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CASE REPORT

A Case of Recurrent Severe Hypocalcemia with Prolonged Hospitalization and Readmissions After Single Dose of Denosumab in Metastatic Prostate Cancer Patient

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Abstract

Denosumab is a human monoclonal antibody used to prevent skeletal-related events in prostate cancer patients with bone metastasis. Hypocalcemia ranging from mild to severe requiring prolonged hospitalization have been reported with the use of denosumab in patients with known risk factors such as chronic kidney disease, vitamin D deficiency, low parathyroid hormone level, hypomagnesemia, extensive osteoblastic metastasis, prior use of bisphosphonates, and comorbidities impairing calcium absorption. We present a case of a metastatic prostate cancer patient with extensive osteoblastic metastasis who developed severe recurrent hypocalcemia after a single dose of denosumab requiring a total of 58 days of high dose intravenous and oral calcium supplementations with three inpatient hospital admissions. This case highlights the risk of severe hypocalcemia associated with denosumab use even after the disease control with oncologic therapy and in the absence of other predisposing risk factors. This case also emphasizes monitoring calcium levels closely in all patients treated with denosumab. In the event of severe hypocalcemia, prolonged hospitalization should be expected, and discharge planning should be done meticulously, which may help decrease the overall length of hospital stay, readmissions, and morbidity.

Keywords: Recurrent hypocalcemia, Denosumab, Readmission, Prolonged hospitalization, Metastatic prostate cancer

1. Introduction

Prostate Cancer is the second most common cause of cancer death in men, frequently associated with widespread bone metastasis.[1,2] Denosumab, a monoclonal antibody against RANKL (Receptor activator of nuclear factor-kB ligand), is commonly used for the prevention of skeletal-related events (SREs) in prostate cancer patients with bone metastasis which includes pathological fracture, spinal cord compression, and pain necessitating radiation therapy or surgery.[3,4] Hypocalcemia ranging from mild to severe requiring prolonged hospitalizations has been reported with the use of denosumab.[5–7] Chronic kidney disease with low GFR (<30 ml/min/1.73sqm), vitamin D deficiency, low parathyroid hormone level (PTH), hypomagnesemia, extensive osteoblastic metastasis, prior use of bisphosphonates and comorbidities impairing calcium absorption (previous intestinal/bowel surgeries) are known risk factor for hypocalcemia after denosumab use.[8–10] The median half-life of denosumab ranges from 25 to 35 days, and denosumab-induced hypocalcemia usually resolves within 30 days.[11] We present a case of a patient with metastatic prostate cancer with extensive osteoblastic metastasis who developed severe recurrent hypocalcemia after a single dose of denosumab

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Table 1. Comparison of labs on the day of presentation Vs. before denosumab administration (5 weeks before the day of presentation).

	Reference range	On the day of presentation	Before denosumab administration (5 weeks before day of presentation)
Hemoglobin	13.5–17.0 gm/dl	9.1 mg/dl	9.6 gm/dl
Platelet	150–450 × 10^3 ul	126 × 10^3/microliter	164 × 10^3/microliter
Sodium	135-146 mEq/L	139 mEq/L	141 mEq/L
Creatinine	0.5–14.0 mg/dl	0.55 mg/dl	0.59 mg/dl
Blood urea Nitrogen	7.0–30 mg/dl	15 mg/dl	20 mg/dl
Calcium	8.5–10.4 mg/dl	5.0 mg/dl	8.5 mg/dl
Albumin	3.2–4.6 mg/dl	4.2 mg/dl	3.8 mg/dl
Magnesium	1.5–2.5 mg/dl	2.1 mg/dl	Not checked
Vitamin D 25-OH	20–40 ng/ml	27.0 ng/ml	Not checked
Vitamin D 1,25 OH (360.0 (pg/ml)	19.9–79.3 pg/ml	360 pg/ml	Not checked
Alkaline phosphate	20–125 U/L	2501 U/L	884 U/L
Prostate Specific antigen)	<4.0 ng/ml	33.20 ng/ml	>100 ng/ml
PTH level	12–88 pg/ml	239 pg/ml	Not checked

requiring a total of 58 days of high dose intravenous and oral calcium supplementations with three inpatient hospital admissions.

