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Severe Refractory Hypocalcemia in a Patient with Metastatic Prostate Carcinoma Following Denosumab Injection

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Abstract

An 86-year-old male with a history of metastatic castrate sensitive prostate cancer received a single dose of Denosumab for his bony metastases. Two weeks later, he presented to the hospital due to left foot cellulitis and was incidentally found to have profound hypocalcemia whereas his serum calcium was normal at the time of Denosumab injection. A thorough workup was undertaken which showed severe Vitamin D deficiency. He was diagnosed with Denosumab induced hypocalcemia with underlying Vitamin D deficiency which was refractory to supplemental calcium and Vitamin D. This case demonstrates the potential of Denosumab to cause profound hypocalcemia which can be resistant to therapy. Bone metastasis is a common clinical encounter and Denosumab is an effective therapy to prevent skeletal related events (SRE). Therefore, given its widespread use, it is extremely important to identify and treat risk factors that may aggravate hypocalcemia when treated with Denosumab.

Keywords: Denosumab; Hypocalcemia; RANKL; Skeletal related events; Vitamin D deficiency

Introduction

Denosumab, a monoclonal antibody that inhibits RANKL, is an effective treatment for metastatic bony disease. It has proven benefit to prevent and delay skeletal related events (SRE). It is important to realize its potential to cause profound hypocalcemia especially in the presence of underlying risk factors such as Vitamin D deficiency or reduced creatinine clearance. This teaching point is emphasized by this case, an 86-year-old male, who developed refractory severe hypocalcemia after receiving Denosumab for his skeletal metastatic disease from prostate cancer.

Case Report

We report an 86-year-old Caucasian male with a history of hypertension, hyperlipidemia, Hailey-Hailey disease, stroke and prostate cancer. He was diagnosed with castrate sensitive metastatic prostate cancer four months prior to presentation. He was started on androgen deprivation therapy (ADT) with anti-androgen (Bicalutamide) and GnRH analog (Leuprolide). Because of an extensive bone disease, he was given a dose of Denosumab. Two weeks after receiving Denosumab, he presented to the hospital because of fever, left foot pain and swelling. Venous thromboembolism was excluded with a negative Doppler ultrasonography and he was diagnosed with skin and soft tissue infection. Intravenous antibiotic therapy with Vancomycin was administered. Incidentally, he was noted to have profound hypocalcemia on laboratory analysis.

On presentation, his vital signs included blood pressure of 126/58 mmHg, pulse of 84 per min, respiratory rate of 18 per min and temperature of 101.6°F. Physical examination was significant for left lower extremity swelling and tenderness to palpation up to mid-calf. A slight erythema was evident. Cardiovascular examination demonstrated a known grade III/VI holosystolic murmur in the mitral area with radiation to axilla. His respiratory, abdominal, neurological and musculoskeletal examinations were unremarkable. Chevostek and Trousseau signs were absent. Pertinent laboratory investigations were as follows: white blood cells - 3.3×10^3 per µl, hemoglobin - 8.8 g/dl, and platelets - 236×10^3 per µl, urea - 24 mg/dl, creatinine - 1.34 mg/dl (creatinine clearance - 50 ml/min), sodium - 135 mEq/l, potassium - 4.5 mEq/l, chloride - 106 mEq/L, bicarbonate - 17 mEq/L, glucose - 121 mg/dl, aspartate aminotransferase - 10 U/l, alanine aminotransferase - <6 U/l, alkaline phosphatase- 58 U/l, total bilirubin - 0.6 mg/dl, albumin 3 g/dl, magnesium - 1 mg/dl, calcium - 4.5 mg/dl and phosphorus - 3.4 mg/dl. Corrected serum calcium level was determined to be 5.3 mg/dl. A corrected QT interval was noted to be 488 milliseconds. It is interesting to note that despite such a low serum calcium level, the patient did not demonstrate any signs or symptoms pertaining to hypocalcemia.

Etiology of hypocalcemia was further investigated. He was found to be severely Vitamin D deficient (25-hydroxycholecalciferol level of 15.6 ng/ml). A parathyroid hormone level was 383.6 pg/ml (normal range 15-68 pg/ml). He was thought to have secondary hyperparathyroidism in the presence of Vitamin D deficiency. A 24-hour urinary calcium excretion was very low (<2 mg/dl, normal range 50-150 mg/dl), therefore excluding hypercalciuria. Urinary N-terminal telopeptide was not checked. A retrospective laboratory data review showed that his corrected calcium count was 9.2 mg/dl at the time of Denosumab administration 2 weeks earlier. However, at that time, his vitamin D level was unavailable and he was not supplemented with Vitamin D. Based on these findings, he was diagnosed with Denosumab induced hypocalcemia.

