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Case Report

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A 59-year-old Female Post Bariatric Surgery with Severe Vitamin D Deficiency and Severe Hypocalcemia Induced by Denosumab Injection for Osteoporosis

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Abstract

Denosumab is a human monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL) and blocks the interaction between RANKL and RANK on the surface of osteoclasts, thereby preventing osteoclast formation resulting in decreased bone resorption and increased bone mass in osteoporosis. A rare yet serious side effect of this treatment option is severe hypocalcemia, and thus current guidelines recommend concurrent calcium and vitamin D supplementation. Here, we report a case of a 59-year-old female with history of gastric bypass, primary hyperparathyroidism, and osteoporosis presents two weeks after initiating denosumab therapy with symptoms of severe hypocalcemia. Serum calcium and vitamin D levels revealed severe acute deficiencies that responded to continuous intravenous replacement followed by high dose oral supplementation over a nineteen-day hospitalization. There are currently no reported cases of acute denosumab-induced hypovitaminosis D. Our case may represent a previously undocumented adverse effect of denosumab that clinicians should be aware of when treating severe drug-induced hypocalcemia.

Introduction

Denosumab is a human monoclonal antibody that binds receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits interaction between RANKL and RANK on the surface of osteoclasts, which prevents osteoclast formation and causes decreased bone resorption and increased bone mass [1]. Osteoporosis is characterized by low bone mass, microarchitectural disruption, and increased skeletal fragility. It is common in those who have undergone Roux-en-Y gastric bypass surgery, which causes reduced gastric acid levels necessary for adequate calcium absorption and decreased vitamin D due to relative bypass of its primary absorption points in the duodenum and proximal jejunum [2,3]. Denosumab is a reasonable option for osteoporosis treatment in patients with gastric bypass surgery due to intestinal malabsorption and risk of anastomotic ulceration with oral bisphosphonates [4]. A rare yet potentially fatal adverse effect of denosumab is severe hypocalcemia and Vitamin D deficiency, which is often prolonged secondary to its long half-life and therefore difficult to treat in many cases [5]. We present a case of denosumab-induced severe hypocalcemia in a patient with history of gastric bypass who also was found to have acute severe hypovitaminosis D despite post-treatment vitamin D supplementation. Thus we hypothesize a potentially causal relationship between denosumab and acute severe vitamin D deficiency in high-risk patients, specifically with intestinal malabsorption and resultant predisposition to becoming vitamin D deficient.

Case Presentation

A 59 year old Caucasian female with history of Roux-en-Y gastric bypass presented to the emergency department with progressive numbness of her face, arms, and legs over a two week period. Her symptoms also included fine hand tremors bilaterally and increased limb pain of the bilateral thighs. No seizure-like activity, confusion, or abdominal pain were reported. Approximately two months prior to presentation, the patient was found to have hypercalcemia due to primary hyperparathyroidism. She underwent a bone densitometry scan as part of her outpatient workup, which revealed osteoporosis of the left arm. Two weeks prior to admission she received a single dose of denosumab 60mg subcutaneously, after which she experienced generalized urticaria, shortness of breath, and limb pain of the bilateral lower extremities. Her rash and dyspnea resolved with supportive care, however her bilateral limb pain persisted in addition to her presenting symptoms mentioned above. Vital signs on admission: blood pressure 104/57 mmHg, pulse 78, respiratory rate 18, and temperature 97.6. Physical exam elucidated a positive Chvostek sign and diminished sensation of the bilateral face, arms, and legs. Motor strength was 4/5 in the bilateral lower extremities and 4/5 in the bilateral upper extremities. Mild tremors were also noted in bilateral upper extremities. Otherwise heart, lung, abdominal, and neck exam were within normal limits. Comprehensive metabolic panel on admission as seen in Table 1 included normal electrolytes, mildly elevated creatinine, and low calcium 5.4 mg/dL (10.4 mg/dL prior to denosumab) with normal albumin. Other significant laboratory values included parathyroid hormone 985.4 pg/ml, 25-hydroxyvitamin D less than 7.0 ng/ml (19.6 ng/ml prior to denosumab), and phosphorus 2.0 mg/dL. Electrocardiogram showed prolonged QTc interval.

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After a total of 8 grams of IV calcium gluconate in divided doses failed to normalize the patient's serum calcium within the first 24 hours, on day 2 of hospitalization she was initiated on calcium gluconate continuous infusion. Oral calcium and vitamin D supplementation were started as well: calcitriol oral solution 0.25 mcg twice daily and calcium carbonate 1000 mg every 6 hours. Calcium gluconate infusion was stopped on day 3 when her serum calcium reached 8.1 mg/dL. Hypocalcemia persisted with difficulty maintaining corrected serum calcium levels >8 mg/dL on serial monitoring (Figure 1), and thus oral replacement therapy with calcium and vitamin were increased. The patient also required periodic repletion for hypophosphatemia with sodium phosphate. Calcium carbonate dosing was increased to 5000 mg by mouth every 4 hours. Intravenous calcium gluconate doses of 1-2 g were required daily in addition to oral therapy during hospitalization to maintain serum calcium greater than 8mg/dL. Finally after stabilization of her serum calcium and vitamin D levels and resolution of symptoms, the patient was discharged on day 19 with high dose oral calcium (6000 mg every 4 hours), vitamin D (ergocalciferol) and calcitriol (0.5 mg PO every 6 hours) supplements. She was advised to follow up at outpatient clinic with close clinical and laboratory monitoring.

