Importance of correct management of bisphosphonate-related osteonecrosis of the jaw: case report and literature review

Abstract:
Introduction: Osteonecrosis results from local and systemic factors that compromise blood flow in bone tissues, being relatively frequent in maxillary bones. In recent years, there has been an increase in the incidence of new cases of medication-related osteonecrosis of the jaw (MRONJ). Objective: The aim of this study is to report a case of hard palate osteonecrosis associated with the use of bisphosphonate and to review the literature on the major clinical features, diagnosis, and management of this disorder. Case report: An 84-year-old female patient presented with a lesion to the midline of the hard palate with exposed necrotic bone. Family members reported that the patient had been on ibandronate sodium for nearly 5 years. Based on clinical and radiographic findings, the diagnosis indicated MRONJ. The patient underwent a surgical procedure for debridement of necrotic bone and closure of the exposed tissue by means of Z-plasty. After a 4-month follow-up, there were no clinical and radiographic signs of recurrence. Conclusion: The present case and the literature highlight the importance of proper anamnesis combined with clinical, radiographic, and laboratory findings to make an accurate diagnosis in order to provide the best therapeutic approach. In addition, the importance of dental surgeons knowledge about the association between bisphosphonate therapy and osteonecrosis is very important, given the several indications of this drug and, thus, the high probability of attending to patients treated with this medication, with the aim of reducing the occurrence of new cases of MRONJ and, consequently, morbidities and their aggravation.

Keywords: Bisphosphonate-associated osteonecrosis of the jaw; Osteonecrosis; Diagnosis; Treatment Outcome
INTRODUCTION

In recent years, there has been an increase in the incidence of new cases of medication-related osteonecrosis of the jaw (MRONJ), which is the main complication from the use of these drugs. In the dental setting, this complication often occurs in patients on bisphosphonate therapy subjected to clinical procedures such as tooth extractions and periodontal treatment without proper precautions. However, these lesions can develop spontaneously in association with small injuries to the oral mucosa.

Bisphosphonates are widely used in the treatment of bone disorders, such as osteoporosis, Paget’s disease, multiple myeloma, and osteolytic bone metastasis. Bisphosphonates may be classified into at least two groups with different molecular modes of action: non-nitrogen containing bisphosphonates, and the more potent nitrogen-containing bisphosphonates (which include pamidronate, alendronate, and others).

The etiopathogenesis of MRONJ has not been clearly established; however, its mechanism of action is related mainly to inhibition of bone resorption resulting from the inhibition of osteoclastic activity and induction of osteoclast apoptosis, as well as antiangiogenic effects, increase in soft tissue toxicity, and immune system dysregulation. Furthermore, studies have shown that bisphosphonates can affect osteoclast-mediated bone resorption in a variety of ways that include effects on osteoclast recruitment, differentiation, and resorptive activity.

MRONJ is defined by the presence of necrotic areas within the bones that do not heal in less than 8 weeks in patients who were or are on systemic use of bisphosphonates or and who were not subjected to head and neck radiation therapy. In early stages, a radiographic workup may fail to detect manifestations of the disease and patients may not present with any symptoms. When bone exposure is more pronounced, the most common clinical sign is the presence of rough areas in the soft tissue around the necrotic bone, with possible signs of secondary infection. In advanced stages, patients may complain of intense pain and paresthesia.

The protocol for prevention of MRONJ should include thorough dental assessment of all patients to be treated with bisphosphonates in order to verify the presence of possible infections and compromised teeth. If it is possible to postpone bisphosphonate therapy, preventive dental procedures and invasive dentoalveolar surgeries should be performed to eliminate foci of infection. Maintaining good oral hygiene is paramount and all patients should be informed of how important that is.

Treatment of MRONJ is based on the stage of evolution of the disease and on the extent of the lesions. Conservative therapy includes the use of antibiotics, painkillers, antiseptics, and antifungals. In more advanced stages and in those which are refractory to treatment, invasive surgical procedures are recommended, including curettage and debridement, sequestrectomy, and segmental or marginal resection of the necrotic bone tissue.

Accordingly, the aim of this study is to report a case of MRONJ in an 84-year-old female patient and to review the literature on clinical and radiographic aspects of this condition, highlighting the importance of its diagnostic accuracy and proper management.

CASE REPORT

A dark-skinned, 84-year-old female patient was referred to the Stomatology Clinic, for assessment of a denture-induced lesion to the hard palate. The anamnesis indicated mild pain in the region for 4 months, coinciding with the placement of a new denture. The patient also revealed she had Alzheimer’s disease, was on monotherapy with clonazepam, and had a family history of diabetes.