Vitamin D supplementation was initiated in the form of cholecalciferol at a daily dose of 8000 international units. Likewise, calcium replacement was commenced immediately at a dose of 2500 mg three times a day. He received daily intravenous calcium gluconate (1 gram) replacement without any improvement in serum calcium level. On day 6, he was given continuous calcium infusion (11 grams of calcium gluconate in one liter of normal saline which was administered over 24 hours), with resultant slight improvement in the serum calcium level. At the same time, his magnesium level was corrected with oral and intravenous magnesium supplementation. Despite aggressive vitamin D and calcium supplementation, his calcium level was never corrected (Figure 1). Throughout his hospital stay, his corrected

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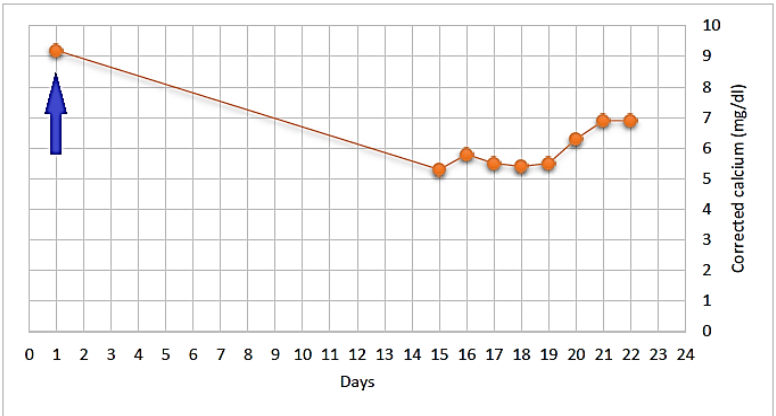

Figure 1: Trend of serum corrected calcium levels. Blue arrow (day 1) indicates denosumab administration. The patient was admitted on day 15.

calcium level ranged from 5.2 mg/dl to 6.9 mg/dl. He, however, remained asymptomatic from profound hypocalcemia. Unfortunately, he deteriorated clinically and opted for hospice after 8 days of inpatient treatment.

Discussion

Skeletal system is a frequent site of metastasis for many cancers occurring in up to 70% of advanced breast and prostate cancers. Bone metastases are characterized as osteoblastic or osteoclastic in reference to the predominant process as a result of metastasis. Lesions can be osteoblastic, osteolytic or mixed depending on the primary cancer, for example, osteolytic lesions are characteristic of multiple myeloma while osteoblastic lesions prevail in prostate cancer [1]. Bone metastasis has significant impact on patients' morbidity and mortality. A significant amount of time and resources are spent to manage patients with bone metastasis with either curative or palliative intent [2].

Complications of bone metastasis include pain, derangement of calcium homeostasis, ineffective hematopoiesis and SREs. SREs are a composite of local bone complications defined as pathological fracture, cord compression and need for surgery or radiation for pain or impending fracture [2]. SREs are a common tool utilized by clinicians to assess the degree of morbidity caused by bony metastasis. Understanding of the pathogenesis of bone metastasis had led to development of strategies to minimize the complications. Bisphosphonates and RANKL inhibitor, Denosumab, are bone targeted agents which have been approved for prevention of SRE in patients with metastatic prostate cancer to bones.

Advanced stage prostate cancer is commonly complicated by bone metastasis and at times, presents as a SRE secondary to metastatic lesions. It is important to note that SREs are a result of not only metastatic lesions but also as a consequence of androgen deprivation therapy (ADT) which causes enhanced bone demineralization and increased risk of fractures [3]. Even though, radiographically osteoblastic lesions are predominant in prostate cancer, yet there is an increased activity of both osteoblasts and osteoclasts as evidence by increased osteoclastic markers such as N-terminal telopeptide [3]. Bone metastasis in prostate cancer is a complex process involving interplay of intriguing pathways that lead to increased bone turnover. RANKL, synthesized by osteoblasts, stromal cells and T lymphocytes, is a transmembrane molecule that undergoes proteolytic cleavage. Soluble RANKL binds to its receptor RANK on the surface of precursor and mature osteoclasts leading to their activation. An intermediary protein in this pathway is osteoprotegerin which acts as a decoy receptor for RANKL and inhibits its interaction with RANK. Prostate cancer cells play a central role in amplifying this process in a vicious cycle by virtue of their interaction with osteoblasts, osteoclasts and stromal cells. These cells secret parathyroid hormone related peptide (PTHrp) which stimulates the stromal cells and osteoblasts to synthesize and release more RANKL. RANKL promotes osteoclastogenesis and promotes synthesis of molecules like tumor growth factor-β (TGF-β), insulin like growth factors (IGFs) and fibroblast growth factors (FGF) by the osteoclasts which, in turn, exert trophic effect on the tumor cells; hence the vicious cycle [1,4].

