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Exacerbation of Denosumab-Related Osteonecrosis of the Jaw After Discontinuation of Denosumab: A Case Report

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Abstract: Denosumab, a bone antiresorptive agent, is used to treat patients with osteoporosis or bone metastasis. It has been reported that denosumab, like bisphosphonates, causes osteonecrosis of the jaw (ONJ). Some clinical case reports have shown that the discontinuation of denosumab ameliorates ONJ. Herein, the authors present a case in which denosumab cessation exacerbated osteonecrosis in a patient who suffered from denosumab-related osteonecrosis of the jaw (DRONJ). A 56-year-old female patient was referred to us with swelling and pain in the left buccal region. The patient had metastatic breast cancer (cT3N1M1, stage IV) and had been treated with a triplet regimen of paclitaxel, capecitabine, and bevacizumab. In addition, denosumab (Ranmark®, 120 mg) had been subcutaneously injected for 3 years. She had no history of bisphosphonate use or radiotherapy in the head and neck region. Her left mandibular second molar was extracted at a dental clinic with only slight pain. Clinical examination revealed swelling and pain in the left buccal region, bone exposure in the intraoral left mandibular region with pus discharge, limited mouth opening, and subcutaneous abscess formation with fever. After the cessation of denosumab, image inspection revealed a spreading radiolucent lesion and extensive periosteal reaction in the bilateral mandible. It should be noted that DRONJ may worsen despite denosumab holidays.

Keywords: Denosumab-Related Osteonecrosis of the Jaw, Denosumab, Discontinuation, Exacerbation

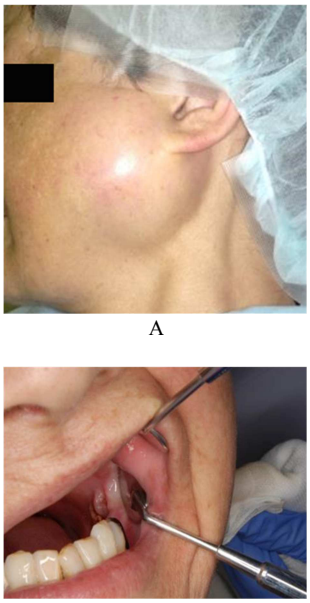
1. Introduction

Denosumab, a human monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B ligand, is commonly used to prevent and treat skeletal complications of bone metastatic cancer, multiple myeloma, and osteoporosis. Denosumab reduces the risk of hip and new vertebral fractures compared to placebo [1]. Moreover, treatment with denosumab increases hip and spine strength, femoral cortical mass, surface density, and thickness in association with modeling-based bone formation [2-4]. Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse effect of antiresorptive drugs, including bisphosphonates (BRONJ) and denosumab (DRONJ). The incidence of MRONJ is between 0.001% and 1% in patients with osteoporosis and up to 20% in those with cancer [5]. The prevalence of BRONJ is 0.21%, whereas that of DRONJ is 0.04% [6, 7]. The main mechanism of action of bisphosphonates is that they limit the bone remodeling capacity of osteoclasts, resulting in the suppression of bone turnover [8]. With denosumab, the bone turnover returned to normal after discontinuation. This is the most significant feature of denosumab compared to bisphosphonates [9]. Herein, we report a case in which denosumab cessation exacerbated osteonecrosis in a patient with DRONJ.

2. Case Report

A 56-year-old female patient was referred to us in 2016 with swelling and pain in the left buccal region. The patient had metastatic breast cancer (cT3N1M1, stage IV) and was treated with a triplet regimen of paclitaxel, capecitabine, and bevacizumab. In addition, denosumab (Ranmark®, 120 mg) had been injected subcutaneously since 2013. She had no history of bisphosphonate use or radiotherapy in the head and neck region. The left mandibular second molar was extracted at a dental clinic in 2015 with only slight pain. Clinical examination revealed swelling and pain in the left buccal

region, bone exposure in the intraoral left mandibular region with pus discharge, limited mouth opening, and subcutaneous abscess formation with fever (Figures 1A and 1B).



