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Case Report

Osteonecrosis of the Jaws Induced by Antiresorptive Drugs:A Clinical Case Report

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Abstract

Antiresorptive drugs, such as bisphosphonates and the RANK-ligand inhibitor denosumab, are potent inhibitors of bone remodeling used to treat diseases affecting bone metabolism. Despite their wide use as therapeutic agents to reduce morbidity in cancer patients and to treat postmenopausal osteoporosis, in recent years, there have been reports of osteonecrosis of the jaws caused by bisphosphonate drugs and, even more recently, associated with RANK-ligand inhibitors (denosumab).

The purpose of this report is to briefly review the literature on osteonecrosis of the jaws induced by antiresorptive drugs and present a clinical case of osteonecrosis associated with the use of denosumab.

Keywords: Denosumab, Bisphosphonates, Osteonecrosis of the Jaws, Dental Implants.

Introduction

Bisphosphonates are synthetic analogues of inorganic pyrophosphate that have a high affinity for calcium. These agents are quickly absorbed from the circulation and selectively concentrate in bone, binding to the bone hydroxyapatite with high affinity [1]. During bone resorption, bisphosphonates are incorporated into osteoclasts, leading to cell inactivation and subsequent apoptosis, and reducing bone resorption and remodeling [2]. These drugs are indicated for the treatment of multiple myeloma, bone metastasis, hypercalcemia of malignancy, and for the prevention and treatment of osteoporosis and Paget's disease [3]. Although bisphosphonates have proven clinical efficacy, several cases of osteonecrosis of the jaws in patients receiving chronic bisphosphonate therapy have been reported beginning with the first case stating these adverse effects in 2003 [2, 4].

In 2010, the Food and Drug Administration (FDA) approved the subcutaneous administration (60 mg every six months) of a new drug, denosumab(Prolia®, Amgen Inc., California, USA), for post-menopausal women with osteoporosis at high risk of fractures. Denosumab was described by Pageau in 2009 as a human monoclonal antibody targeting RANK-ligand (RANK-L) with high affinity and specificity, thus preventing activation of the RANK receptor on the surface of osteoclasts. The absent RANKL/RANK interaction inhibits the formation, function, and survival of osteoclasts, thus reducing bone resorption of trabecular and cortical bone. In addition, denosumab mimics the endogenous effect of osteoprotegerin[5]. In contrast to bisphosphonates, RANK ligand inhibitors do not bind to bone and their effects on bone remodeling are mostly diminished within 6 months of treatment cessation [6]. Denosumab is currently the only RANKL-targeted therapy available, offering a new approach in the treatment of osteoporosis [7], binds RANKL with high affinity and specificity, thereby inhibiting osteoclastogenesis, as demonstrated by numerous studies [7,8], and also increasing bone mass and reducing the risk of fractures [9]. In addition, denosumab is suitable to the treatment of osteoporosis, treatment of primary and metastatic bone cancer, tumor giant cells and rheumatoid arthritis [10,11].

In 2007, the American Association of Oral and Maxil-

lofacial Surgeons (AAOMS) defined bisphosphonate-related osteonecrosis of the jaws as an exposure of necrotic bone in the mouth for more than eight weeks in patients who have never been irradiated in the head or neck and receiving these drugs [12]. In May 2014, the AAOMS recommended changing the nomenclature from bisphosphonate-related osteonecrosis of the jaw (BRONJ) to medication-related osteonecrosis of the jaw (MRONJ). This change is justified by the increasing number of osteonecrosis cases involving the maxilla and mandible associated with other resorptive agents such as denosumab [6]. The first case of osteonecrosis associated with denosumab was described by Taylor et al. in 2009 [13].

The definition of osteonecrosis of the jaws was modified to fit the current clinical reality. MRONJ was defined as the presence of exposed bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks in patients currently or previously treated with antiresorptive or antiangiogenic agents with no previous radiation therapy or metastatic disease to the jaws [6]. This report presents a case of osteonecrosis of the jaws in a patient receiving denosumab who underwent surgical implantation.

Case Report

E.R.M, a female, 57-year-old, Caucasian patient, visited the Specialization in Implant Dentistry Clinic at the Graduate Center of São Leopoldo Mandic - Vila Velha - ES for mandibular rehabilitation. She did not report any previous changes in overall clinical health and reported receiving only one dose of Prolia® (denosumab 60mg) to control mild osteoporosis. After tomographic and clinical assessment, four implants (all on four technique) [9] and an immediate provisional fixed prosthesis were installed in November 2013.