On intraoral examination, there was a lesion along the midline of the hard palate measuring 1.0 cm in diameter, with an ulcerated central area and raised and erythematous borders (Figure 1a). Based on the clinical features of the lesion, its location, and the history of lesions caused by ill-fitting dentures (which leads to ischemia to the hard palate tissue, compromising blood irrigation of the minor salivary glands of the anatomic site), the patient was initially diagnosed with necrotizing sialometaplasia.

Complementary tests and exams (whole blood count, fasting glucose level, occlusal X-ray, and panoramic X-ray) were requested (Figure 2), but their results were unnoteworthy. In the follow-up visit at 3 weeks, the ulcerated area was found to have enlarged and the central area of the lesion revealed bone necrosis (Figure 1b). Given the clinical picture, family members were asked about whether the patient was using any other medication that was not informed in the first appointment. It was found the patient had been taking ibandronate sodium (150mg monthly) for approximately 5 years to treat osteoporosis. The diagnosis of MRONJ was then made.
Figure 1. Clinical aspect of the ulcerate lesion on the hard palate. (A) Initial aspect of the lesion, with raised and erythematous borders and ulcerated central area. (B) Clinical aspect of the lesion after 3 weeks, showing central area of bone necrosis.

Figure 2. Panoramic and occlusal radiographs with aspect of normality.

The patient was referred to the Oral and Maxillofacial Surgery Outpatient Clinic for treatment in accordance with the American Association of Oral and Maxillofacial Surgeons (AAOMS) guidelines. The disease was classified as stage II. Serum carboxy-terminal cross-linking telopeptide of type I collagen (CTX) value was 143 pg/mL. Also, a surgical procedure under local anesthesia was carried out for debridement of the necrotic bone, and Z-plasty, a surgical technique commonly used to improve the functional and cosmetic appearance of the area, was performed for closure of the exposed region.

Analgesic and anti-inflammatory drugs were prescribed for relief of pain and inflammation, in addition to an antibiotic to prevent possible surgical wound infection. The lesion healed properly without bone exposure or postoperative infection and the patient remains under follow-up. After a 3-month follow-up, there are no clinical and radiographic signs of recurrence (Figure 3).

DISCUSSION

Bisphosphonates are analogous to inorganic pyrophosphates, which bind selectively to hydroxyapatite and accumulate at sites of active bone remodeling. These drugs inhibit bone resorption, inducing the inactivation of osteoclasts, as well as their function and maturation. As both the mandible and the maxilla have large blood supply and a high rate of bone remodeling compared with other bones, bisphosphonates tend to accumulate in these anatomic structures. Therefore, the follow-up and dental assessment of patients treated with this medication and other drugs, such as Denosumab and antiangiogenic drugs which alter the bone metabolism, are essential for good outcomes. The present case report underscores the importance of proper diagnosis and treatment of this disorder.

AAOMS establishes three diagnostic criteria to determine whether a patient has MRONJ: 1- Current or previous bisphosphonate therapy; 2- Osteonecrosis in the maxillofacial region for at least 8 weeks; and 3- No radiation therapy applied to the maxilla. The American Society for Bone and Mineral Research (ASBMR) also adopts the AAOMS criteria for the diagnosis of osteonecrosis of the jaw.

All these
diagnostic criteria were observed during anamnesis and physical examination of the patient described in the present report.

Owing to the association of osteonecrosis with several factors, it is extremely important that the patients’ records be properly filled in during clinical examination and anamnesis\(^5,9\). If this is neglected, this disorder could be misdiagnosed. This is consistent with the present report, since the correct diagnosis of the lesion was possible only after the disclosure of family members about the therapy with ibandronate sodium, a drug that is largely used for the treatment of osteoporosis.

Although some studies have suggested that MRONJ may develop spontaneously without an evident cause, several risk factors are currently associated with the higher incidence of this disorder\(^10,13,16\). A few local factors stand out in this case, namely, oral surgery, denture-induced injury, and oral ulcers; in addition to systemic factors such as obesity and diabetes; and demographic factors such as age, sex, alcohol consumption, and smoking. Moreover, genetic factors could also play a role\(^3,16\). In the case reported herein, the repetitive mechanical injury caused by the ill-fitting denture might have contributed to the development of the lesion, since this type of injury predisposes to MRONJ.

The radiographic findings of MRONJ have been described in the literature as osteosclerosis, increased bone density, thickening of the lamina dura, subperiosteal bone deposition, widening of the periodontal ligament space, and postoperative remodeling failure\(^4,19,20\). According to a review conducted by Arce et al.\(^19\), these radiographic findings are not specific to MRONJ, as they may be present in other conditions, such as osteomyelitis, osteoradionecrosis, metastatic cancer, and Paget’s disease.

However, no specific radiographic finding associated with this necrotic process was found in our case report. Furthermore, assessment of the radiographic image may not provide significant data and this could be related to limited decalcification in the early stages of development of this pathology\(^4\). Therefore, this type of complementary exam is not included in the diagnostic criteria for MRONJ; it only provides clinicians with information about the course, extent, and progression of the disease\(^19,20\).

