostate-specific antigen (PSA): 938 ng/mL. His corrected serum calcium 3 weeks before was 9 mg/dL. ECG showed a significantly prolonged corrected QT interval (QTc) measuring 550 ms (figure 1) in comparison with 441 ms (figure 2) on a previous ECG 3 months back. He was admitted to the hospital and received a total of 6 g of intravenous calcium gluconate and 2 µg of intravenous calcitriol on the day of admission. This was followed by haemodialysis with high calcium bath, which resulted in the improvement of corrected calcium to 7.72 mg/dL in 24 hours. Repeat ECG the next day showed a QTc of 410 ms (figure 3). He received multiple doses of calcium gluconate over the course of the next 3 days. His corrected serum calcium, although never normalised, remained steady at 7.5–7.8 mg/dL during the hospital stay. He was discharged 5 days after admission on oral calcium carbonate 1500 mg four times a day and calcitriol 0.25 mg daily with close monitoring as an outpatient.

OUTCOME AND FOLLOW-UP

On repeat measurement 3 weeks later, the serum calcium was 7.2 mg/dL, but the patient remained asymptomatic. A follow-up ECG done at that time showed a QTc interval of 431 ms (figure 4). Given the severity of hypocalcaemia during the recent

Figure 1 ECG obtained at the time of presentation showing QTc interval of 550 ms (QTc interval has been calculated using Bazett's formula). aVR stands for augmented vector right; aVL stands for augmented vector left; aVF stands for augmented vector foot.

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Figure 2 ECG obtained 3 months prior to current presentation showing QTc interval of 441 ms (QTc interval has been calculated using Bazett's formula). aVR stands for augmented vector right; aVL stands for augmented vector left; aVF stands for augmented vector foot.

hospitalisation, denosumab was not resumed, while the use of bisphosphonates as alternative therapy was precluded by the presence of ESRD.

DISCUSSION

Denosumab is a fully human monoclonal antibody that is being increasingly used for treatment of osteoporosis and prevention of SREs in bone metastases from solid tumours.¹ It mimics the naturally occurring decoy receptor, osteoprotegerin, which inhibits RANK (receptor activator of nuclear factor-kappa B)–RANK ligand (RANKL) interaction. Blockade of RANK–RANKL interaction leads to reduced osteoclast maturation, inhibition of bone resorption, increase in cortical and cancellous bone mass, and improvement in trabecular microarchitecture.⁴ When compared with bisphosphonates, it offers improved efficacy, better tolerability and convenient administration via subcutaneous injection.² However, despite these benefits, denosumab has been associated with severe hypocalcaemia, which can result in QT prolongation, polymorphic ventricular tachycardia, laryngospasm and seizures.^{3–9} RANK–RANKL interaction is an important pathway responsible for calcium metabolism blocking which leads to reduced release of calcium from the bone.¹⁰ Risk factors for denosumab-induced hypocalcaemia include osteoblastic metastases, elevated PSA levels, high alkaline phosphatase, vitamin D deficiency, concomitant bisphosphonates use, and renal dysfunction with creatinine clearance of less than 30 mL/min and/or dialysis dependence.³ Our patient had metastatic prostate cancer, an elevated PSA, a high

Figure 3 ECG obtained on the second day of admission showing QTc interval of 410 ms (QTc interval has been calculated using Bazett's formula). A premature ventricular beat is also seen. aVR stands for augmented vector right; aVL stands for augmented vector left; aVF stands for augmented vector foot.

Figure 4 ECG taken 3 weeks after discharge showing QTc interval of 431 ms (QTc interval has been calculated using Bazett's formula). aVR stands for augmented vector right; aVL stands for augmented vector left; aVF stands for augmented vector foot.

alkaline phosphatase and ESRD, thus posing a high cumulative risk for development of hypocalcaemia on receiving denosumab. Denosumab, like other monoclonal antibodies, is cleared by the reticuloendothelial system and so does not require dose adjustment in patients with hepatic or renal dysfunction. This leads to the suggestion that it may be a preferable choice in comparison with bisphosphonates in patients with advanced kidney disease.¹¹ Yet several cases of hypocalcaemia in patients receiving denosumab in the setting of renal disease have been reported.^{1–9,12} Denosumab blocks PTH-dependent osteoclastic activity, which is one of the main driving mechanisms for maintaining calcium homeostasis in kidney disease.⁹ Moreover, patients with impaired renal function have potential vitamin D deficiency due to reduced 1-alpha hydroxylase activity, which increases the risk of hypocalcaemia further.¹³ Denosumab-induced hypocalcaemia can last weeks to months despite therapy requiring frequent monitoring. The risk of hypocalcaemia has been found to be highest in the first 2 weeks.¹⁴ High doses of calcium and vitamin D are typically given for treatment. Dialysis using high calcium dialysate can be offered in severe, resistant cases.⁹ Screening and correction of hypocalcaemia and hypovitaminosis D, if present, prior to initiating denosumab especially in patients at risk should be done in order to prevent this potentially fatal complication.³

Learning points

- Denosumab can cause severe hypocalcaemia in high-risk patients, such as those with chronic kidney disease and osteoblastic metastases.
- Serum calcium should be closely monitored in patients receiving denosumab, especially during the first few weeks of therapy.
- It is imperative to screen for and correct hypocalcaemia and hypovitaminosis D prior to initiation of denosumab therapy.

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