A

B

Figure 1. *Photos taken on the day of admission.*

A. Photo of left buccal swelling
B. Intraoral photo of left mandible

Panoramic radiography and computed tomography (CT) showed extensive osteosclerosis in the left mandible and periosteal reaction in the bilateral mandible, reaching the left mandibular condyle (Figures 2 and 3).

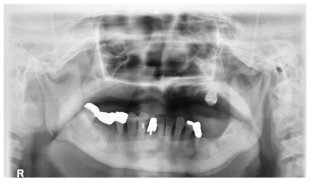


Figure 2. *Panoramic X-ray taken on the day of admission.*

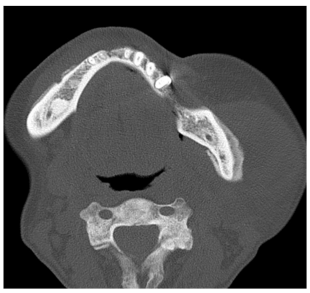


Figure 3. *CT scans taken on the day of admission. Horizontal section on the level of connecting line between tooth 48 and the left ramus.*

Bone scintigraphy revealed a high accumulation of 99mTc-HMDP in the left mandible, including the condyle (Figure 4).

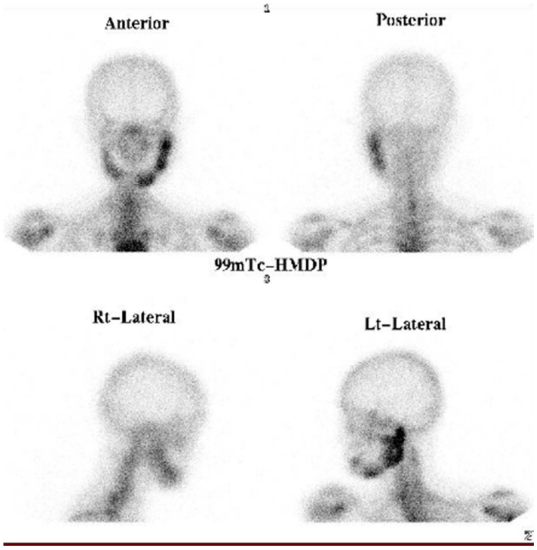


Figure 4. *Bone scintigraphy.*

The white blood cell count and C-reactive protein levels were 9,340/μL and 6.87 mg/dL, respectively. Thus, the author requested the patient's oncologist to cease Ranmark®, and the patient was admitted to our hospital (designated as day 0). The author performed an incisional drainage on the left buccal region and also initiated treatment with intravenous ceftriaxone (2.0 g/day, from day 0 to day 7) and metronidazole (1.5 g/day, from day 1 to day 5) under the control of routine analgesia (non-steroidal anti-inflammatory drugs and acetaminophen). Subsequently, cefcapene pivoxil hydrochloride (300 mg/day, from day 7 to the day of discharge) was administered orally. A small region of the intraoral bone (10 mm × 8 mm) in the left molar area of the mandible was removed. As the widespread bone metastasis had been detected on recent bone scintigraphy and positron emission tomography, including the spinal bone, the removed bone was pathologically checked, and no evidence of malignancy was found. Bone curettage was performed several times under local anesthesia. Consequently, primary closure was not achieved, and pus from the necrotic bone was removed, relieving pain. After discharge, the patient continued to take oral clarithromycin (200 mg/day). Four months after the discontinuation of denosumab, she complained of swelling and pain in the left buccal region. Panoramic X-ray and CT revealed expansion of the radiolucent area accompanied by periosteal reaction and bone resorption with respect to teeth 45 and 48 (Figures 5 and 6), suggesting acute osteomyelitis. We administered ceftriaxone (2.0 g/day) for 3 days and extracted teeth 45 and 48 because of their high mobility.