2. Case presentation

A 72-year-old man with the past medical history of diabetes mellitus on metformin, hypertension on amlodipine, and two-month history of prostate cancer with diffuse osseous metastasis who was treated with androgen deprivation therapy (luteinizing hormone-releasing hormone (LHRH) agonist/Goserelin; antiandrogen Bicalutamide followed by denosumab 120 mcg subcutaneous after two weeks of androgen deprivation therapy for prevention of skeletal-related events presented to hospital with dizziness, tingling, and numbness of extremities and perioral area. Vitals on admissions were blood pressure of 132/62 mmHg, heart rate of 86 bpm, temperature of 36.9-degree Celsius, respiratory rate of 20 breaths per min, and oxygen saturation of 99% on room air. Physical examinations were unremarkable with negative Chvostek and Trousseau's signs. Laboratory findings were significant for hemoglobin 9.1 gm/dl, platelets 126 × 103/microliter, sodium 139 mEq/L, creatinine 0.55 mg/dl, blood urea nitrogen 15 mg/dl, Glomerular filtration rate (GFR) > 60 ml/min/1.73sqm, calcium of 5.0 mg/dl, ionized calcium 0.76 mM/L, albumin 4.2 mg/dl, magnesium 2.1 mg/dl, alkaline phosphate 2501 U/L, vitamin D 25-OH 27.0 ng/ml, vitamin D 1,25 OH level 360.0 pg/ml, parathyroid hormone level 239 pg/ml and prostate-specific antigen 33.20 ng/ml. The comparison of blood work from five weeks ago before denosumab administration revealed a normal calcium level of 8.5 mg/dl, albumin level of 3.8 mg/dl, and creatinine of 0.55 mg/dl with elevated prostate-specific antigen >100 ng/ml and alkaline phosphate 884 U/L which suggested denosumab induced hypocalcemia (Table 1). The electrocardiogram (EKG) demonstrated sinus rhythm with right bundle branch block and prolonged corrected QTc interval of 491 ms. The patient reported taking oral calcium 1000 mg daily and vitamin D 800 U daily after denosumab administration, which his oncologist prescribed.

He was given IV calcium gluconate 4-g bolus followed by continuous infusion of calcium gluconate 100 mg/ml (10%) 11 g in sodium chloride 0.9% (1000 ml) at a rate of 50–100 ml/h along with oral calcium carbonate 5000 mg four times daily and calcitriol 2 mcg twice a day. Calcium was checked every 6–8 h on the first day, and his calcium levels improved gradually, and he was discharged on oral calcium 5000 mg four times daily and calcitriol 0.5 mcg twice a day on the seventh day of hospitalization (Fig. 1). However, after five days, he presented back to the emergency room (ER) with similar symptoms of dizziness and perioral numbness, and tingling sensations. His calcium level was 5.0 mg/dl again, and EKG showed sinus rhythm with prolonged Qtc interval 470 ms. He reported compliance with oral calcium and calcitriol at home. Physical examinations were unremarkable with negative Chvostek and Trousseau's signs. He was readmitted and started on a high-dose continuous infusion of calcium gluconate 11 g at a rate of 50–100 ml/h. His calcium levels gradually improved, and calcium gluconate infusion was gradually decreased to 25 ml/h and stopped. On oral calcium supplementation, his calcium level remained stable for more than 24 h (Fig. 2). On the ninth day of hospitalization, he was discharged on oral calcium carbonate 5000 mg four times a day, calcitriol 0.5 mcg twice a day, and ergocalciferol 50,000 IU weekly. His calcium levels were rechecked at the primary care