In May 2014, she returned for a definitive prosthesis. On clinical examination, the bone was exposed at the left distal implant and was accompanied by purulent discharge, which according to the patient, was present for over 60 days with no pain noted (Figure 1). The patient was prescribed 2% chlorhexidine gel to clean the area and amoxicillin 500 mg every 8 hours for 15 days. In addition, the serum CTX concentration was measured, and panoramic radiographs were obtained (Figure 2). She was re-examined 7 days later with no clinical improvement noted and showed changes in the CTX (0.36 ng/ml). We explored the lesion surgically (Figure 3) and carefully removed the bone sequestrum without performing curettage of the surgical cavity (Figure 4). The region was abundantly irrigated with saline (Figure 5), guided bone regeneration was performed using Alobone Poros (Osseocon Biomateriais, Rio de Janeiro-RJ, Brazil) (Figure 6), and the area was covered with an absorbable collagen membrane (Gen-Derm, Genius Baumer, Mogi-Mirim-SP, Brazil) (Figure 7). The flap was repositioned and sutured to completely cover the wound using 4.0 nylon sutures (Ethicon, Somerville, NJW L Gore, USA) and a simple suture pattern to secure the flap (Figure 8).

Figure 1: Second clinical assessment performed in May 2014. Showing osteonecrosis six months after installing the implants.

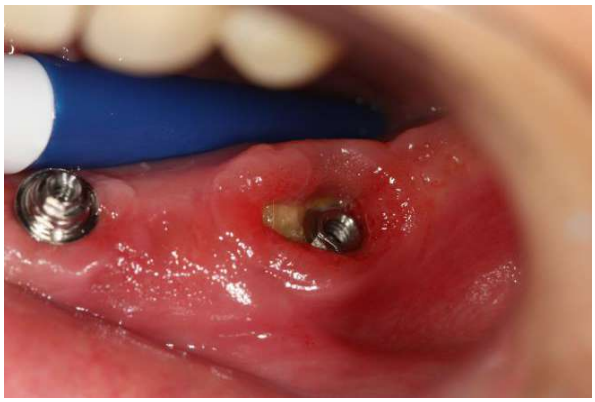


Figure 2. Panoramic radiography performed in May 2014. A radiolucent lesion is visible mesial to the implant adjacent to tooth #35.

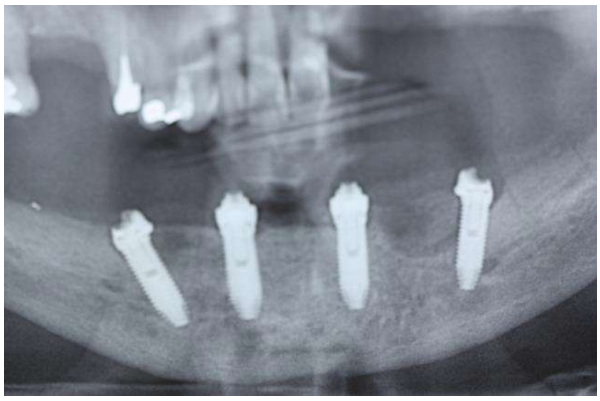


Figure 3: Surgical exploration of the osteonecrosis lesion. Exposure and excision of the bone sequestrum.

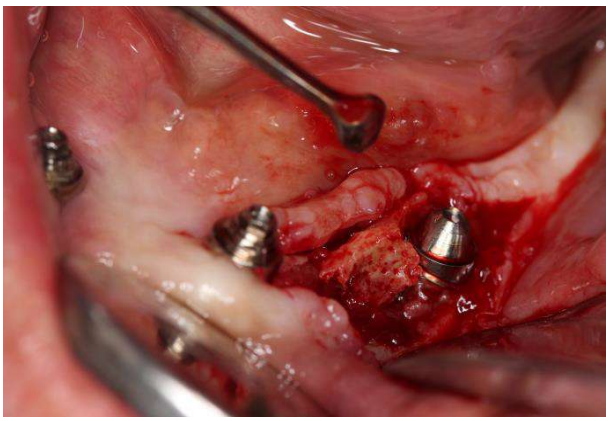


Figure 4: Excised bone sequestrum.
Removal of the bone sequestrum did not require curettage of the area.

