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Rebound Hypercalcemia Following Discontinuation of Denosumab in a Pediatric Patient: A Case Report

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Abstract

Denosumab is a human monoclonal antibody approved for the treatment of osteoporosis, giant cell tumor of bone and skeletal metastasis of solid tumors. Rebound hypercalcemia following discontinuation of denosumab is a known side effect that is more frequently reported in skeletally immature patients. We report the case of a 12-year-old female patient with history of giant cell tumor of the cervical spine who was treated with denosumab for almost 2 years. She presented with clinical manifestations related to hypercalcemia more than 5 months after denosumab cessation, the diagnosis was based on bone turnover markers and nuclear medicine scan.

Introduction

The present report describes a 12-year-old female patient, female patient who was diagnosed with rebound hypercalcemia following denosumab cessation. This case provides a reference for the clinical diagnosis and management of rebound hypercalcemia following discontinuation of denosumab.

Case Presentation

A 12-year-old female patient with no prior medical history initially presented with progressive neck pain was admitted to a hospital following the neck sprain. Magnetic Resonance Imaging (MRI) showed an osteolysis of the Second Cervical (C2) vertebral body and pathological analysis revealed C2 giant cell tumor of bone (classic). The patient was treated with Denosumab started in April 2021 within 5 months before surgical intervention and laboratory monitoring showed a normal range of serum calcium. Denosumab treatment was stopped after an 18-month period in April 2023. She presented to a hospital with a 2-month history of dizziness, fatigue, chest pain, vomiting and hypertension starting 5 months after the last dose of denosumab. Laboratory examination showed severe hypercalcemia with a peak serum calcium level of 4.49 mmol/L (reference range, 2.2-2.7 mmol/L), acute kidney injury with a high level of serum creatinine (194 umol/L, reference range, 27-66 umol/L). The family history was unremarkable. She was treated with a combination of intravenous hydration, furosemide, Nitrendipine, and calcitonin during hospitalization. Symptoms improved only slightly and serum calcium gradually decreased to 3.11 mmol/L (reference range, 2.1-2.8 mmol/L). Therefore, the patient was referred to the Department of Pediatrics of the Second Hospital of Hebei Medical University (Figure 1).

Diagnostic assessment

The initial clinical evaluation revealed severe hypercalcemia (3.56 mmol/L; reference range, 2.1-2.8 mmol/L), hypomagnesemia (0.67 mmol/L; reference range, 0.75-1.02 mmol/L), acute kidney injury (serum creatinine 137 umol/L, reference range, 27-66 umol/L), hypertension (145/114 mmHg, 1 mmHg = 0.133 kPa). Serum Parathyroid Hormone (PTH) level was 12.70 pg/ml (reference range, 12.00-65.00 pg/ml) and 25-OH vitamin D level was 36.00 mmol/L (>50nmol/L). The ratio of urine calcium to creatinine was 0.8. Parathyroid ultrasound, radionuclide imaging of parathyroid, and Computed Tomography (CT) scan of the mandible were unremarkable. Bone turnover markers were investigated because of the slightly decreased levels of calcium. Procollagen type 1 N-terminal Pro-peptide (P1NP) was 670.20 ng/ml (reference range, 15.13-58.59 ng/ml), beta-collagen degradation product (beta-CTX) was 1.190 ng/ml (reference range, ≤ 0.573 ng/ml), calcitonin <0.50 pg/ml (reference range, 0.00-6.40 pg/ml), total parathyroid hormone <3.00 pg/ml (reference range, 15.00-68.3 pg/ml), and Osteocalcin (OC) was 21.98 ng/ml (reference range, 7.70-21.70 ng/ml), suggesting osteoclast overactivity. Whole-body bone scan and Positron Emission

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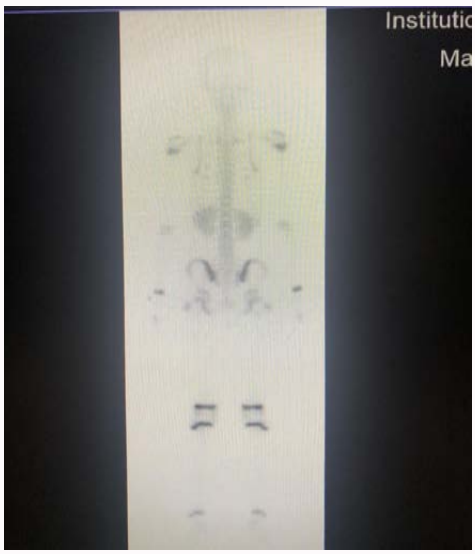

Figure 1:

Tomography/Computed Tomography (PET/CT) imaging revealed fractures of the 7th to 9th ribs, an increased density at the upper end of the humerus, scapula acromion, clavicle head, subscapular angle, and costochondral junction, as well as an increased radiotracer uptake symmetrically within multiple growth plates. Combined with clinical history, rebound hypercalcemia following discontinuation of denosumab therapy was found to be the only explanation.