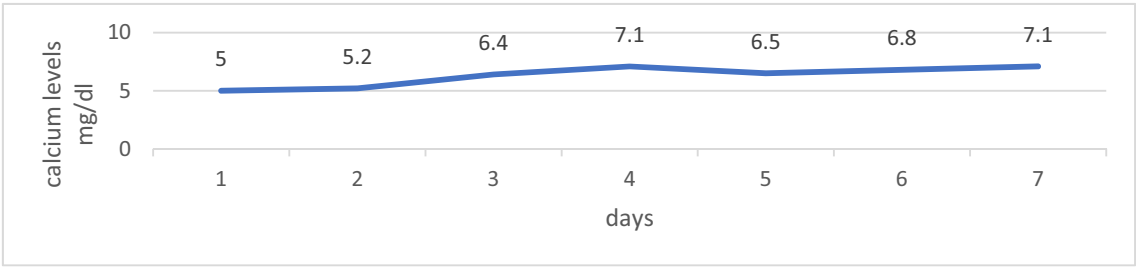

Fig. 1. Calcium levels during the first hospitalization of 7 days.

physician (PCP) office four days after the discharge, and he was noted to have a calcium level of 5.6 mg/dl and an ionized calcium level of 0.70 mM/L with an albumin level of 4 mg/dl. He was asymptomatic during this visit; however, he was readmitted for IV calcium administration and close monitoring due to a critically low calcium level. He was restarted on high-dose IV calcium gluconate along with oral calcium carbonate and calcitriol as above. His calcium level improved very gradually (Fig. 3). His urinary calcium was checked on the 14th day of hospitalization, and it was nil (zero). On the 16th day of hospitalization, he required approximately 18 g of IV calcium gluconate per day and 15 g of oral calcium carbonate daily. On the 19th day of hospitalization, his IV calcium gluconate requirement decreased to approximately 6.6 g per day which seemed feasible for outpatient administration at clinical decision unit (CDU). A peripherally inserted central catheter (PICC) line was placed on the 20th day of hospitalization, and he was discharged home on the 21st day of hospitalization as his calcium level remained stable with 6 g of IV calcium gluconate daily. He received 6 g of IV calcium gluconate daily at CDU for the next 21 days, and his calcium levels gradually improved (Fig. 4). His calcium levels remained stable on every other day check for a week on oral calcium carbonate 5000 mg four times a day and calcitriol 0.5 mcg twice a day. His calcium carbonate dose was decreased to 2000 mg daily and calcitriol to 0.5 mcg daily. His calcium level remained above 8 mg/dl in follow-up visits. His hypocalcemia lasted approximately two months, and he received a high dose of IV calcium gluconate for about 58 days and had three admissions during the period.

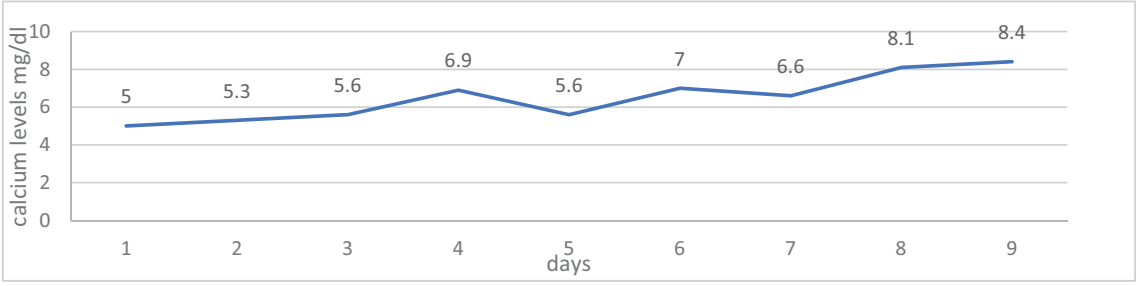

Fig. 2. Calcium levels during the second hospitalization of 9 days.

