Clinical case

Denosumab-induced osteonecrosis of the jaw: A case report

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ABSTRACT

Osteonecrosis of the jaw (ONJ) induced by antiresorptive drugs, mainly bisphosphonates (BP), is widely described in the scientific literature. In recent years, there have been reports of ONJ induced by other antiresorptive drugs such as Denosumab, Bevacizumab and Sunitinib used in cancer patients. Denosumab is a monoclonal antibody used in the treatment of osteoporosis and in the prevention of fractures following treatment of some types of cancer.

In this article, we present the case of a patient who developed ONJ. The patient had periodontal disease and osteoporosis, which had been treated for years with Alendronate (oral bisphosphonate) and currently with Denosumab. In addition, she had a poorly adapted removable prosthesis. This paper discusses the risk of ONJ associated with such drugs, and the possible influence of certain local factors on the occurrence of this condition, as well as the preventive and therapeutic measures that should be adopted in these cases.

KEYWORDS

Osteonecrosis of the jaw; Denosumab; Oral bisphosphonates; Osteoporosis.

INTRODUCTION

Osteonecrosis of the jaw (ONJ) is a clinical entity associated with alteration of the blood supply, inhibition of osteogenesis, and an increase in osteocyte apoptosis. It results in ulcerated mandibular or maxillary lesions with exposure of necrotic bone. ONJ has been associated with diseases such as lupus, falciform cell anemia and Caisson's disease. It has also been related to the use of some drugs like corticosteroids and bisphosphonates, and with radiation therapy of the head and neck.[1-8]

Currently, cases of ONJ caused by the use of new antiresorptive drugs such as Denosumab, Bevacizumab and Sunitinib have been reported.[2,5] Denosumab (Prolia®) was approved in 2010 by the European Medicines Agency. It is used for the treatment of osteoporosis in postmenopausal women who are at an increased risk of fractures and for the treatment of bone loss associated with hormone suppression therapy in men with prostate cancer and women with breast cancer who are treated with aromatase inhibitors. Denosumab is a human monoclonal antibody (IgG2) that, due to its mechanism of action, leads to inhibition of the formation, function and survival of osteoclasts, which results in a decrease in bone resorption in cortical and trabecular bone. It acts by increasing bone mineral density on the one hand, but also reducing bone remodeling ability or bone turnover on the other.[9]

Evaluating the long-term efficacy and safety of Denosumab is important when it is used for the treatment of osteoporosis, given that it is a chronic disease that requires long-term treatment. Although few studies, analyze these complications over the long term, there seems to be an increased risk of ONJ in the group treated with Denosumab compared with controls. [10]

The occurrence of this complication makes its management and considerations equivalent to those of bisphosphonates.

CLINICAL CASE

We present the case of a 63-year-old patient, nonsmoker, with osteoporosis (initially treated with oral bisphosphonates and currently with Denosumab) with no other systemic pathology who came in for consultation due to two-month history of an ulcer at the right inferior alveolar border that caused pain.

The patient has been taking Alendronate 70 mg 1 tablet weekly since 2006 as treatment for osteoporosis. Treatment with the bisphosphonate was discontinued in 2013 and after one year without medication in 2014, the rheumatologist decided to start treatment with Denosumab (Prolia®), 60 mg subcutaneously every 6 months. Two months after the first injection, the patient came in for consult complaining of jaw pain associated with the appearance of an ulcer on the lingual surface of the right inferior alveolar ridge.

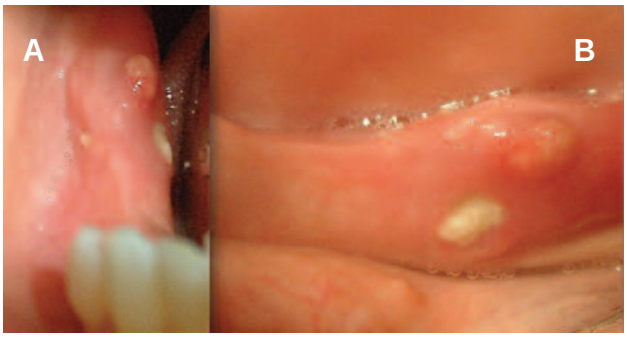

Figure 1. Initial images. a) Image on the left shows the frontal view of the right inferior alveolar border. Ulceration of the internal surface is seen along with the presence of two fistulas, one distal to the ulcer and the other on the vestibular surface. b) Image on the right, coronal view of the ulcer and distal fistula.