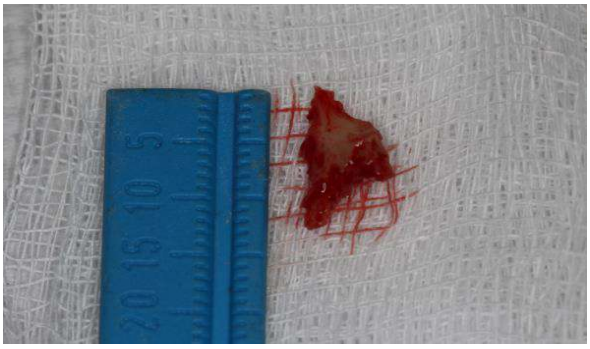


Figure 5: Clinical appearance post-excision.
The area was rinsed thoroughly with saline after careful and minimally atraumatic removal of the bone sequestrum.

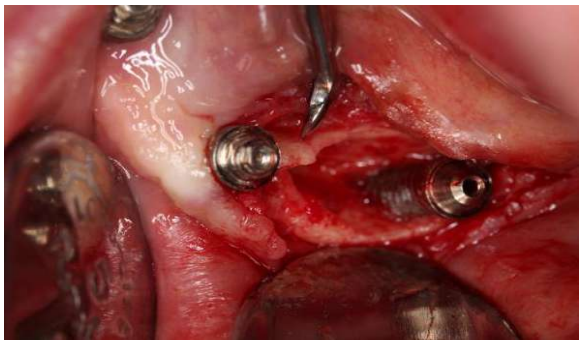


Figure 6: Guided bone regeneration.
The implanted biomaterial comprised Alobone Poros (Osseocon Biomateriais, Rio de Janeiro-RJ, Brazil).

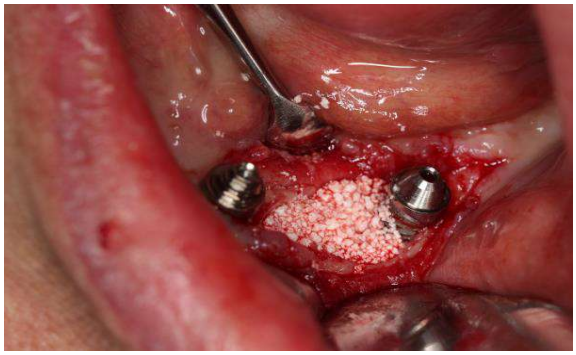


Figure 7. Covering the lesion.
The defect was covered with an absorbable collagen membrane (Gen-Derm, Genius Baumer, Mogi Mirim-SP, Brazil).

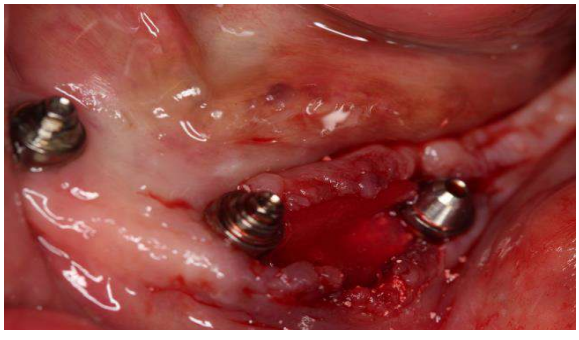
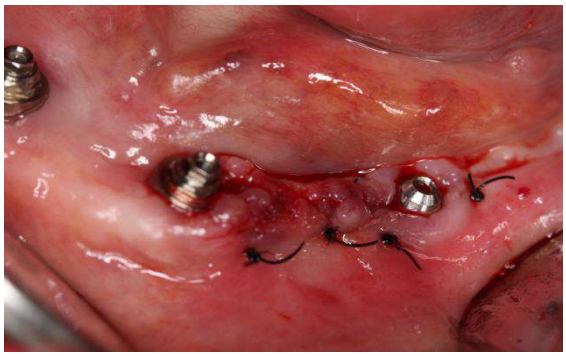


Figure 8: Surgical closure.
The total flap was closed using 4-0 nylon in a simple pattern.



Postoperatively, the amoxicillin dose was maintained 500 mg every 8 hours for 7 days, acetaminophen 750 mg every 6 hours as analgesia, and 0.12% chlorhexidine for oral rinsing until suture removal. There were no postoperative complications or reports of discomfort, pain, hemorrhage, or infection at the surgical site. After 30 days, the patient was re-examined, and good wound healing was observed in the peri-implant region (Figure 9). Panoramic radiography was repeated at 60 days postoperatively and showed good wound healing at the site and incorporation of the biomaterials (Figure 10).

Figure 9: Postoperative clinical appearance.
At 30 days postoperatively, the site has healed well.

