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Case Report

Medication-related Osteonecrosis of the Jaw. Two Cases

Manuel A Linares C[1]*, Marisol Benito[2] and Mariluz Benito[3]

[1]*Oral Surgeon, Faculty of Dentistry, University of Zulia, Maracaibo, Venezuela*

[2]*Periodontist, Department of Oral Medicine. Faculty of Dentistry, University of Zulia, Maracaibo, Venezuela*

[3]*Pediatric Dentist, Clinical and Pathology Area, Research Institute, Faculty of Dentistry, University of Zulia, Maracaibo, Venezuela*

***Corresponding Author**: Manuel A Linares C, Oral Surgeon, Faculty of Dentistry, University of Zulia, Maracaibo, Venezuela.

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Abstract

Medication-related osteonecrosis of the jaw, is defined as the exposure of necrotic bone in the maxillofacial region spontaneously or after a dental procedure, more than 8 weeks after the clinical diagnosis, in a patient with antiresorptive and/or antiangiogenic therapy, with no history. of radiotherapy in said region. The purpose of this investigation is to describe the clinical characteristics of osteonecrosis of the jaws associated with medication, by presenting two cases with a history of treatment with bisphosphonates who attended the consultation meeting the clinical criteria of osteonecrosis of the jaws associated with medication. The use of anti-resoperative and/or antiangiogenic therapies for various diseases may be related to the presence of Osteonecrosis of the Maxillae. It is important to highlight the complications related to the prescription of these drugs, as well as the multidisciplinary work for prevention, especially in patients who have a higher risk of suffering from it.

Keywords: *Osteonecrosis; Jaws; Medication; Antiresorptive; Bisphosphonates*

Abbreviations

MRONJ: Medication-related Osteonecrosis of the Jaw; BRONJ: Osteonecrosis of Jaws Induced by Bisphosphonates; AAOMS: American Association of Oral and Maxillofacial Surgery; BF: Biphosphontates (BF); HUM: University Hospital of Maracaibo; AOPES: Attended the Dental Care of Systemic Patients; TID: Ter in Die; IV: Intravenous; PO: By Mouth; CTX: C-terminal Crosslinking Telopeptide; PRF: Platelet-rich Fibrin; CA: Cancer; bmps: Morphogenetic Proteins

Introduction

Medication-related osteonecrosis of the jaw (MRONJ), was first described (Marx, 2003), 1 in a series of 36 lesions of bone exposure in the jaws in patients under treatment with Pamidronate or Zoledronic Acid; with the name of "Osteonecrosis of Jaws induced by bisphosphonates" (BRONJ) [1-3]. In 2007, the American Association of Oral and Maxillofacial Surgery (AAOMS) standardized the definition of BRONJ, such as the presence of exposed bone in the maxillofacial region that does not heal after 8 weeks of clinical diagnosis in a patient who has been exposed to therapy with bisphosphonates (BF), with no history of radiotherapy in the craniofacial region; exposure of bone tissue may occur spontaneously or after an invasive stomatologic procedure [4-7].

In 2014, the Special Committee of BRONJ of the AAOMS, requested the change of nomenclature to "Osteonecrosis of the maxilla related to medication" (MRONJ), justified by the appearance of new cases of osteonecrosis of the jaws associated with bisphosphonates, other antiresorptive therapies (Denosumab®) and antiangiogenic [8]. The pathophysiology of the disease is not entirely clear, however, the hypotheses proposed try to explain the frequent location in the jaw, the altered bone remodeling or the excessive suppression of bone resorption [9-11], the inhibition of angiogenesis [12], constant microtrauma, suppression of innate or acquired immunity, vitamin D deficiency [13], soft tissue toxicity due to BF, inflammation and/or infection [14].

The MRONJ is located more frequently in the jaw (65% of the cases) and in two thirds of the patients there is a history of trauma, extraction, implant or any other type of oral surgery, with the rest of the cases of appearance spontaneous [15]. Clinically, lesions at the intraoral level are presented as single or multiple areas of exposure of necrotic bone to the buccal environment. Other signs and symptoms include: pain, tooth mobility, swelling, purulent exudate, paresthesia of the affected area. At extraoral examination, the presence of fistulas and increased soft tissue volume of the cervicofacial region can be observed [16].

In the studies of images and radiographs, several degrees of osteosclerosis and osteolysis are frequently observed in a mottled trabecular pattern, periosteal reaction, bone fragmentation and bone abductions. Observed in the panoramic or periapical radiography, a thickening or loss of the lamina dura, a widening of the space of the periodontal ligament, and the persistent extraction alveoli [17,18].