Denosumab is a humanized monoclonal IgG2 antibody that inhibits RANKL eliminating a pivotal step in the vicious cycle. Loss of RANKL-RANK signaling fails to activate osteoclasts. Ultimately, bone resorption from skeletal metastasis is reduced by Denosumab, therefore, preventing SRE. In addition, Denosumab has direct inhibitory effects on the tumor cells by inhibiting their growth, adhesion to stromal cells and inducing apoptosis [3]. Randomized controlled trials have demonstrated its superiority over bisphosphonate therapy in metastatic castration resistant prostate cancer [5]. Furthermore, it has been shown to be effective in reducing fractures as a result of ADT in non-metastatic prostate cancer [6]. Denosumab has also been shown to potentially delay bone metastasis in prostate cancer [7].

Hypocalcemia is a common adverse effect of Denosumab therapy. Under normal circumstances, parathyroid hormone prevents hypocalcemia by homeostatic efflux of stored calcium from the bones. This is dependent on RANKL which is a key mediator for osteoclast differentiation, activation and survival. Therefore, inhibition of RANKL by Denosumab hampers mobilization of calcium from bone stores to maintain normal serum calcium level. In a large randomized control trial comparing Denosumab with Zoledronic acid in preventing skeletal related events in castration resistant metastatic prostate cancer, hypocalcemia was found in 13% of Denosumab treated patients as compared to 6% of Zoledronic acid treated patients. However, grade 3 or higher hypocalcemia occurred in 5% of Denosumab treated group as compared to 1% of Zoledronic acid treated group. Importantly, there were no fatal events as a result of hypocalcemia [5]. Another randomized control trial evaluating bone metastasis free survival in non-metastatic castration resistant prostate cancer patients reported 1% occurrence of grade 3 or 4 hypocalcemia in Denosumab group (while none in the placebo group). Only 1 patient developed symptomatic hypocalcemia [7]. Other studies have also reported hypocalcemia when it is used

in advanced cancer with metastasis to bones and multiple myeloma, however there were no fatalities as a result of hypocalcemia [8,9]. In all these trials, Denosumab dose was 120 mg every 4 weeks. A lower dose (60 mg every 6 months) is approved for prevention of fractures while on ADT in non-metastatic prostate cancer. One major study reported a much lower incidence (0.1%) of hypocalcemia in patients on ADT [6]. Based on these trials, it can be deducted that the probability of causing hypocalcemia was much higher with higher dose of Denosumab.

Denosumab induced hypocalcemia is transient and oral calcium supplementation is usually sufficient to correct calcium imbalance. However, very rarely, hypocalcemia can be severe and refractory to oral supplementation as in our patient. Based on literature search, only a few case reports have reported severe resistant hypocalcemia demonstrating its extreme rarity [10-13]. Studies are lacking to determine the risk factors and exact incidence of Denosumab induced hypocalcemia. Furthermore, the degree of hypocalcemia is very unpredictable. A retrospective analysis involving patients with metastatic castration resistant prostate cancer on Denosumab suggested a higher prevalence of hypocalcemia than previously reported. Of the 60 patients analyzed, 9 developed severe hypocalcemia to a degree that they required hospitalization and intravenous calcium supplementation. Aggressive metastatic disease as reflected by higher PSA and alkaline phosphatase levels, and baseline Vitamin D deficiency tended to be risk factors for severe hypocalcemia whereas prior bisphosphonate therapy and concurrent steroid administration did not appear to be risk factors [14]. Another analysis identified reduced creatinine clearance (less than 50 ml/min) and no prior exposure to bisphosphonates as risk factors for severe hypocalcemia [15]. It is interesting to note that prior treatment with Zoledronic acid did not appear to be a risk factor despite its long half-life in the bones. This may have been related to higher PTH levels which can occur after Zoledronic acid administration. Higher baseline PTH levels in these patients may prevent severe drop in calcium levels after Denosumab therapy [16]. In a recent study, serum alkaline phosphatase was found to be an independent risk factor, especially if the baseline level was greater than 500 IU/l. Likewise, a higher baseline urine N-terminal telopeptide was also found to be correlated independently with the development of hypocalcemia especially when levels were greater than 100 nmol bone collagen equivalents/mmol creatinine [17].

Conclusion

In conclusion, Denosumab is associated with hypocalcemia which can be profound and resistant to therapy. Clinicians and oncologists should be vigilant of this unpredictable side effect. Risk factors for hypocalcemia such as old age, extensive bony metastases, vitamin D deficiency, reduced creatinine clearance (less than 50 ml/min), malabsorption syndromes, certain medications (such as phenytoin, calcitonin etc.) and concomitant electrolyte abnormalities such as hypomagnesemia or phosphate derangements should be identified before Denosumab therapy. In case of prostate cancer, higher baseline PSA, serum alkaline phosphatase and urine N-terminal telopeptide levels are independent risk factors for more pronounced hypocalcemia. Aggressive measures such vitamin D replacement should be undertaken to avoid or minimize these risk factors. Calcium level should be monitored 1-2 weeks following the injection as the risk of hypocalcemia is highest around that time.

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