Discussion

Severe hypocalcemia is a rare adverse effect of denosumab occurring in less than 0.1% of post-menopausal females with osteoporosis, according to a 3-year, randomized, double-blind, placebo-controlled, multinational study [6]. Its long half-life (approximately 25-28 days) and prolonged effect makes this deficiency especially difficult to correct [7]. Treatment regimens and length of hospitalization for this condition vary from case to case based on various comorbidities of the patients involved. We present a patient with history of bariatric surgery who was found to have denosumab-induced severe hypocalcemia with concurrent acute severe vitamin D deficiency. Although our patient did exhibit low pre-treatment vitamin D levels, we observed an acute decrease in serum vitamin D levels shortly following administration of denosumab (Table 2). Treatment guidelines recommend calcium and vitamin D supplementation for patients taking denosumab [1], but vitamin D deficiency in and of itself is not a listed adverse effect. Our patient's gastric bypass surgery predisposed her to intestinal malabsorption and deficiency of vitamin D, which proved to be a significant obstacle in restoring and maintaining normal serum calcium levels. We hypothesize that denosumab may exacerbate existing vitamin D deficiency in at-risk patient populations.

Few other cases highlighting vitamin D levels in denosumab-treated individuals have been reported in literature [8, 9]. One patient with osteoporosis and intestinal malabsorption secondary to Crohn's disease who presented with denosumab-induced severe hypocalcemia experienced symptom resolution after a three-day hospitalization. This patient was found to have severe vitamin D deficiency, but pre-treatment serum vitamin D levels were not drawn. Treatment included high dose IV calcium gluconate followed by oral calcium and vitamin D supplementation [8]. Another case of denosumab-induced severe hypocalcemia occurred in a patient with history of bariatric surgery

Table 1. Summary of Laboratory Values on Admission

Laboratory data	Value	Reference Range
Sodium (mmol/L)	139	136-145
Potassium (mmol/L)	3.7	3.5-5.2
Chloride (mmol/L)	109	96-110
Bicarbonate (mmol/L)	20	24-31
Glucose (mg/dL)	89	70-99
Blood urea nitrogen (mg/dL)	14	5-25
Creatinine (mg/dL)	1.17	0.44-1.00
Calcium (mg/dL)	5.4	8.5-10.5
Albumin (g/dL)	3.6	3.5-5.0
Alkaline phosphatase (iU/L)	194	38-126
Aspartate aminotransferase (iU/L)	16	10-42
Alanine aminotransferase (iU/L)	<9	10-60
Parathyroid Hormone (pg/ml)	985.4	12-88

Table 2. Serum 25-Hydroxy Vitamin D Levels Before and After Denosumab Administration

Time in course of illness	Serum 25-Hydroxy Vitamin D Level (ng/ml)
14 days prior to admission (pre-denosumab)	19.6
Day 3 (post-denosumab)	< 7.0
Day 19 (time of discharge)	21.0

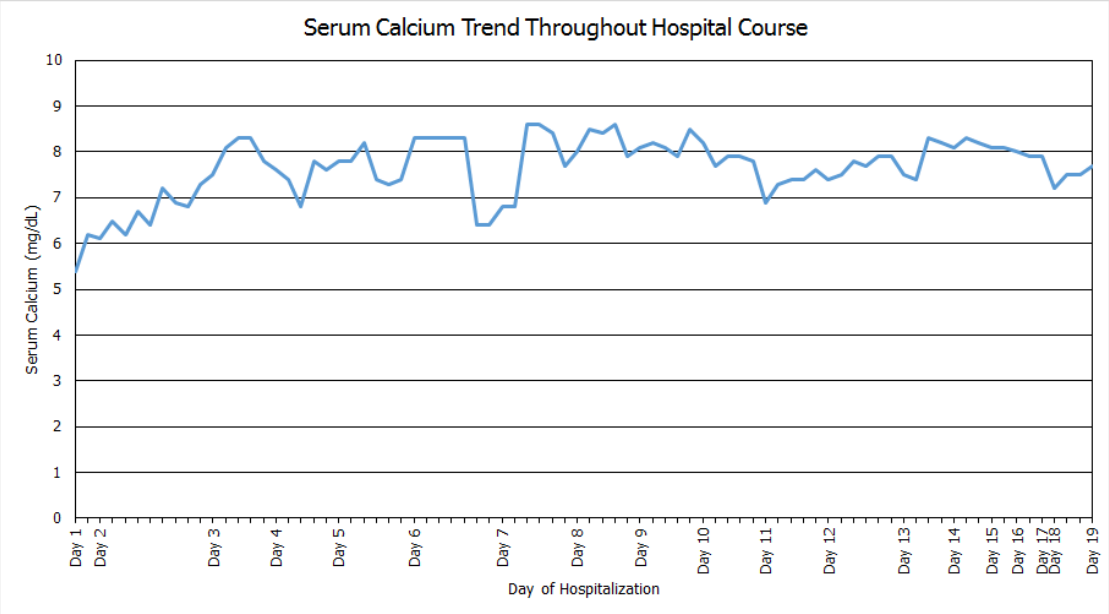

Figure 1. Corrected serum calcium trend from admission to discharge

with mild vitamin D deficiency, yet vitamin D levels remained unchanged after administration of the RANKL inhibitor. The patient improved with eight weeks of IV calcium followed by oral calcium, phosphorus and vitamin D supplementation [9].

There are limited cases in the literature that report severe hypovitaminosis D in patients treated with denosumab. Therefore, it is important for clinicians who use this medication to consider vitamin D deficiency and implement laboratory monitoring before and after denosumab administration. Identifying and closely following this potential side effect guides optimal therapy and may prevent serious complications of drug-induced hypocalcemia.

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