The scintigraphy, although lacking in specificity and high resolution, is useful in the diagnosis of MRONJ; evidencing that the uptake of the isotope can take place in a metabolically active area, where the blood flow is not substantially interrupted, which is not the case in the necrotic bone. However, the sites around the necrotic areas with metabolic activity may reflect inflammatory changes or infection that implies increased bone turnover, which will also be occupied by isotopes [19,20].

Histologically, MRONJ is characterized by the presence of bone necrosis, with heterogeneous characteristics, showing areas of bone affected with chronic inflammation and leukocytic infiltrate, plasma cells and microbial colonies that are observed towards the surface of the bone. In addition to a significant number of osteoclasts [3,21,22]. The aim of the treatment is focused on the prevention of the clinical-pathological entity, the AAOMS Special Committee in MRONJ supports a multidisciplinary approach for the treatment of patients who benefit from antiresorptive or antiangiogenic drugs. The application of clinical and imaging stomatological examination, the implementation of adequate preventive measures before starting antiresorptive and antiangiogenic treatment reduces the risk of MRONJ [8,23].

The treatment of the ONJM is complex and controversial, the AAOMS has developed treatment recommendations based on the different stages of MRONJ (See table 1). If the systemic conditions permit, the interruption of bisphosphonates can be beneficial in the stabilization of MRONJ, reducing the risk of development in a new site and the symptoms clinical However, it should be noted that many bisphosphonates with medium-long lifetimes and MRONJ can be seen long after the bisphosphonate therapy has ended.

Stages	Therapeutic strategies
At risk- No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates	• No treatment indicated • Patient education
Stage 0- No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms.	• Systemic management, including use of pain medication and antibiotics
Stage 1- Exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection	• Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2- Exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	• Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse • Pain control • Debridement to relieve soft tissue irritation and infection control
Stage 3- Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e. inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement or resection for longer-term palliation of infection and pain

Table 1: *Stages of the MRONJ and therapeutic [8].*

Aim of the Study

The aim of this study was to report the clinical characteristics of two cases of MRONJ and its therapeutic approach.

Case Report

A series of cases of two male patients with a diagnosis of Osteonecrosis of the Maxillary associated with medication who attended the dental care of systemic patients (AOPES) in the dentistry service of the University Hospital of Maracaibo (HUM).

Case 1

A 76-year-old male patient attended the Systemic Patients Care Service (AOPES) of the Dentistry Service of the University Hospital of Maracaibo (HUM), presenting an increase in tongue volume, pain and dysphagia since approximately 7 days of evolution. The patient is in hospitalization due to chemotherapy treatment, presenting a history of multiple myeloma under therapy with Ibandronic acid (Bondronat®) 6g/6mL for PO for a year, Thalidomide and Dexamethasone. In the physical examination, mucocutaneous pallor, dry skin, deformity in the right femoroacetabular joint with inability to walk is observed. In the intraoral examination, there were multiple areas of bone

exposure in the jaw, ulcerations of the mucosa, referring to more than 8 weeks accompanied by halitosis, drainage of spontaneous purulent exudate; partial edentulism, change of coloration and signs of inflammation in the marginal gingiva and the presence of abundant dentobacterial plaque (Figure 1). Concluding with the clinical diagnosis: "Osteonecrosis of the Mandible induced by bisphosphonates". It was suggested to initiate periodontal therapy, through the reinforcement of oral hygiene, mouth rinses with Bicarbonated Water TID, antimicrobial therapy with Amoxicillin-Clavulanic Acid 875 mg/125 mg IV TID + Metronidazole 500 mg IV TID and topical application of vitamin E capsules 400 mg TID.

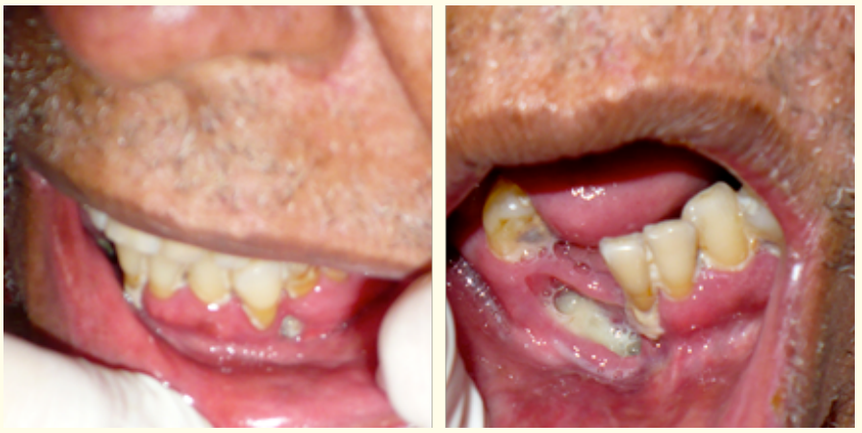

Figure 1: *Intraoral photography: Multiple areas of the bones in a jaw are observed, with presence of pus, bacterial plaque and periodontal disease.*