The route of administration, dosage, and length of therapy with bisphosphonates, as well as age older than 65 years, are important in determining the risk of developing osteonecrosis of the jaw\(^4,9\). In the present case, the patient had been taking oral ibandronate sodium for 5 years. Studies have shown that intravenous bisphosphonates require a shorter time to cause this type of lesion when compared to oral bisphosphonates, which would need at least 3 years before causing MRONJ\(^1,5,10\).

Research has suggested that serum CTX levels can estimate bone remodeling and resorption, demonstrating that patients on oral bisphosphonates for over 3 years whose CTX is lower than 150 pg/mL are more likely to develop MRONJ after surgical procedures\(^10,21\). Serum CTX level in the present case was 143 pg/mL and was considered to be a moderate risk factor, as described by Marx et al.\(^22\). On the other hand, Fleisher et al.\(^23\) assessed 26 patients with a history of bisphosphonate use and found serum CTX levels lower than 150 pg/mL. In their study, the authors observed that all of the 26 patients, among whom 20 had been subjected to tooth extractions and another six had undergone surgical procedures for MRONJ treatment, showed good healing after surgical management, even with low serum CTX levels. As with their study, the present case showed excellent healing of the necrotic area after the surgical procedure.

Furthermore, according to Garnero\(^24\), the current biochemical markers of bone metabolism, including the CTX levels, have some limitations. These include 1) a lack of tissue specificity for bone, as type I collagen is widely distributed in different organs, 2) an inability to distinguish the metabolic activity of the different skeletal compartments, although they can be differently affected by diseases and treatments, 3) they reflect mainly the
function of osteoblast or osteoclast and not the activity of osteocytes although these cells play a pivotal role in the maintenance of skeletal integrity, and 4) they are all protein-based markers, although circulating mRNA could also be of value as early biomarkers. Together, these observations suggest that CTX measurement might not be a sensitive in predicting the risk for MRONJ after surgical procedures. Thus, it is necessary to develop more sensitive alternative strategies.

The clinical staging system for MRONJ was developed by Ruggiero et al. and has been adopted by AAOMS. According to this system, patients with stage 0 disease do not show any clinical evidence of necrotic bone, but nonspecific clinical and radiographic findings and symptoms are observed.

Patients with stage 1 disease have exposed bone or fistula that probes to bone and are asymptomatic without any evidence of infection. Stage 2 is characterized by exposed bone or fistula that probes to bone associated with infection, pain, and erythema in the region of bone exposure with or without purulent drainage. Stage 3 is characterized by bone exposure associated with pain and inflammation of adjacent soft tissues or secondary infection, in addition to pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis that extends to the inferior border of the mandible or maxillary sinus floor.

Minimally invasive surgical procedures are the most widely used for the treatment of MRONJ. Even though the surgical treatment for stage 3 MRONJ is largely accepted, there are different recommendations for surgical treatment of stage 2 disease, especially in U.S. and German guidelines. In a Brazilian population, Lopes et al. evaluated the efficacy of the surgical therapy in 46 patients with MRONJ. These authors observed complete healing of the MRONJ region in 40 of the 46 patients, showing a high rate of clinical control. Similarly, Bodem et al. obtained very good outcomes with surgical therapies in stage 2 and 3 patients treated with zoledronic acid. In agreement with the previously mentioned study, our patient had stage 2 MRONJ, according to AAOMS guidelines and, therefore, she was subjected to surgical treatment for debridement of the necrotic bone, with postoperative healing.

Magopoulos et al. observed that the group of patients who stopped taking bisphosphonate for more than 6 months subjected to antibiotic therapy and debridement of the necrotic bone showed total healing of the lesion compared with the group that did not quit taking the medication. Nevertheless, Khosla et al. did not obtain better results with the discontinuation of bisphosphonates. In the present case, bisphosphonate therapy was not discontinued because of osteoporosis presented by the patient.

The higher incidence of new cases of MRONJ has recently prompted new research into the major complications and risk factors associated with this disease, improving the understanding of health professionals and patients about this condition and providing some guidelines for an efficient treatment protocol, with improvement of the patient conditions and without comorbidities for those individuals that use bisphosphonates.

The clinical case reported herein and the literature findings highlight the importance of proper anamnesis combined with clinical, radiographic, and laboratory findings to make an accurate diagnosis and to select the best therapeutic approach. In addition, the importance of dental surgeons’ knowledge about the association between bisphosphonate therapy and osteonecrosis is also stressed, given the several indications of this drug and, thus, the high probability of attending to patients treated with this medication, with the aim of reducing the occurrence of new cases of MRONJ and, consequently, morbidities and their aggravation.

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from the patient included in the study.

REFERENCES