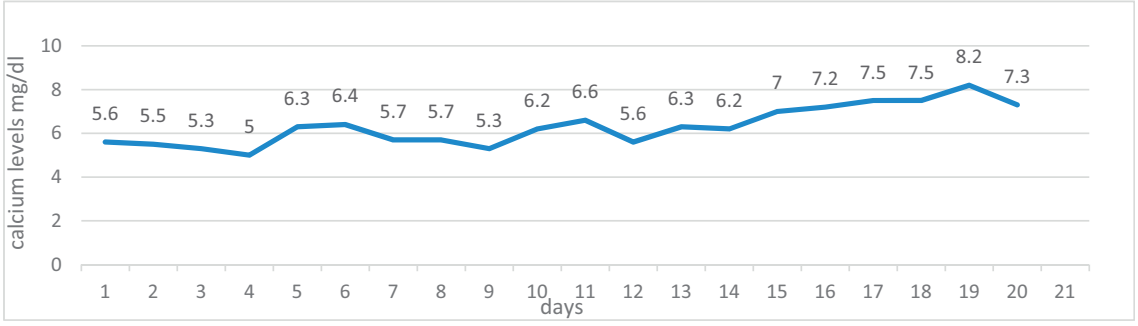

Fig. 3. Calcium levels during the third hospitalization of 21 days.

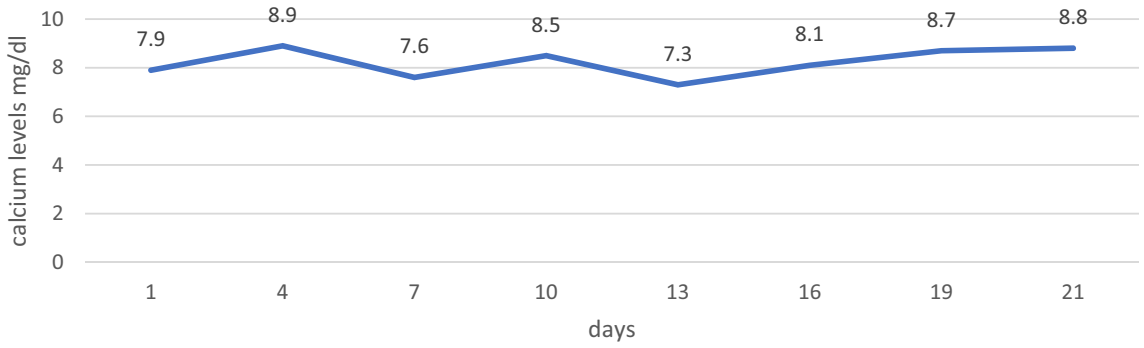

Fig. 4. Calcium levels at Clinical Decision Unit (CDU) of 21 days after discharge from the third hospitalization.

3. Discussion

Advanced prostate cancer is associated with bone metastasis in up to 90% of cases which leads to increased risk of skeletal-related events (SREs) that includes pain, pathological fracture, hypercalcemia, and spinal cord compression, necessitating surgery or radiation therapy leading to significant morbidity and mortality.[1,2] The use of osteoclast inhibitors such as bisphosphonates or denosumab (human monoclonal antibody against RANKL) can significantly reduce the frequency of SREs.[3] Denosumab has become a preferred agent over bisphosphonates as it has been shown to significantly delay time to SREs compared to bisphosphonates.[4] Denosumab via inhibition of RANKL inhibits osteoclast activity leading to inhibition of calcium release from bone which can subsequently cause hypocalcemia.[12]