Case 2

A 72 year-old male patient attended the Periodontics clinic, presenting bone exposure in the right posterior maxillary area. He reported having a history of Diabetes Mellitus 2, prostate cancer in remission, carrier of removable partial denture, treatment with Zoledronic Acid (Aclasta®) IV for 2 years, suspended for a year by medical order.

In the physical examination, no relevant findings were found. Intraoral examination revealed local irritants, defective restorations, dental caries, partial edentulism, periodontal disease, injury was corroborated, in the posterior right area associated with the presence of exostosis of 12 weeks of evolution (Figure 2A). Laboratory tests were indicated: complete hematology, haemostasis, blood chemistry, serology and C-terminal crosslinking telopeptide (CTX). A dental panoramic radiographic study is requested the complementary exams for the moment were within normal ranges, without alterations, just as the CTX was at 300 pg, at low risk. In the panoramic radiography, change of bony trabeculation was observed in the molar region of the first quadrant, accompanied by an extended radiopaque line from the 16th area to the maxillary tuberosity (Figure 2B). We proceeded to perform surgery under local anesthesia where bone sequestration was removed, PRF placement in the surgical bed, prophylactic antibiotic therapy prior to the intervention, at the moment glycemia levels of 77 mg/dl were presented.

After asepsis and antisepsis, under local anesthesia at 2% with adrenaline 1: 100,000, a vestibular flap was made in a straight advance with two vertical discharges in the vestibular, visualizing the entire bone defect, removing necrotic tissue at the edges, irrigating with a solution of 0.9% sodium chloride, at the same time a peripheral route was taken to obtain 18cc of venous blood to obtain platelet-rich fibrin (PRF), the centrifugation technique was performed at 3000 rpm for 10 minutes. minutes and the PRF gel were extracted from the test tubes, which was compressed into gauze to form 3 membranes that were placed in the surgical bed, the surgical bed was completely covered without tension and suturing edges of the mucosa with Vicryl 3-0.

In the postoperative period, Amoxicillin - Clavulanic Acid 500 mg/125 mg PO TID was prescribed for 7 days, Clindamycin 500 mg PO TID for 7 days, ibuprofen 400 mg PO TID for 5 days and mouth rinses with chlorhexidine 0.12% TID for 15 days, in addition all the indications for the care of the treatment were given. Presenting a favorable and asymptomatic evolution, in the postsurgical control at 07 days, 15 days, a month and then at 6 months, going to the visits of control of bacterial plaque and periodontal maintenance (Figure 3).

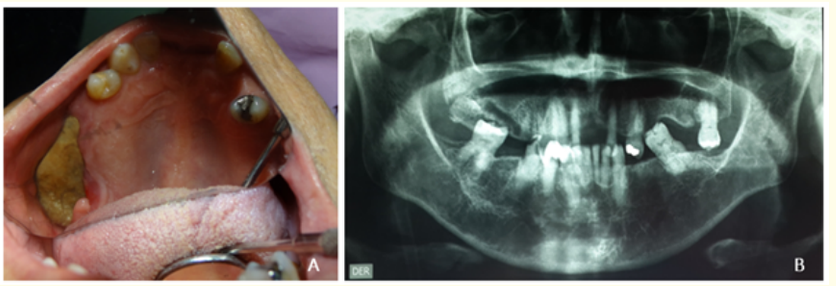

Figure 2: *Preoperative Photographs: a. Intraoral, where the presence of bone exposure in the posterior alveolar region of the right maxilla that extends to the tuberosity was evidenced b. Panoramic Radiography, where the presence of bone sequestration is evident on the right posterior alveolar ridge of the maxilla, causing a segment fracture.*