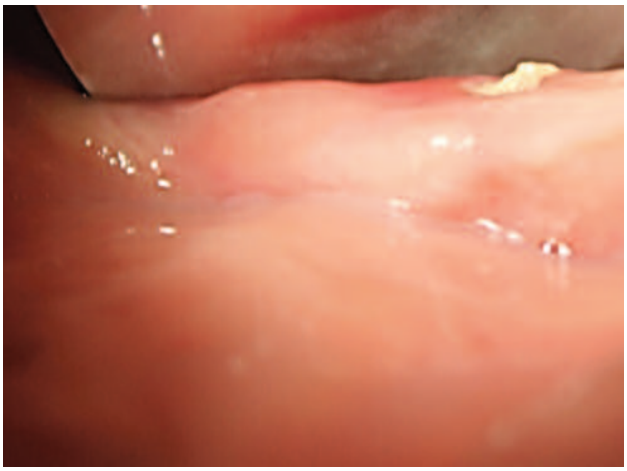

Figure 2. Image seen from the coronal view at one month. We observe ulceration of the internal surface of the mandible, the fistulas have disappeared.

The patient had only been treated for periodontal disease in 2008 and subsequently followed with periodontal reviews every 6 months. Her plaque control was optimal and she did not have any other oral pathology. For the past 8 years, she has had a removable inferior prosthetic with insufficient adjustment and adaptation. The patient has repeatedly shown her refusal to replace it despite professional recommendations.

Intraoral examination revealed a round ulcer at the lingual zone of the inferior alveolar ridge with an erythematous halo measuring 6 mm in diameter (Figure 1) with bone exposure. The lesion coincided with the area of support for the removable inferior prosthesis. A few millimeters more coronal to the ulceration, in the area near the retromolar trigone, we detected two fistulas with purulent exudation.

In addition to insisting on the need to maintain adequate oral hygiene, the patient was prescribed Augmentin Plus® (1000/62.5 mg), 2 tablets twice daily for 10 days and chlorhexidine 0.12% every 12 hours for 15 days. Moreover, she was instructed not to use the removable prosthesis in order to avoid local trauma and was referred to to her rheumatologist in order to assess discontinuation of Denosumab treatment.

The patient was reviewed 15 days later, observing a reduction in the size of the ulcer, although the fistula remained, so it was decided to prolong use of the chlorhexidine mouthwash. The patient came in for

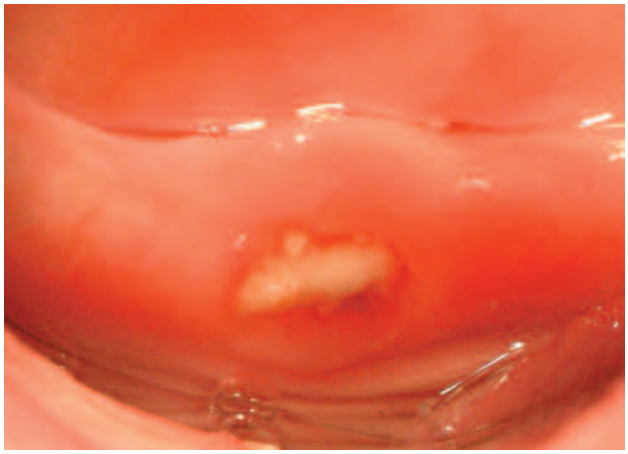

Figure 3. Image seen from the lingual view at one month. We observe ulceration with bone exposure.