In the previously published meta-analysis, the reported incidence of hypocalcemia from denosumab in a cancer patient with bone metastasis was 5.2% (95% CI from 2.8% to 9.3%), most of which were mild and asymptomatic but 2% (95% CI from 0.7 to 5.5%) were severe hypocalcemia (corrected calcium level <7 mg/dl).[10] Incidence of all grade hypocalcemia (Table 2) was higher (14–39.6%) in observational studies.[8,12] The symptoms of hypocalcemia can range from non-specific symptoms such as fatigue, hyperirritability to concerning symptoms of tetany such as perioral numbness, paresthesia of hands and feet, muscle spasms, carpopedal spasms, laryngospasm, and focal or generalized seizures. Severe hypocalcemia is relatively rare; however, it can be a severe and life-threatening condition requiring hospitalization and intravenous calcium administration.[13] Severe hypocalcemia has been seen in patients with underlying risk factors such as vitamin D deficiency, low PTH, hypomagnesemia, chronic kidney disease, extensive osteoblastic metastasis, prior use of bisphosphonates, and comorbidities impairing calcium absorption (previous intestinal/bowel surgeries).[8–10] It has been recommended to use prophylactic oral calcium 500 mg daily and Vitamin D 400 IU daily to decrease the risk of hypocalcemia after denosumab use.[4] The recommended treatment of severe hypocalcemia is intravenous calcium gluconate 1–2-g (90–180 mg of elemental calcium) bolus followed by continuous infusion 0.5–2.0 mg/kg/hr @ 5–10 ml/h along with oral calcium, vitamin D, and calcitriol[13,14] The median half-life of denosumab ranges from 25 to 35 days. Denosumab-induced hypocalcemia usually resolves within 30 days.[11] Prolonged hospitalization may be necessary due to the ongoing requirement of high-dose intravenous calcium, especially in the context of predisposing risk factors.[5–7]

Our patient with metastatic prostate cancer with extensive osseous metastasis had a significant risk for skeletal-related events (SRE). Apart from extensive osteoblastic metastasis, he had no other predisposing risk factor for the development of severe hypocalcemia. Androgen deprivation therapy (luteinizing hormone-releasing hormone (LRHR) agonist/Goserelin, antiandrogen Bicalutamide) was used for disease control before using denosumab to decrease the risk of hypocalcemia. After denosumab administration, he was also compliant with the prophylactic oral calcium and vitamin D supplementation. Despite the appropriate use of denosumab, he developed severe hypocalcemia and required prolonged hospitalization with two readmissions after a single dose of denosumab. He needed 58 days of high-dose intravenous calcium

Table 2. Common Terminology Criteria for Adverse Events grading of hypocalcemia.[15]

Grade	Total corrected Calcium concentration (mg/dl)
1	8.0-Lower limit of Normal
2	7.0-<8.0
3	6.0-<7.0
4	<6.0
5	If death occurs as a result of hypocalcemia

supplementation before his calcium levels normalized, demonstrating the increased morbidity and health care cost that can occur with denosumab-induced hypocalcemia. Several case reports have been published demonstrating severe prolonged hypocalcemia after denosumab use,[6–8] however to the best of our knowledge; patients had multiple underlying risk factors. Hence, we emphasize careful monitoring of serum calcium levels, particularly in the first few weeks of treatment in all patients treated with denosumab. In the event of severe hypocalcemia, prolonged hospitalization should be expected, and discharge planning should be done meticulously. CDU unit could be utilized as demonstrated in our case, which could help decrease hospital length of stay and readmissions.

4. Conclusion

Severe hypocalcemia can occur with a single dose of denosumab in metastatic prostate cancer patients even after the disease control with oncologic therapy (chemotherapy, androgen deprivation therapy) and in the absence of other predisposing risk factors. Hence, it is essential to monitor serum calcium levels closely in all patients for the first few weeks of treatment. Prolonged hospitalizations should be expected in case of severe hypocalcemia, and discharge planning should be done meticulously, which could help decrease readmissions, hospital length of stay, and overall morbidity.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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The authors have received no funding and have no multiplicity of interests to disclose. We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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