

Resolution of a case of denosumab-related osteonecrosis of the jaw after tooth extraction

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Abstract. – Denosumab is an antiresorptive drug that blocks osteoclast maturation, function and survival, improving bone mineral density and reducing the probability of fracture. It has adverse effects and can be the cause of hypocalcemia and osteonecrosis of the jaw.

This report describes the case of a 59-year-old woman with hypothyroidism, antecedents of breast cancer, two strokes, and severe bone osteoporosis. Extraction of tooth 3.6 was performed, and within a month she was administered with a denosumab injection. One month later maxillary osteonecrosis appeared in the lingual distal area of the extraction site. Four months later the case was resolved by means of non-surgical treatment.

Key Words:

Denosumab, Osteonecrosis of the jaw, Osteoporosis, Tooth extraction.

Introduction

Osteoporosis is a skeletal disease that produces a decrease in bone mass density¹. The bones become more porous, weakening them and making them more fragile, so that they present less resistance to impact and so a high risk of fracture. To treat osteoporosis – in addition to a healthy lifestyle including a balanced calcium-rich diet and daily exercise – drugs such as denosumab can be prescribed that prevent bone loss and can even regenerate bone. Denosumab is an antiresorptive drug, a human monoclonal antibody (IgG2) that attaches to receptor activator of nuclear factor kappa-B ligand (RANK-L) receptor that blocks osteoclast maturation, function, and survival, improving bone mineral density and reducing the probability of fracture²⁻⁴. The recommended dose is a subcutaneous injection of 60 mg every 6 months. Denosumab has various adverse effects, of which the most important are hypocalcemia

and osteonecrosis of the jaw (ONJ), which often appear in patients with cancer⁴⁻⁶. Osteonecrosis of the jaw (ONJ) is a rare oral condition that impairs the jaw bone's ability to heal and may produce a wound that does not heal. The bone is not covered by oral tissues and this bare bone can become infected, leading to pain and swelling.

Patients in treatment with denosumab are advised to maintain good oral hygiene and receive regular dental care. The drug should not be prescribed to patients requiring or in recovery from surgery⁷.

Medication-related osteonecrosis of the jaw (MRONJ) due to an adverse reaction to antiresorptive and antiangiogenic drugs, can affect patients' quality of life, and would appear to be caused by a combination of lack of vascular supply and lack of bone regeneration and remodeling. It occurs more often in cases in which the drug is administered parenterally. When treating MRONJ, the objective is to control inflammation and/or infection of the bone and soft tissues and manage the progression of bone necrosis. Dealing with ONJ includes good oral hygiene maintenance, pain management, and treatment with antibiotics and antibiotic mouthwashes⁸. This article describes the case of a female patient who underwent extraction of tooth 3.6, receiving a denosumab injection within one month, followed by the appearance of MRONJ in the distal area of the extraction site. Osteonecrosis was resolved by treatment with antibiotics and chlorhexidine mouthwash.

Clinical Presentation

This is the case of a 59-year-old woman with physical functional diversity resulting from poliomyelitis and meningitis, which had left her wheelchair-bound since 1968. In 2006, half of the thyroids had been removed (on the left side) due to microcalcifications, for which she was currently



Figure 1. Ortopantomography shows bone sequestrum at distal area of 3.6.

receiving no treatment, as this would have adverse effects on her osteoporosis, so that she now suffered hypothyroidism. In 2009, she was diagnosed with breast cancer and received chemotherapy with partial removal of the breast. In the same year she was also diagnosed with severe bone osteoporosis and scoliosis. It should also be noted that the patient presented hypocalcemia, bronchial asthma, C5-C6 disc protrusion, microcytic anemia, right carpal tunnel inversion, and was a heavy smoker. The patient had suffered two strokes, the last in 2017, which had increased her physical functional diversity. The patient's medical history noted the following drug allergies: amoxicillin/clavulanic acid and diazepam (which produced headache); she also had an allergy to grasses and problems with general anesthetics.