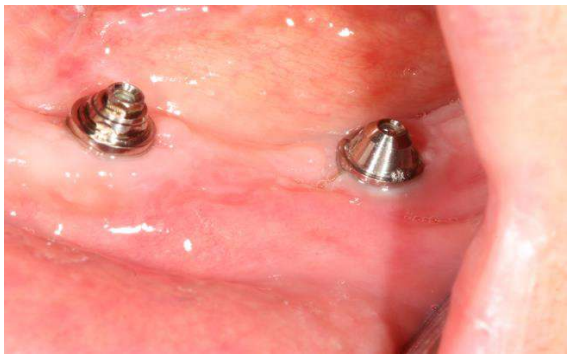
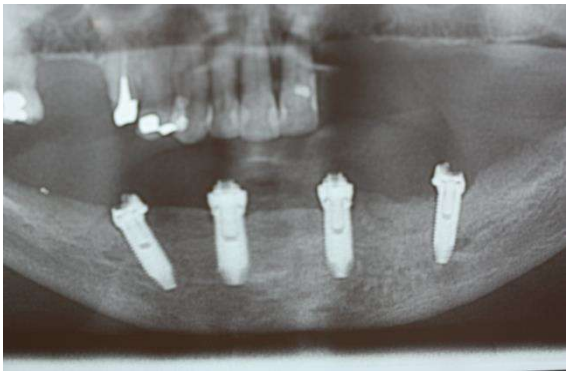


Figure 10: Postoperative panoramic radiography.
Radiography was repeated 60 days after removing the bone sequestrum. The biomaterial shows good incorporation into the jaw.



Discussion

This report describes the development of osteonecrosis in a patient administered denosumab, a drug used to treat postmenopausal osteoporosis and bone destruction due to rheumatoid arthritis or metastatic cancer. Osteonecrosis of the jaws is a complex disease most commonly associated with the use of bisphosphonates. Most reported cases of osteonecrosis of the jaws are associated with intravenous drug forms such as pamidronate and zoledronate[15]. The recent occurrence of osteonecrosis cases associated with denosumab use reflects its brief existence on the market, as it was approved by the FDA in June 2010. Clinical trials have shown that denosumab has a safety profile similar to that of bisphosphonates, and it is equally or more effective in preventing bone loss caused by postmenopausal osteoporosis, rheumatoid arthritis, or cancer treatment [5]. Denosumab also has excellent clinical results compared to bisphosphonates, with greater increases in the mineral density of bone, suppression of bone remodeling markers [16,17], and efficacy even in patients previously resistant to bisphosphonates [18]. We believe that the potent inhibition of osteoclastic activity by denosumab, played a central role in the development of osteonecrosis in this patient.

In a recent study of patients administered denosumab, the risk of developing medication-associated osteonecrosis was 0.04% (4 cases per 10,000 individuals) [13]. Due to this low risk of osteonecrosis, there was no contraindication to rehabilitating this patient with dental implants, but she was advised from the outset of the possible risks of lesions, even if low. The patient later stated, after observing the appearance of the lesion, that she consumed four doses of the drug preoperatively and not just one as she initially reported. This reaffirms the particular attention required for the clinical history, as sometimes the patient, even if unintentionally, may omit information that is important in choosing the most appropriate treatment. In this case, omitting the administered drug dose directly interfered with therapeutic planning.

The test used to evaluate the patient in this clinical case report, the serum CTX dosage, measures the C-terminal telopeptide concentration in the blood and is an auxiliary examination to assess the risk of developing osteonecrosis of the jaw. CTX values of less than 100 pg/ml indicate high risk, values between 100 pg/ml and 150 pg/ml indicate moderate risk, and CTX values above 150 pg/ml indicate minimal risk of developing the disease [14].

Various treatments have already been proposed for osteonecrosis of the jaw, such as hyperbaric oxygen therapy, low-power laser, platelet-rich plasma, antibiotics, and corticosteroids [3,4], but none have been proven effective. In this case, we chose antibiotic therapy, surgical removal of the bone sequestrum, and reconstruction using biomaterial, well established and documented in the scientific literature technique of guided bone regeneration [21].

Conclusion

Based on the current revised data describing medication-related osteonecrosis, the risk of developing the disease in osteoporosis patients using bisphosphonates, either orally or intravenously, as well as those using denosumab is real, but remains very low. Osteonecrosis of the jaws must be considered in any individual using the antiresorptive class of drugs. The long period of drug treatment presents an additional risk factor. Patients who will receive bisphosphonate or denosumab treatment should first consult a dental surgeon to remove any source of infection. This report describes a situation that may become increasingly common, considering the increased use of this drug class in the treatment of cancer and osteoporosis.

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