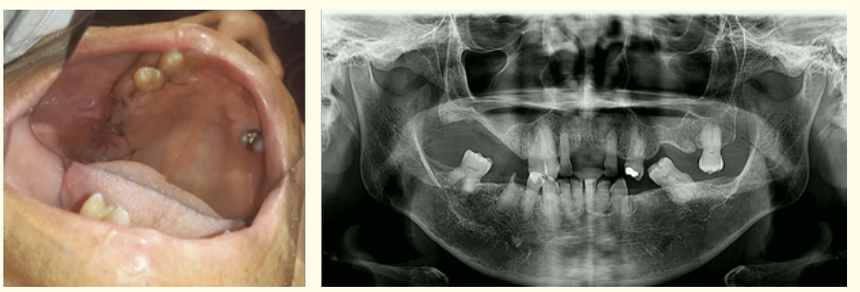

Figure 3: *Post-operative: a. Intraoral photography where frank scarring of the post-surgical zone is evident, without the presence of fistulas or secretions. b. Panoramic X-ray.*

Results and Discussion

The use of antiresorptive and/or antiangiogenic therapies for various pathological clinical entities may be related to the presence of Osteonecrosis of the Maxillary, as collateral damage in the jaws. In this sense, it is important to highlight the complications related to the use of these drugs, as well as the training of doctors and dentists, so that a joint preventive action can be carried out in these patients, especially in those who present a higher risk. of suffering from drug osteonecrosis.

In the present series of cases, two clinical cases of patients with treatment with bisphosphonates who presented the intravenous route as a route of administration for the treatment of malignant neoplasms are described. However, the route of intravenous administration is used for oncological indications. The effects of intravenous BFs in the bone can persist even 12 years after discontinuing the treatment, they seem to have the same behavior with respect to the use of the oral dose [24]. The incidence of osteonecrosis has been recorded from 0.8 to 12% with parenterals and has been lower with those of oral administration (estimated between 0.01 and 0.04%), with a latency time of up to three years with intravenous administration and disease what needs to be treated [25].

However, in one of the cases presented, he was treated orally, developing MRONJ over a period of one year, in contrast to what was described in the literature. However, the local and systemic conditions of the patient, such as the presence of infectious processes, inflammatory diseases and constant occlusal trauma, promote continuous bone remodeling, a process of scarring and altered regeneration, playing a fundamental role in the pathophysiology of the MRONJ [26].

Over the last few years there have been different updates on MRONJ, however, there is no effective prevention protocol and prospective studies are missing. Therefore, it is mandatory, before initiating the treatment with antiresorptive or antiangiogenic agents, to carry out a previous odontological review that eliminates the predisposing factors: periodontal disease, poorly adjusted removable prostheses, need for extractions [27].

The therapeutic strategies of the MRONJ have been debated in the literature starting from the conservative approach to the most radical treatment. Some very conservative guidelines (oral hygiene, topical chlorhexidine and bimodal intravenous antibiotic therapy with previous culture, hyperbaric chamber) to surgical guidelines that include curettage to obtain vascularized bone, removal of mobile fragments, marginal or segmental resections that include complex bone reconstructions, depending on the extent of the necrosis, the stage and evolution of the disease. In the case described of the patient with a history of CA of the prostate, sequestrectomy was indicated in the right tuberosity and the application of platelet concentrates in the surgical bed, supporting in the literature where Salgado-Peralvo., et al. [28], described the use of Platelet Rich Fibrin (PRF) in a patient with MRONJ, being promising due to the association of this condition with a suppression of bone remodeling, antiangiogenic effects, a reduction in the immune response and soft tissue toxicity.

Kim., *et al*. [29], should be considered of significant importance since it was the first to show promising results in the treatment after the application of L-PRF in a group of patients who presented BRONJ. These authors evaluated the action of the morphogenetic proteins (BMPs) associated with the matrix of L-PRF by the possibility of contributing to the induction of bone healing and the added leukocytes in the platelet concentrates by their antimicrobial activity, immunological regulation and the ability to produce large amounts of vascular endothelial growth factor, and although more studies are needed to elucidate these functions, they obtained quite positive results.

Conclusion

The development of MRONJ, is a clinical picture of important repercussion for the patient and for the dentist. Its incidence will increase in the coming years, due to the increase in the consumption of these drugs. The preventive and therapeutic measures should be known by dentists and medical specialists who treat this pathology. Nevertheless, therapeutic success depends on several factors such as the location of the lesion, the size of the lesion or the moment of diagnosis, so that, despite they are quite encouraging results and they open a new path in the treatment of this pathology, more studies are needed to demonstrate the true efficacy of the therapy.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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