CASE REPORT

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A Case of Denosumab-associated Hyperparathyroidism: Differential Diagnosis Challenge

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Abstract

Denosumab is a relatively new medicine that has become the second option in the treatment of bisphosphonate-resistant or intolerant osteoporosis. An 85-year-old female patient was referred to the outpatient clinic of our department with a complaint of waist pain. She stated that her waist pain started 2 weeks before her visit and she had taken the fourth denosumab injection. Her laboratory results revealed normal serum calcium, phosphorus, and vitamin D levels (8.8 mg/dL, 3.1 mg/dL, and 32 ng/L, respectively) before denosumab injection. She had a sensitive point with pain on her lumbar vertebrae. Lower extremity movements were painful and muscle strength was bilaterally reduced. Vital signs and other systemic examinations were normal. Her laboratory tests for serum parathormone (PTH), calcium, phosphorus, and vitamin D levels showed 487 ng/L, 8.6 mg/dL, 0.6 mg/dL, and 30 ng/mL, respectively. She did not have any chronic renal and other bone metabolism diseases, except for osteoporosis. Her X-ray revealed a loss of height in L3 lumbar vertebrae. The spinal magnetic resonance indicated an acute fracture. However, we could not explain hyperparathyroidism in the absence of hypocalcemia and low vitamin D levels. Therefore, we started to investigate primary hyperparathyroidism in the patient. Neck ultrasonography did not show any associated abnormal findings with the parathyroid glands. Parathyroid scintigraphy resulted in normal parathyroid gland activity. During her follow-up, the PTH level decreased with time. Spontaneous regression of PTH led us to suspect an association between denosumab injection and hyperparathyroidism. Mazokopakis (1) reported a similar case in the literature in 2018, reporting a 62-year-old female patient with normal electrolytes and a high PTH level after three months of denosumab injection. The hypocalcemic effect of denosumab combined with inadequate oral calcium and vitamin D intake may have triggered exaggerated PTH secretion.

Keywords: Bone health in older people, clinical geriatrics, denosumab, drugs and aging, geriatrics, osteoporosis

Introduction

Denosumab is a relatively new medicine that has become the second option in the treatment of biphosphonate-resistant or intolerant osteoporosis. Subcutaneous injection with 6-month intervals, approval of its usage in stage 3-4 CKD and not having gastrointestinal side effects are advantages of denosumab. However, it has some disadvantages like requiring monitoring serum levels of calcium and vitamin D before each injection.

Case Report

An 85-year-old female was referred with waist pain to the outpatient clinic of our department. She told that the pain started about 3 weeks ago while she was sitting in the chair. During the last 3 weeks, the pain existed and it was relieved with lying on the bed, aggravated with movement. She needed paracetamol 3 times a day and ibuprofen 2 times a day to alleviate the pain. She said that 2 weeks before the waist pain started, she had had the fourth denosumab injection. When we checked laboratory results history, we found normal serum calcium, phosphorus, and vitamin D levels (8.8 mg/dL, 3.1 mg/dL, 32 ng/L respectively) before denosumab injection. After the injection, she did not apply to the clinic. In her physical examination, she came to the examination room with a wheelchair. She had a sensitive point with pain on her lumbar vertebrae. Lower extremity movements were painful and muscle strength was reduced bilaterally. Vital signs and other systemic examinations were normal. On her laboratory tests serum parathormone (PTH), calcium, phosphorus, vitamin D levels were 487 ng/L, 8.6 mg/dL, 0.6 mg/dL, 30 ng/mL respectively. She did

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not have a chronic renal disease and another bone metabolism disease except for osteoporosis. Her X-ray revealed a height loss in L3 lumbar vertebrae. Spinal magnetic resonance indicated that it was an acute fracture. However, we could not explain hyperparathyroidism in the absence of hypocalcemia and low vitamin D levels. Thus, we started to investigate primary hyperparathyroidism in the patient. Neck ultrasonography did not show any abnormal findings associated with parathyroid glands. Parathyroid scintigraphy resulted with normal activity in parathyroid glands. During her follow-up, the PTH level reduced with time. The challenging point for us was that the patient had normal serum calcium and vitamin D level with normal renal function.

Discussion

In the literature, Mazokopakis (1) first reported a similar case in 2018, a 62-year-old woman with normal electrolytes and high PTH level after 3 months of denosumab injection. In a cohort of 60 patients with metastatic prostate cancer who received at least one dose of denosumab (120 mg), 42 patients (70%) developed hypocalcemia, seven (11.6%) developed high-grade hypocalcemia, and nine (15%) required hospitalization for intravenous calcium supplementation (2). In our case, although the patient's baseline serum calcium, phosphorus and vitamin D levels were normal, the levels were close to the lowest threshold for all markers. Her risk for malnutrition was high and she was not eager to take oral nutritional supplements. Together with inadequate oral calcium and vitamin D intake, hypocalcemic effect of denosumab might have triggered exaggerated PTH secretion. Previous literature suggests that hypocalcemic effects of denosumab starts after the injection, reaches the nadir level on 17th day and resolves spontaneously on the 25th day (3). In this case, her serum calcium and vitamin D levels were normal before denosumab injection. Five weeks after the denosumab injection, on her presentation with osteoporotic vertebral fracture, laboratory tests revealed normal serum calcium and vitamin D levels again. Probably, bone fracture and transient hypocalcemic period which we could not detect during the 5-week period contributed together for hyperparathyroidism.

Conclusion

In conclusion, physicians should take into consideration that high PTH levels might be associated with denosumab therapy if the possibility of primary hyperparathyroidism is eliminated by neck ultrasonography and parathyroid gland scintigraphy. Close following-up the patient and replacing inadequate or near inadequate levels of serum calcium and vitamin D are key factors for preventing denosumab- associated hyperparathyroidism. It should be kept in mind that PTH level may stay at high levels although serum calcium and vitamin D levels return to normal, especially when it exists together with acute bone fracture. Denosumab-associated hyperparathyroidism can spontaneously recover in 2 to 3 months if the patient takes adequate calcium and vitamin D. When clinicians encounter such a clinical course, replacing calcium and vitamin D, close monitoring and eliminating other possible causes of primary or secondary hyperparathyroidism are essential.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.F.S., S.F.A., Concept: S.Ş., Design: Z.F.S., S.F.A., Data Collection or Processing: E.T., Analysis or Interpretation: S.Ş., Z.F.S., S.F.A., Literature Search: E.S.S., S.F.A., Writing: E.T., E.S.S., S.F.A.

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