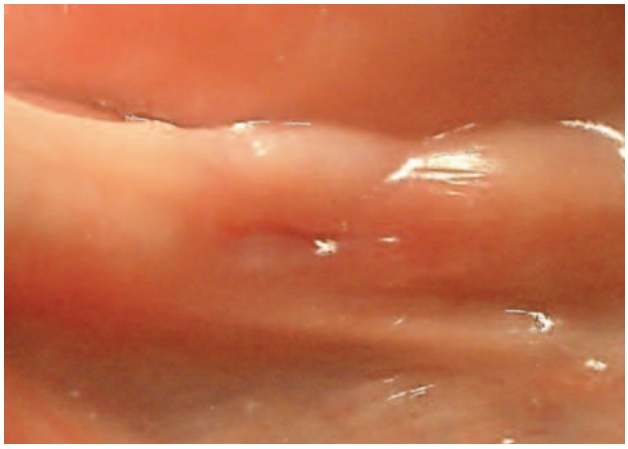

Figure 5. Image of the right inferior alveolar border 6 months after the appearance of the lesion and one month after the surgical intervention.

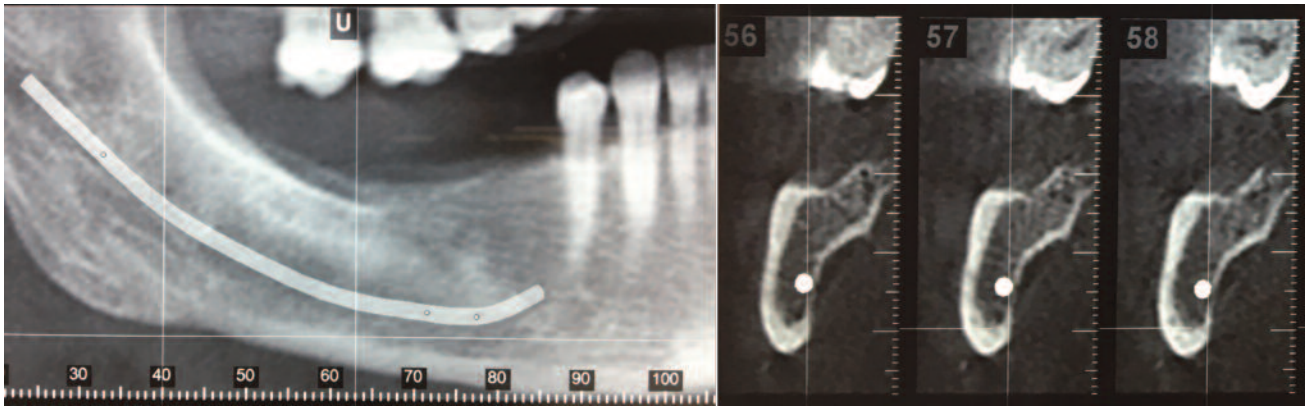

Figure 4. Mandibular CT. Image from the left, frontal slice. Image from the right, sagittal slice. We observe some bone rarification, radiodense and radiotransparent areas.

follow-up at one month. The fistula had disappeared but the bone exposure had increased (Figures 2 and 3).

A Computed axial tomography (CT) of the jaw was performed, revealing images compatible with bone rarefication in the mandibular body. It was possible to distinguish areas of osteocondensation surrounded by radiotransparent zones (Figure 4).

Due to clinical manifestations such as the appearance of an ulcer with bone exposure, purulent exudate and radiographic alterations, as well as the history of pharmacological treatment, a possible ONJ associated with the use of treatment for osteoporosis was suspected.

The patient was referred to the Maxillofacial Surgery Unit at Ciudad Real General Hospital where curettage and extirpation of the sequestered bone together with application of local antiseptic measures were performed. The patient was followed one month after surgery, observing adequate healing of the area (Figure 5).

Currently, the patient is free from recurrence. Her old prosthesis was replaced by another properly fitted and, although she is still being followed, her rheumatologist has not considered it suitable to restart treatment with any antiresorption drug.

