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Title: Denosumab-related osteonecrosis of the jaw following non-surgical periodontal therapy: A case report.

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ABSTRACT

Introduction: Osteonecrosis of the jaw associated with bisphosphonates is currently called medication-related osteonecrosis of the jaw (MRONJ), given that in addition to bisphosphonates, jaw osteonecrosis has been related to the administration of other antiresorptive and antiangiogenic drugs, such as denosumab, sunitinib, bevacizumab and ipilimumab.

Case Presentation: A 77-year-old patient with osteoporosis treated with subcutaneous injections of denosumab at an interval of 6 months is presented. The patient developed MRONJ after receiving a non-surgical periodontal therapy. Although the MRONJ was initially classified as a stage I lesion in this patient, cone beam computed tomography images confirmed the presence of a significant osteolytic lesion. Treatment consisted of the administration of chlorhexidine mouthwash and systemic doxycycline, exodontia of the involved teeth, sequestrectomy and complete surgical debridement of the necrotic bone.

Conclusion: To our knowledge, this is the first case reported in the literature of MRONJ following nonsurgical periodontal therapy in a patient with osteoporosis treated with denosumab. The risk of MRONJ development after a periodontal procedure and how to prevent this complication are still unknown.

Keywords: Medication-related osteonecrosis of the jaw, Denosumab.

CLINICAL RELEVANCE

Scientific rationale for the study: The early diagnosis of medication-related osteonecrosis of the jaw (MRONJ) can prevent or reduce its morbidity. Although the prevalence of MRONJ is low among patients diagnosed with osteoporosis, the number of cases is increasing in view of the widespread use of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor therapies.

Principal findings: The first case report on MRONJ following nonsurgical periodontal therapy in an osteoporotic patient treated with denosumab.

Practical implications: Dentists should be aware of the possible diagnosis of MRONJ

in patients receiving or who have received antiresorptive or antiangiogenic drugs, even after dental procedures that are considered low-risk.

INTRODUCTION

Bisphosphonate (BP)-associated osteonecrosis of the jaw (ONJ) was initially described in 2003 (Marx, 2003) and represents a complication of antiresorptive therapy especially prevalent in patients with cancer (Khan et al., 2015). Currently, it is denoted as medication-related osteonecrosis of the jaw (MRONJ), and its definition corresponds to an area of exposed bone or bone that can be probed through an intraoral or extraoral fistula that has persisted for longer than 8 weeks in patients who have received antiresorptive or antiangiogenic drugs, such as BPs, denosumab, sunitinib, bevacizumab and ipilimumab, who have neither undergone radiotherapy nor presented evidence of metastasis in this anatomic region (Ruggiero et al., 2014).

Denosumab consists of a fully human monoclonal antibody (IgG2) that mimics the action of osteoprotegerin, the physiological inhibitor of RANKL, binding to its analogue receptor, receptor activator of nuclear factor kappa-B (RANK), on the surfaces of osteoclasts (Charopoulos et al., 2011).

Denosumab acts as a regulator of bone remodeling, improving the structure, density and strength of the bone and significantly decreasing the incidence of fractures in patients with osteoporosis (Silva-Fernández et al., 2013). Denosumab also reduces the incidence of skeletal-related events in patients with cancer (Lipton, 2016) and is prescribed for the treatment of hypercalcemia of malignancy in these patients (Thosani & Hu, 2015).

Recent studies suggest that the rate of MRONJ in patients with cancer treated with RANKL inhibitors at a standard dose (120 mg of denosumab every 4 weeks) is similar to the rate found in patients receiving zoledronate (Henry et al., 2011, Van den Wyngaert et al., 2011); and it is significantly higher than the rate in patients with osteoporosis/osteopenia receiving denosumab (Papapolous et al., 2012), generally at a dose of 60 mg subcutaneously every 6 months (O'Halloran et al., 2014). Only 2.1% of all MRONJ cases diagnosed in patients with osteoporosis have been related to the administration of denosumab; therefore, the incidence of denosumab-related ONJ is considered very low (Aljohani et al, 2017). In 2016, Bagán et al. found only 15 cases in the literature, to which they added a series of 10 new patients (Bagán et al., 2016).

A case of MRONJ following a nonsurgical periodontal therapy in a patient with osteoporosis undergoing denosumab administration is described in the present study.