The patient's usual medication consisted of: acetylsalicylic acid (100 mg/24 h); atorvastatin (20 mg/ 24 h); hydrochlorothiazide (25 mg/24 h); denosumab (60 mg 1 syringe/183 days); and cholecalciferol (25.000 UI/ 2.5 ml/ twice a week). The patient was prescribed denosumab by her general practitioner. Attending the Special Patients Dental Clinic at the School of Dentistry, University of Gra-

nada (Spain) in May 2018, she underwent extraction of tooth 3.6 (among other treatments) as it presented type 3 mobility with an abscess in the furcation area. The patient received a first single denosumab injection on June 18th 2018. Three months later her doctor referred the patient to the dental clinic with suspected ONJ, a lesion in the posterior region of the third quadrant. Clinical and radiographic exploration confirmed that the lesion was denosumab-related ONJ, presenting bone exposure, with mucosa ulceration causing pain (Figures 1-2). According to the classification proposed by Bagan et al⁹ in 2008 the lesion was classed as stage 2a ONJ (exposed bone necrosis or a small oral fistula without exposed bone necrosis, but with symptoms controlled with medical treatment)⁹. Therefore, a conservative treatment was considered to manage this type of ONJ.

Treatment consisted of 0.12% chlorhexidine irrigation three times per day in the area of the bone necrosis and one capsule of 300 mg clindamycin every 8 hours for 14 days, after which the patient was to return to the clinic. When the patient returned to the Special Patients Dental Clinic two weeks later, it was observed that bone sequestrum had been eliminated spontaneously



Figure 2. Denosumab-related ONJ.



Figure 3. Resolution of ONJ 2 weeks after conservative treatment. Bone sequestrum was eliminated spontaneously.



Figure 4. Bone sequestrum brought by the patient.

(Figures 3-4). The patient was advised to continue with the 0.12% chlorhexidine irrigation regime and to attend weekly check-ups at the clinic. We advised her doctor to wait for 3 or 4 months before resuming antiresorptive therapy, making sure the wound had closed completely and bone quality was adequate, when resolution of the case would be confirmed radiographically. Periodontal maintenance was carried out during the following check-up visits. It could be seen that the mucosa was evolving adequately. A final radiographic control was carried out before the next dose of denosumab was administered.

Discussion

Osteoporosis is a kind of bone metabolic disease with high mortality and morbidity¹⁰. Denosumab is an antiresorptive drug that inhibits osteoclast formation, activation and survival, and has been shown effective against bone fracture and so is considered a first-line drug for treating osteoporosis. Nevertheless, it can cause two adverse reactions: MRONJ and hypocalcemia. With regard to the etiology of MRONJ, several risk factors for its appearance have been identified⁸: dose and duration of exposure to the medication, advanced age, smoking, poor oral hygiene, invasive dental procedures, use of removable dental prostheses, periodontal disease, presence of particular comorbidities (anemia, coagulopathy, infection), cancer and some of its treatments (chemotherapy, radiotherapy of the head and neck). The patient presented various risk factors for ONJ: a dental extraction, poor oral hygiene, and heavy smoking. She also present-

ed functional diversity and experienced difficulty in all four limbs making it difficult to maintain adequate oral hygiene, this being a very important factor for avoiding ONJ⁸. Motor functional diversity conditioned the approach to treatment, as the patient could not be treated in a dental chair. We insisted on the importance of maintaining good oral hygiene and giving up smoking. To treat denosumab-related ONJ, we followed the recommendations made by Bagan et al⁹, opting for non-invasive therapy. Conservative treatment consisted of 0.12% chlorhexidine irrigation three times per day in the area of the bone necrosis and 300 mg clindamycin taken orally, one capsule every 8 hours for 14 days. This proved effective and the case was resolved. In this sense, some authors¹¹ observed that conservative treatment using chlorhexidine and clindamycin for cases of symptomatic exposed bone has a success rate of 90.1%. Several authors concur that for treating ONJ, treatment should be conservative using chlorhexidine mouthwashes and antibiotics^{12,13}, reserving surgical treatment for symptomatic patients¹⁴. After treatment, the area was checked radiographically before a further dose of denosumab could be injected and it would be interesting to check vitamin D, parathyroid hormone and risk fracture¹⁵.

Conclusions

Treatment with 0.12% chlorhexidine irrigation and clindamycin has been shown effective for resolving denosumab-related ONJ. Before treatment with denosumab it is essential to inform patients of the importance and necessity of oral hygiene maintenance; regular oral health check-ups are needed every 6 months to monitor for possible ONJ. Invasive dental treatments must be avoided during treatment with denosumab. Coordination between the doctor and oral health care professional is essential for reducing the risk of MRONJ.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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