Case Report

Rapid Onset of Osteonecrosis of the Jaw in an Osteoporosis Patient Treated with Denosumab: A Case Report

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Background: Osteonecrosis of the jaw (ONJ) can occur in osteoporotic patients receiving denosumab. To the authors' knowledge, the present study is the first report of denosumab-related ONJ in Thailand.

Case Report: The authors described the case of a 79-year-old woman with post-menopausal osteoporosis in whom ONJ rapidly developed after the third subcutaneous injection of denosumab (60 mg once half a year). She had previously suffered from decreased bone density while taking intranasal calcitonin (200 IU daily for two years). Three months following the third denosumab dose, she had a tooth extracted and then developed ONJ stage 1 of the right lower jaw. She had no history of head and neck radiotherapy. Denosumab was discontinued and conservative treatment with antibiotic mouth rinse was initiated. Teriparatide was administered as a subcutaneous injection (20 mcg once daily) as treatment for her osteoporosis. Over the following two months, she experienced good recovery.

Conclusion: Essential preventive measures of denosumab-related ONJ include dental consultation before antiresorptive initiation and waiting four to six months after the patient's last denosumab dose before performing invasive dental procedures.

Keywords: Antiresorptive agent, Calcitonin, Denosumab, Osteonecrosis of the jaw, Osteoporosis

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Denosumab is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor approved by the U.S. Food and Drug Administration (FDA) for treatment of men and post-menopausal women with osteoporosis at high risk of fracture or glucocorticoid-induced osteoporosis, treatment of bone loss in patients with prostate or breast cancer undergoing hormone ablation therapy, and to reduce skeletal-related events in cancer patients[1]. This medication increases bone density by inhibiting osteoclast differentiation and associated bone resorption. One major adverse event associated with prolonged usage of antiresorptive agents is osteonecrosis of the jaw (ONJ). The incidence of osteonecrosis in osteoporotic and cancer patients exposed to denosumab was found to be 5·2 per 10,000 participant-years and 70 to 90 per 10,000 participant-years, respectively[2,3]. Long-duration denosumab therapy is also a risk factor for developing ONJ[4]. A previous study found that the median number of denosumab doses until symptom onset was 12, but that accelerated development occurred (with a median onset of 4.5 doses) if the patients had received bisphosphonates prior to denosumab administration[5].

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Case Report

Patient information

A 79-year-old woman had been diagnosed with post-menopausal osteoporosis at the age of 74 (in 2015) based on bone mineral density (BMD) T-scores of –3.5 and –3.4 at the lumbar spine and femoral neck, respectively. Her lumbar spine and femoral neck BMD Z-scores were –1.0 and –0.9, respectively. The patient initially received 200 IU of intranasal calcitonin daily

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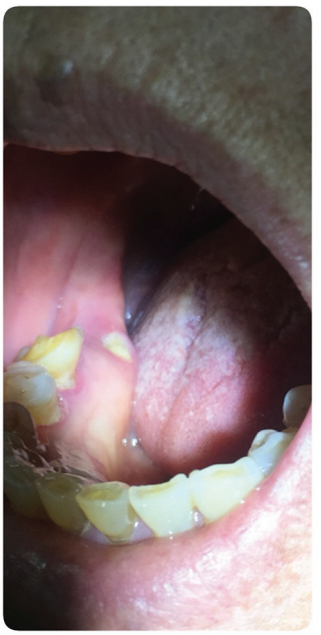

Figure 1. Exposed necrotic bone on the lingual aspect of the right side of the mandible, in the region of tooth 47.

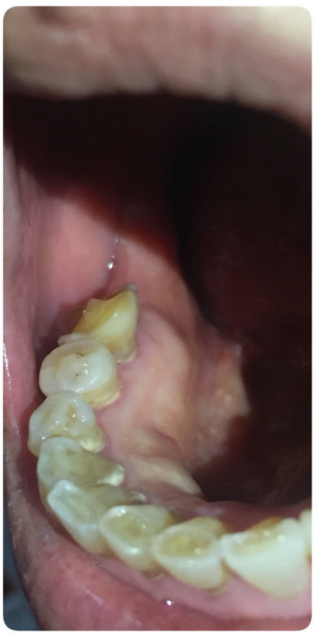

Figure 2. Resolved ONJ in the region of tooth 47 after 2-month cessation of denosumab and 2-month administration of teriparatide.

for two years and was then switched to denosumab due to her BMD T-scores at the lumbar and femoral neck had decreased to –3.6 and –3.5, respectively. She underwent three subcutaneous injections of 60 mg denosumab every six months between January 2017 and May 2018. Though, she used to undergo teeth extraction due to dental caries, the comprehensive oral examination before denosumab initiation was normal. Her underlying medical problems were hypertension, paroxysmal atrial fibrillation, and benign distal common bile duct (CBD) stricture post biliary stenting. She had been taking daily dose of calcium carbonate with elemental calcium 600 mg per day, 1-alphacalcidol 0.25 mcg per day, enalapril 10 mg per day, and warfarin 18 mg per week. The patient had no history of the head and neck radiotherapy.

Clinical findings, timeline, and diagnostic assessment

Three months following the third denosumab dose, she developed pulpitis in the region of tooth 47 (lower right second molar), so the tooth was extracted. Three months later, she presented with asymptomatic exposed necrotic bone on the lingual aspect of the right side of the mandible at the same region (Figure 1) and was diagnosed with ONJ stage 1.