CASE REPORT

A 77-year-old woman was referred to the Special Care Dentistry Department of the University of Santiago de Compostela (Spain) in December 2016. Three months earlier, she had received basic periodontal therapy (scaling and root planing) for the treatment of chronic periodontitis (Figure 1). Since then, an asymptomatic bone exposure had been detected at the level of the lower incisors, which showed increased mobility (Figure 2). It should be noted that the patient's history included the discontinuous administration of BPs over the last 10 years, including ibandronic acid (150 mg

monthly) for discontinuous periods of 6–12 months, the last in 2013. In 2016, the patient started receiving biannual injections of 60 mg of denosumab subcutaneously (Prolia®, Amgen S.A., Barcelona, Spain), with a total of 2 injections; the last injection was administered in August 2016, and prednisone was concomitantly administered for 2 months.

The intraoral radiographies revealed the presence of a mixed radiolucent/radiopaque lesion suggesting bone sequestrations located between the lower lateral incisors (Figure 3). Cone beam computed tomography images confirmed the presence of an osteolytic lesion that destroyed the buccal and lingual bone plates that covered the incisor dental group and the lingual plate at the level of the lower left canine (Figure 4). The diagnosis of stage I MRONJ was established based on the clinical-radiological findings (exposed and necrotic bone in asymptomatic patients without evidence of infection).

Laboratory tests revealed C-terminal cross-linked telopeptide of type I collagen and N-terminal propeptides of type 1 procollagen serum levels fell within the postmenopausal reference range (223 pg/ml and 39.2 ng/ml, respectively). Serum levels of alkaline phosphatase, hydroxyvitamin D and calcium were normal.

Surgical treatment of the lesion was planned, and antimicrobial treatment with a 0.2% chlorhexidine mouthwash (twice per day) and doxycycline (200 mg/day) was established from 7 days prior to the surgery until 3 weeks after the surgical procedure. Extraction of the teeth involved in the sequestration and complete surgical debridement of the necrotic bone until reaching clinically vital bone margins were performed (Figure 5), followed by a primary closure. The patient is asymptomatic, without any evidence of bone exposure or continuity solution of the covering mucosa after 6 months of clinical and radiological follow-up (Figure 6).

DISCUSSION AND CONCLUSION

Taking into account that marketing and clinical use of denosumab were approved in 2010, many patients diagnosed with MRONJ were previously treated with BPs (Aljohani et al., 2017). It is likely that inhibition of bone resorption by BPs was still present when our patient started denosumab and osteonecrosis developed, which makes it difficult to establish the role of each of these drugs in the development of the MRONJ, as has been suggested in previous series (Bagán et., 2016). However, a time frame longer than 12 months between the discontinuation of BPs and the onset of denosumab treatment, as in the present case, is sufficient for the bone to recover its metabolic activity, and, consequently, to be able to attribute the appearance of MRONJ to denosumab (Pichardo & van Merkesteyn, 2016).

Our patient developed MRONJ 4 years after the suspension of BP treatment and after receiving only 2 injections of denosumab. The treatment duration represents one of the main risk factors for the development of BP-related ONJ (Palaska et al., 2009). Recently, it has been estimated that a period of 6.0 and 2.2 years of oral alendronate and intravenous zoledronate therapy, respectively, is required for 50% of patients to develop MRONJ (Fung et al., 2017). In contrast, cases of denosumab-related ONJ tend to occur early. The mean number of doses of denosumab administered to patients with osteoporosis from the series published by Bagán et al. (Bagán et al., 2016) was 3, but cases of MRONJ after the administration of a single dose of denosumab without a history of prior consumption of BPs have been described (Pichardo et al, 2013), confirming that no clear association between the dose or duration of denosumab treatment and the development of MRONJ has been confirmed to date (Yoshimura et al, 2017).

Most cases of MRONJ appear as a consequence of invasive dental procedures, mainly dental extractions (Diniz-Freitas & Limeres Posse, 2016; Bagán et al., 2016). Experts have noted that the risk of MRONJ after a surgical periodontal procedure that requires bone exposure and manipulation is comparable to the risk associated with dental extractions (Ruggiero et al., 2014). In contrast,

nonsurgical periodontal procedures should not be considered “high-risk” because these procedures do not cause evident trauma to the supporting tissues. Although the actual risk of developing MRONJ from these procedures is still unknown (Ruggiero et al., 2014), some authors have insinuated that MRONJ can be caused by lesser traumas in patients treated with denosumab than in patients receiving BPs (O’Halloran et al., 2014).

It has been suggested that periodontal disease is a significant triggering factor for the development of MRONJ (Yamazaki et al., 2012; McGowan et al., 2017). This possibility is of special importance in patients who receive denosumab, given in a published series, most cases of ONJ developed spontaneously, without any known triggering event like dentoalveolar surgery, ill-fitting dentures or local trauma (Yarom et al. 2017). Anaeerobic periodontopathogenic bacteria have been detected in nectrotic bone in MRONJ and in perilesional areas that are clinically healthy, including *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* (Hallmer, 2017). However, their role in the etiopathogenesis of MRONJ has not yet been clarified.