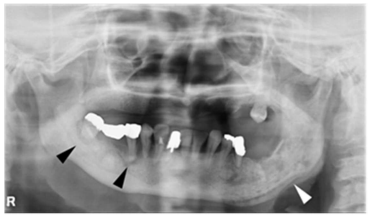


Figure 5. *X-ray taken after 4 months of denosumab cessation. (black arrowhead indicates bone resorption of teeth, and white arrowhead indicates expansion of the radiolucent area accompanied by periosteal reaction.*

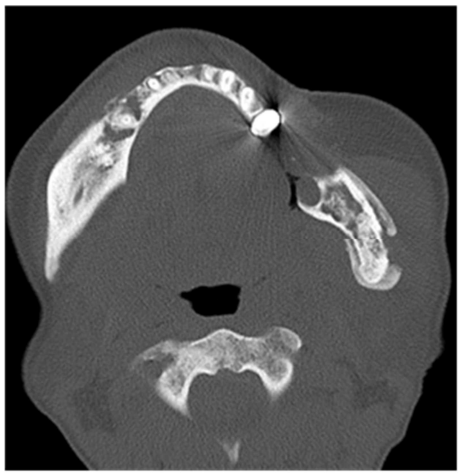


Figure 6. *CT scans taken after 4 months of denosumab cessation. Horizontal section on the level of connecting line between tooth 48 and the left ramus.*

3. Discussion

Denosumab, unlike bisphosphonates, does not accumulate in bone, and the half-life of denosumab is 26 days, which is very short [10]. Discontinuation of denosumab, a denosumab holiday, appears to be useful for promoting the healing of ONJ. Indeed, some cases have reported that denosumab holidays are effective [11-13]. In addition, DRONJ lesions tend to heal faster than BRONJ lesions [14]. In contrast, denosumab holidays have no advantage in promoting spontaneous healing [15]. Two retrospective studies demonstrated that denosumab holidays have no apparent effect on ameliorative outcomes [16, 17]. In a rat model of ONJ, discontinuation of osteoprotegerin-Fc (OPG-Fc) (denosumab surrogate for rodents) before tooth extraction prevented osteonecrosis development, whereas discontinuation of OPG-Fc after tooth extraction did not improve osteonecrosis [18], indicating that denosumab cessation should be performed prior to surgical treatment. Chronic inflammation prior to denosumab cessation disturbs the amelioration of ONJ. A recent retrospective study revealed that tooth extraction is significantly related to the development of DRONJ, and a drug holiday of less than 9 months is ineffective for the amelioration of DRONJ [19]. In our case, it was conjectured that the exacerbation of ONJ despite discontinuation of denosumab was caused by the presence of severe chronic inflammation in the bone marrow.

There are two types of bone formation: remodeling-based and modeling-based. Remodeling-based bone formation is a coupled process that is managed through the balance between bone resorption by osteoclasts and the formation of osteoblasts. However, modeling-based bone formation is not a coupled process that occurs both spatially and temporally in osteoblasts. These types of bone formations are independent of each other. Although denosumab inhibits remodeling to suppress osteoclast function, it does not impede modeling. Denosumab sustained modeling-based bone formation during adulthood in female cynomolgus monkeys undergoing ovariectomy as an osteoporosis model [20]. However, bisphosphonates tend to cease both the remodeling- and modeling-based pathways. The femoral cortical bone in women with osteoporosis responds rapidly to denosumab treatment [3]. In this case, we speculate that extensive bone formation in the periosteal region of the mandible occurred because of both local inflammation and “modeling dominant” cortical bone formation caused by denosumab.

4. Conclusion

We should be aware that drug holiday is not always effective for amelioration of ONJ development in DRONJ patients. Prospective research on drug cessation in patients with DRONJ will provide an answer to this problem. Further research is needed to develop an effective strategy to prevent and treat DRONJ.

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