Treatment, outcome and follow-up

A single dose of zoledronic acid was administrated due to persistence of hypercalcemia. The treatment leads to improvement of clinical and biochemical parameters with normal calcium (2.52 mmol/l), blood pressure and renal function. Her clinical condition and laboratory values were normal of 9 months post hospital discharge at the time of this report.

Discussion

Hypercalcemia is defined as a serum calcium concentration that is greater than two standard deviations above the normal mean, which may vary with age and sex. The causes can be classified as Parathyroid Hormone (PTH) -dependent and Parathyroid Hormone (PTH) -independent. The clinical manifestations are diverse and atypical, differing significantly from those in adults [1]. In the case, we present a 12-year-old female patient who developed PTH-independent hypercalcemia (serum calcium 4.49 mmol/L, total parathyroid hormone <3.00 pg/ml) after 5-month of denosumab discontinuation. Given that other causes such as vitamin D overdose, vitamin A overdose, application of phosphorus preparations, and recurrence or bone metastasis of giant cell tumor of bone, could be excluded, the patient was diagnosed with rebound hypercalcemia following discontinuation of denosumab.

Denosumab is a fully humanized antibody that specifically binds Receptor Activator of Nuclear Factor-kappa B Ligand (RANKL), preventing its binding to the Receptor Activator of Nuclear Factor Kappa B (RANK) that leads to osteoclast differentiation and activity [2]. It is available for treatment of skeletal disorders including Aneurysmal Bone Cyst (ABC), Central Giant Cell Granuloma (CGCG), and Giant Cell Tumor of bone (GCT). Giant Cell Tumor (GCT) is one of the most common benign bone tumors predominantly occurring in young adults aged 20 to 40 and rarely affects children [3]. Denosumab is clinically beneficial for the treatment of GCT, which is usually located in a metaphysis and is uncommon in the cervical spine [4]. Patients are recommended to continue treatment with denosumab because cessation of denosumab may correlate with the possibility of subsequent local recurrence [5]. The present report describes a 12-year-old female patient female patient with the diagnosis of GCT who was treated with surgical treatment and almost 2-year course of neoadjuvant denosumab. She suffered from severe hypercalcemia with complaints of vomiting and dizziness combined with acute kidney injury and hypertension starting 5 months following denosumab cessation. Serum calcium levels remained abnormal with initial management included hydration, furosemide, and calcitonin. The hypercalcemia resolved after treatment with zoledronic acid.

The pharmacokinetics and pharmacodynamics of denosumab which is used as an off-label treatment for pediatric bone disorders have not yet been studied in children. Wang et al. reported a 9-year-old boy with fibrous dysplasia treated with a 7-month course of denosumab and found reversal of bone turnover suppression after treatment discontinuation, suggesting that denosumab did not have significant adverse effects on growth [6]. Rebound hypercalcemia is a rare adverse effect predominantly occurring in male adolescents, with a duration of less than 1 to 7 months following denosumab cessation [7]. Rapid bone resorption following osteoclast hyperactivation may be the mechanism behind this rebound hypercalcemia, suggesting the effect of denosumab on bone turnover is rapidly reversible. The extent of the increase in serum calcium may be determined by bone turnover and calcium stores [8]. Following denosumab treatment, increased metaphyseal density has been present in the dense metaphyseal bands. The release of minerals in the zone may be the underlying cause of hypercalcemia following denosumab cessation [9].

Management strategies typically involve intravenous hydration, furosemide, calcitonin, corticosteroids, bisphosphonates, and/or repeat dosing of denosumab. However, Serum calcium is normalized with bisphosphonates in cases of severe and refractory hypercalcemia. Sydlik et al. suggested that consistent use of bisphosphonates is worth considering to prevent rebound hypercalcemia, while the timing and/or frequency or dosage of bisphosphonates require investigation [10]. Emily Seale et al. reported an effective method alternating doses of denosumab and zoledronic acid for prevention of the rebound hypercalcemia in a child with Osteogenesis Imperfecta (OI) type IV. The ratio of urine calcium to creatinine, parathyroid hormone, and bone turnover markers were found to predictive of the phenomenon [11]. Further research is needed into the timing or frequency of laboratory monitoring during or following denosumab therapy [12].

Denosumab has demonstrated considerable efficacy in the treatment of skeletal disorders. Rebound hypercalcemia, which has been observed to occur with greater frequency in children following discontinuation of Denosumab, represents a significant safety concern. It is therefore imperative to closely monitor serum calcium levels during the discontinuation period and to promote health education for early detection.

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