In the present case, nonsurgical periodontal treatment (scaling and root planing), which was likely the triggering procedure, was conducted only 1 month after the last injection of denosumab. There is no evidence in patients undergoing treatment with BPs that protocols of temporary drug interruption (i.e., drug holidays) can prevent the development of MRONJ secondary to invasive dental procedures (Diniz-Freitas & Limeres-Posse, 2016; Hasegawa et al., 2017). This is probably due to the fact that BPs, once incorporated into the bone matrix, remain united to the bone for years (e.g., the terminal half life of alendronate is approximately 10 years). In contrast to BPs, denosumab does not bind to hydroxyapatite; therefore, the effect of denosumab on bone remodeling, although more efficient, is less durable (Russel et al., 2008; Fukumoto & Matsumoto, 2017), and is mostly ineffectual within 6 months of treatment cessation (Ruggiero et al., 2014). Accordingly, some authors have proposed interruption protocols for denosumab of 6 months prior to a surgical procedure to facilitate bone regeneration (Epstein et al., 2013, Robinson & Scully, 2014).

There is no high-quality evidence on the efficacy of antibiotic prophylaxis for patients treated with antiresorptive drugs who undergo dental extractions. However, it appears that antibiotics combined with other perioperative measures, such as ostectomy and primary wound closure, exert a certain preventive effect (Gaudin et al., 2015; Diniz-Freitas and Limeres-Posse, 2016). The efficacy of antibiotic prophylaxis in preventing medication-related osteonecrosis of the jaw (MRONJ) before undergoing periodontal therapy for patients treated with receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors is, however, still unknown. The treatment modalities for MRONJ are typically classified as pharmacological and surgical. The management of stage I MRONJ includes the prescription of antimicrobial mouthwashes, clinical follow-up on a quarterly basis, patient education and the review of the indications for antiresorptive therapy (Ruggiero et al., 2014). However, the staging proposed by the American Association of Oral and Maxillofacial Surgeons (USA) underestimates the extent of the lesions, and computed tomography is required to obtain an accurate definition of the limits of the involved bone (Bedogni et al., 2014). In the present case, the advanced dental mobility and the presence of bone sequestration led us to choose a less conservative therapy in an attempt to completely remove the necrotic bone; otherwise, the risk of recurrence or progression of the disease would remain (Carlson & Basile, 2009; Carlson, 2014). In this regard, although conservative treatment can stop the progression of the disease and fight superinfection, better results have been obtained with surgical treatment; therefore, an aggressive surgical approach has been proposed as the first option in the treatment of MRONJ (El-Rabbany et al., 2017; Hayashida et al., 2017), even in the early stages of the condition (Ristow et al., 2015).

In summary, to our knowledge, this is the first case reported in the literature of MRONJ following nonsurgical periodontal therapy in a patient with osteoporosis treated with denosumab Unfortunately, to date there have been no evidence-based protocols aimed at preventing MRONJ in

patients with periodontitis who receive denosumab, even though its pharmacokinetics could justify its suppression 6 months before starting periodontal therapy. Dentists should be aware of the development of MRONJ related to new therapeutic modalities of osteoporosis (RANKL inhibitors) including denosumab. The risk of appearance of these lesions following a periodontal procedure and how to prevent them are still unknown.

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Figure Legends

Figure 1. Periodontal chart at first appointment.

Figure 2. Initial clinical image showing exposed bone in the buccal and lingual zones of the anterior mandible, without signs of infection.

Figure 3. Intraoral radiographs showing the presence of periradicular radiolucent areas.