DISCUSSION

ONJ is a bone alteration seen in patients treated with radiation therapy or with different antiresorption drugs used to control osteoporosis. Although the exact etiology is not known, certain risk factors favoring its development have been identified: previous treatment with bisphosphonates, advance age, deficient oral hygiene, dental procedures (endodontics and oral surgery), use of removable prosthetics, oral trauma, presence of certain comorbidities (like preexisting oral disease, anemia, coagulopathy, infection), tobacco use and certain concomitant treatments (like chemotherapy, anti-angiogenic biological medications, corticosteroids, radiation therapy of the head and neck).[1,11]

Denosumab has become a suitable option for the treatment of osteoporosis because it contributes to a constant increase in bone mineral density. Even so, cases of ONJ associated with this drug have been described in the literature. A review by Ramirez *et al.*[2] found thirty-five articles published between 2007 and 2012 that related antiresorption and anti-angiogenic drugs with the risk of the appearance of ONJ. Of these, nine associated Denosumab with ONJ.[2-5]

A subsequent review by Oliveira *et al.*[12] arrived at the conclusion that the majority of cases of ONJ caused by Denosumab occurred in women around 60 years of age who received the drug for the treatment of osteoporosis (47%). The most common location for the appearance of ONJ was the mandible.[12]

As bisphosphonates, Denosumab is an antiresorption drug that shares similar mechanisms of action. Denosumab is a humanized monoclonal antibody (IgG2) that is directed at and binds with high affinity and specificity to for RANKL (nuclear factor-kappa B receptor activator), impeding activation of its receptor, RANK, on the surface of precursors of osteoclasts and in osteoclasts. By blocking RANKL/RANK interaction, it inhibits the formation, function and survival of osteoclasts, which leads to a decrease in bone reabsorption in trabecular and cortical bone. Therefore, Denosumab may have the same adverse effects as bisphosphonates, as described in the technical sheet, and in the previously mentioned bibliography.[2-5]

Although there are not many studies evaluating the long-term risk of ONJ in patients treated with Denosumab. Some studies consider it to be similar to oral bisphosphonates, oscillating between 0.09% and 0.34%[2]. Other studies indicate that if the only treatment for osteoporosis is Denosumab, administered in short periods, the risk of ONJ is similar to that of controls, although the risk increases with the duration of treatment.[10]

The patient presented had received previous treatment with oral bisphosphonates for 7 years (Alendronate, 70 mg/weekly). Eighty-eight percent of ONJ cases associated with oral bisphosphonates are related to the

use of Alendronate. In these cases, the risk of ONJ increases starting at 3 years of use, but this time period is shortened when administration is also associated with other drugs also involved in the pathogenesis of ONJ.[7] In addition, some authors state that the effect of bisphosphonates persists for a very long time after discontinuing the drug and may, in some cases, last as long as 10 years.[8,13,14] Many of the reported cases of Denosumab-associated ONJ had received previous treatment with bisphosphonates for a time of no less than 5 years.[15,16] Therefore, the use of Alendronate in our case may be considered an additional etiological factor in the development of ONJ.

We have found only one case report of ONJ induced by the administration of Denosumab and bisphosphonates simultaneously, which may indicate the existence of a possible synergistic action between both antiresorptive drugs. Further research is needed to demonstrate this synergistic relationship of both treatments when administered simultaneously.[17]

In the appearance of ONJ associated with antiresorptive drugs, the possible influence of certain local factors has been highlighted: tooth extractions, poor oral hygiene and poorly fitting prosthetics, among others.[13] The case described included a poorly fitting removable inferior prosthetic as a risk factor. This is related to repeated microtrauma in the alveolar mucosa that may promote the development of ONJ in this patient. The pathogenic participation of ONJ produced by antiresorption drugs on the presence of poorly fitting prosthetics has been previously documented in the literature. Sopeck *et al.*[15] in 2010 performed a randomized double-blind study in which 1026 patients were treated with Denosumab and 1020 with zoledronic acid. In this trial, after three years receiving treatment, 2% of patients treated with Denosumab and 1.4% of those treated with intravenous bisphosphonates developed ONJ. In the majority of cases, the associated etiological cause was a poorly fitting prosthetic (90% vs. 75%), so we believe it is important to check the fit of removable dental prosthetics in all patients who are going to start or are on treatment with these drugs.[13,15,18,19]