Therapeutic intervention

Denosumab administration was discontinued and conservative treatment with antibiotic mouth rinse was initiated. Follow-up BMD test results showed T-scores of –3.3 at the lumbar spine and –3.1 at the femoral neck, so 20 mcg of teriparatide was administered via subcutaneous injection once daily for the treatment of both ONJ and osteoporosis.

Follow-up and outcomes

Over the two months follow-up, she experienced good recovery and the ONJ was resolved (Figure 2). She continued teriparatide for treating osteoporosis.

Discussion

ONJ is defined as exposed bone in the maxillofacial region persisting for longer than eight weeks after identification by a health care provider in patients taking antiresorptive or antiangiogenic agents and have no history of radiation therapy of head and neck[3,6]. The pathophysiology of ONJ is still unclear. Over-suppression of bone resorption, angiogenesis inhibition, suppression of monocyte and macrophage function, inflammation or infection, and genetic susceptibility may contribute to the development of ONJ[3,7]. Risk factors associated with increased risk of ONJ in osteoporosis patients are suppuration, dental extraction, bisphosphonate administration, and treatment with denosumab[7]. Notwithstanding,

the risk of developing ONJ in osteoporotic patients remains small due to the low level of exposure to antiresorptive agents. Previous studies found that osteoporosis patients with ONJ, the median duration of bisphosphonate exposure was 4.4 years and the median number of denosumab doses was 12 doses (mean cumulative dose of denosumab was 2,293 mg)[3,5]. Although, the overall rate of ONJ was low in denosumab-treated women reporting invasive oral procedures and events, tooth extraction was an important oral event preceding the development of ONJ[8]. In the present study patient, dental extraction was the precipitating factor of ONJ, which developed after only three doses of denosumab.

Conducting thorough examination of the oral cavity before antiresorptive therapy would decrease the incidence of ONJ. If patients required invasive dental surgery during antiresorptive therapy (as the case study did), the procedure should be performed at four to six months after the last denosumab dose. This is because denosumab's half-life is approximately one month, and its antiresorptive effects diminish within six months after cessation, which is supported by the increase in bone turnover markers that occurs before the next denosumab dose at six months[3,9]. The timing of antiresorptive re-administration depends on fracture risk. Patients with low risk of fracture can resume antiresorptive treatment two months after the invasive dental procedures when the damage to the alveolar bone has healed. However, patients with high risk of fracture may receive urgent re-administration of antiresorptive as early as two weeks after undergoing invasive dental procedures when epithelialization of the surgical site is almost complete[9].

Treatment of ONJ is determined based on the stage of the disease. The recommended treatments are antibiotic mouth rinse in stage 1, oral antibiotics combined with antibiotic mouth rinse in stage 2, and surgical debridement in stage 3[3,9]. The prognosis of denosumab-related ONJ is less serious than that of bisphosphonate-related ONJ, since the inhibitory effects of denosumab are transient and reversible, and administration of teriparatide is shown to resolve ONJ symptoms and promote recovery[9]. The median (range) resolution times of ONJ in bisphosphonate-treated and denosumab-treated have been found to be 8.7 (3.7 to 18.3) months and 8.0 (0.2 to 25.6) months, respectively(10). In the present patient, ONJ was resolved in only two months, which confirmed the good prognosis of denosumab-related ONJ and suggested that teriparatide had a beneficial effect on the healing of ONJ wounds. It is important that all physicians who prescribe denosumab treatment for osteoporosis (particularly endocrinologists, orthopedists, and gynecologists) be aware that ONJ can occur in association with such treatment. A dental examination should be conducted at the appropriate time. Moreover, dentists, oncologists, and oral surgeons should be aware of the possibility that patients being considered for dental extractions or other oral surgery are on denosumab treatment, and the patients should be informed of the risk of this potential complication.

To the authors knowledge, this is the first report of denosumab-related ONJ in Thailand. Dental consultation before antiresorptive initiation and waiting at least four to six months after the patient's last denosumab dose before performing invasive dental procedures are essential preventive measures.

What is already known on this topic?

Denosumab, an antiresorptive therapy, has been associated with ONJ.

What this study adds?

Denosumab-related ONJ can rapidly occur in osteoporotic patients receiving dental extraction. Dental consultation before antiresorptive initiation and waiting at least four to six months after the patient's last denosumab dose before performing invasive dental procedures are essential preventive measures.

Ethical approval and consent to participate

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Conflicts of interest

The authors declare no conflict of interest.

References

1. U.S. Food and Drug Administration. Prolia (denosumab) [Internet]. 2018 [cite 2019 Apr 12]. Available From: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125320s186lbl.pdf.
2. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol 2017;5:513-23.
3. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on

medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014;72:1938-56.
4. Inada A, Hosohata K, Oyama S, Niinomi I, Mori Y, Yamaguchi Y, et al. Evaluation of medication-related osteonecrosis of the jaw using the Japanese Adverse Drug Event Report database. Ther Clin Risk Manag 2019;15:59-64.
5. Yarom N, Lazarovici TS, Whitefield S, Weissman T, Wasserzug O, Yahalom R. Rapid onset of osteonecrosis of the jaw in patients switching from bisphosphonates to denosumab. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:27-30.
6. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3-23.
7. Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, et al. Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the international task force on ONJ. J Clin Densitom 2017;20:8-24.
8. Watts NB, Grbic JT, Binkley N, Papapoulos S, Butler PW, Yin X, et al. Invasive Oral Procedures and Events in Postmenopausal Women With Osteoporosis Treated With Denosumab for Up to 10 Years. J Clin Endocrinol Metab 2019;104:2443-52.
9. Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, et al. Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. J Bone Miner Metab 2017;35:6-19.
10. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012;23:1341-7.