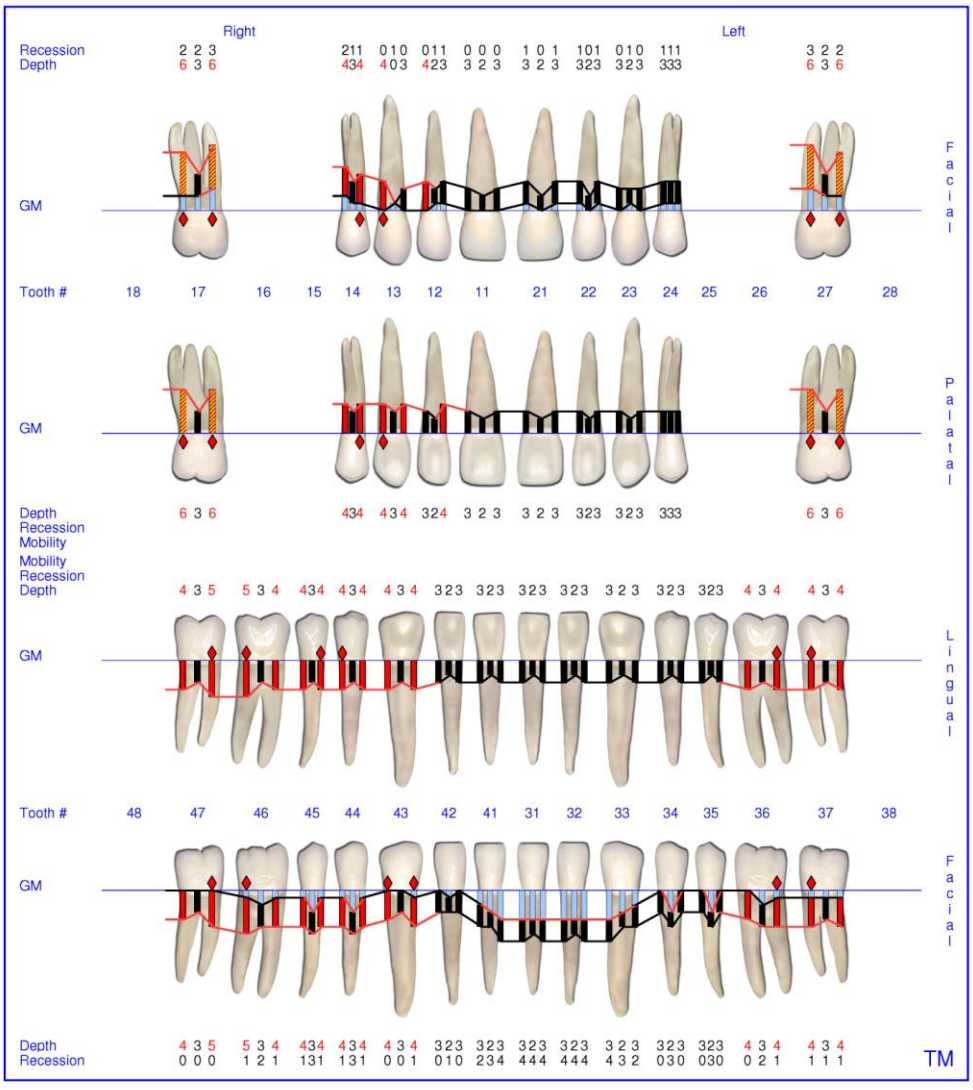
Figure 4. Cone beam computed tomography (CBCT) images showing the extent of the osteolytic process affecting the buccal and lingual cortical plates.

Figure 5. Surgical treatment consisting of extractions of the involved teeth, sequestrectomy and a complete surgical debridement of the necrotic bone until reaching the clinically vital margins, followed by primary closure.

Figure 6. Clinical and radiological aspect at 6 months after surgical treatment.

Periodontal Chart

Chart #:
Name:
Examiner:
Date:



Diagnosis

- ☐ Healthy
- ☐ Gingivitis
- ☐ Periodontitis
  - ○ Slight
  - ○ Moderate
  - ○ Severe
  - ○ Other

PSR

4	3	4
3	3*	3

Legend

Pocket Depth Change

Deeper
- >1mm and <2mm
- >2mm

Improvement
- >1mm and <2mm
- >2mm

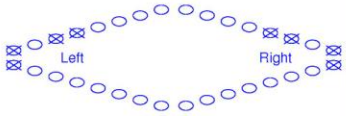
Depth Bar Indicators
- Depth >10mm
- Depth >= 6.0mm
- >=4.0mm & <6.0mm
- Depth < 4.0mm
- Recession
- Recession > 10mm
- Minimal Attached Gingiva
- No Attached Gingiva
- Bleeding
- Suppuration
- Bleeding and Suppuration
- Plaque
- Furcation
- I II III Mobility
- Implant
- Crown

Summary

PACIENTE 1 has 24 teeth, 45 of 144 sites or 31% of the pocket depths are greater than 4.0 mm

Bleeding:	24 sites (16%) bleeding, BOP = 46%
Suppuration:	0 sites (0%) suppurating
Recession:	22 teeth had some recession with 10 having recession equal to or greater than 3.0 mm
Furcation:	0 furcations were found
Mobility:	0 teeth had some degree of mobility
Plaque:	0 (0%) total sites have plaque/calculus, 0 (0%) interproximal, 0 (0%) lingual, 0 (0%) buccal and 0 (0%) molar

Plaque Sites



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