As with bisphosphonates, longer duration treatment with Denosumab increases the risk of developing ONJ.[13] It has been shown that the risk of ONJ in the first year of Denosumab administration is 0.5%, 1.1% at 2 years and 1.3% at 3 years.[21] In our case, the time of administration did not determine the risk of developing ONJ as it appeared early after administration of a single dose of the drug. We have found similar cases in the literature.[12,13] This suggests that the combined administration of Denosumab with previous use of Alendronate may be the cause of ONJ.

Although we lack sound data in this regard, the possible risk of ONJ associated with the use of Denosumab suggests that the same protocols recommended for the administration of bisphosphonates apply. According to different authors, implementation of preventive measures is important, as is the use of dental screening prior to starting treatment with antiresorptive drugs in order minimize the risk of ONJ.[20] The Spanish Medicines and Health Products Agency issued an informative note in 2014 in which they informed the healthcare community about the association between Denosumab and the appearance of ONJ in order to apply the measures necessary to prevent this disease.[21]

Therefore, prior to starting treatment with Denosumab, risk factors for the development of ONJ should be taken into account, dental examination should be performed and appropriate dental treatment applied. In addition, it is recommended that Denosumab not be administered to patients with dental or jaw pathologies that require surgery, nor to patients who have not recovered from previous maxillofacial surgery.[21,22]

It is also recommended that during Denosumab treatment, avoid exposing patients with risk factors for invasive dental procedures, inform patients who are to be treated with Denosumab about the importance of maintaining good oral hygiene, and the need to undergo periodic dental examinations. In addition, patients exposed to risk factors should avoid invasive dental procedures, and contact their healthcare professional immediately at the first sign of any anomaly in the mouth (like loose tooth, pain or inflammation).[21]

In patients developing ONJ during treatment, an individualized plan should be established in close collaboration with a dentist or maxillofacial surgeon with experience in ONJ. It is also considered pertinent to temporarily interrupt treatment with Denosumab until the condition resolves and possible risk factors present are minimized as much as possible.[21]

Discontinuation of the drug as a therapeutic and preventative measure is a controversial issue because bisphosphonates store in the bone matrix and due to its long half-life, the risk remains high despite discontinuing the drug. Even so, periods of drug discontinuation have been established allowing invasive dental procedures, like extractions, to be performed safely.

Denosumab, unlike bisphosphonates, is not stored in the bone matrix, so discontinuation would be more effective in resolving the ONJ process than in the case of bisphosphonates.[2]

In the case presented, after the appearance of signs and symptoms of ONJ, treatment with Denosumab was discontinued, with ONJ resolving after 6 months from the onset of the first symptoms.

The cases reviewed in the literature do not reflect the cure times for ONJ, nor do they explain whether or not the drug was discontinued. As with the case of bisphosphonates, it would be necessary to establish action protocols that indicate the waiting times for performing certain dental interventions, as well as studies that demonstrate de relation between discontinuation of Denosumab and resolution of ONJ.[2,22]

CONCLUSIONS

Denosumab is a drug with a mechanism of action similar to bisphosphonates and may therefore be directly related with the development of ONJ, with a similar incidence to oral bisphosphonates. Because Denosumab prescriptions are increasing for the treatment of patients with osteoporosis, we need to be aware of the risk for patients, control possible risk factors, and take the measures necessary, prior and during treatment with the drug, to prevent the development of ONJ. Further scientific studies are needed to provide evidence on the relationship between Denosumab and the risk of ONJ, that may allow for the establishment of preventive action protocols, and suitable treatments for these patients.

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