

**Stage 3 Medication-related osteonecrosis of the jaw (MRONJ): successful conservative treatment with ozone therapy**

**Osteonecrose dos maxilares associado ao uso de medicamentos (OMAM) em estágio 3: tratamento conservador bem sucedido com ozonioterapia**

**Osteonecrosis de los maxilares relacionada con medicamentos (ONMRM) en estado 3: tratamiento conservador exitoso con ozonoterapia**

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**Abstract**

Background: The medication-related osteonecrosis of the jaws is an uncommon severe complication following utilization of certain drugs, but its occurrence has great impact on the patient's quality of life. Various treatment modalities are used to manage the lesions,

including conservative and surgical procedures. Ozone (O<sub>3</sub>) therapy emerges as *an* alternative of non-invasive therapy that can benefit the affected patient without surgical risks, due to the potential of stimulate the activation and migration of fibroblasts in an injured area. Case presentation: This article reports the conservative treatment of a maxillary stage 3 medication-related osteonecrosis, in a partial edentulous patient previously treated with intravenous bisphosphonate for multiple myeloma, who had previous cardiac illness. Conclusion: The stage 3 medication-related osteonecrosis was successfully treated with ozone (O<sub>3</sub>) gas injection and irrigation with ozonated water, with full coverage of the bone and no suppuration or pain at the end of the treatment. No recurrence was seen after twelve months of follow-up.

**Keywords:** Bisphosphonate-associated osteonecrosis of the jaw; Ozone; Osteonecrosis; Therapeutics.

### Resumo

Introdução: A osteonecrose dos maxilares associada ao uso de medicamentos é uma complicação grave incomum após o uso de certas medicações, mas sua ocorrência tem grande impacto na qualidade de vida do paciente. Várias modalidades de tratamento são utilizadas para o manejo das lesões, incluindo procedimentos conservadores e cirúrgicos. A terapia com ozônio (O<sub>3</sub>) surge como uma alternativa de terapia não invasiva que pode beneficiar o paciente acometido, sem riscos cirúrgicos, devido ao potencial de estimular a ativação e migração de fibroblastos em uma área lesionada. Apresentação do caso: Este artigo relata o tratamento conservador de uma osteonecrose associada ao uso de medicamento em estágio 3 da maxila, em um paciente edêntulo parcial, previamente tratado com bisfosfonato intravenoso para mieloma múltiplo, que apresentava doença cardíaca prévia. Conclusão: A osteonecrose associada ao uso de medicamento em estágio 3 foi tratada com sucesso com injeção de gás ozônio (O<sub>3</sub>) e irrigação com água ozonizada, com recobrimento total do osso e sem supuração ou dor ao final do tratamento. Nenhuma recorrência foi observada após doze meses de acompanhamento.

**Palavras-chave:** Osteonecrose da arcada osseodentária associada a difosfonatos; Ozônio; Osteonecrose; Terapêutica.

### Resumen

Antecedentes: La osteonecrosis de los maxilares relacionada con medicamentos es una complicación grave poco común después de la utilización de ciertos medicamentos, pero su

aparición tiene un gran impacto en la calidad de vida del paciente. Se utilizan diversas modalidades de tratamiento para tratar las lesiones, incluidos procedimientos conservadores y quirúrgicos. La terapia con ozono (O<sub>3</sub>) surge como una alternativa de terapia no invasiva que puede beneficiar al paciente afectado sin riesgos quirúrgicos, debido al potencial de estimular la activación y migración de fibroblastos en una zona lesionada. Presentación del caso: Este artículo informa sobre el tratamiento conservador de una osteonecrosis maxilar en estado 3 relacionada con medicamentos, en un paciente parcialmente edéntulo tratado previamente con bisfosfonato intravenoso por mieloma múltiple, que tenía enfermedad cardíaca previa. Conclusión: La osteonecrosis en estado 3 relacionada con medicamentos se trató con éxito con inyección de gas ozono (O<sub>3</sub>) e irrigación con agua ozonizada, con cobertura total del hueso y sin supuración ni dolor al final del tratamiento. No se observó recurrencia después de doce meses de seguimiento.

**Palabras clave:** Osteonecrosis de los maxilares asociada a difosfonatos; Ozono; Osteonecrosis; Terapéutica.

## 1. Introduction

Medication-related osteonecrosis of the jaws (MRONJ), previously known as bisphosphonate-related osteonecrosis of the jaws, has changed its nomenclature since now it is known that both antiresorptive and anti-angiogenic medications have potential to develop this complication (Ruggiero et al, 2014; Blus, Giannelli, Szmukler-Moncler & Orru, 2017).

The diagnosis of this lesion is defined based on the presence of a non-healing bone exposure area in the jaws for more than 8 weeks of observation, in a patient with current or previous history of antiresorptive or angiogenic therapy, with intra or extra-oral fistula and no history of radiotherapy on the jaw or metastatic disease on the area (Ruggiero et al, 2014). Patients can report pain, swelling, paresthesia of inferior alveolar nerve, besides secondary infection can be present (Jarnbring et al, 2015).

Bisphosphonates (BP) play a significant role on management of patients suffering from neoplastic diseases as well as osteoporosis and osteopenia (Jarnbring et al, 2015; Nisi et al, 2016). Although they improve the quality of life of the patients, they have deleterious influence on their health by increasing the risk of MRONJ development due to their capacity of alter bone remodeling, being the most common linked agent (Ruggiero et al, 2014).

Although it might be a tendency to manage early staged MRONJ lesions with conservative, non-invasive procedures and advanced lesions with aggressive surgical

treatments, the decision on what therapy to employ is still controversial (Ruggiero et al, 2014; Blus et al, 2017; Nisi et al, 2016; Momesso, Lemos, Santiago-Júnior, Faverani & Pellizzer, 2020; Coropciuc et al, 2017). Moreover, the efficient management of these complications is always challenging.

Ozone (O<sub>3</sub>) therapy has been demonstrated to improve the healing process of soft tissue lesions. (Xiao et al, 2017; Isler et al, 2018) The use of ozone (O<sub>3</sub>) applications appears among the non-invasive modalities that can improve the healing process of an osteonecrosis area as main or adjuvant therapy (Ripamonti et al, 2012; Agrillo, Ungari, Filiaci, Priore & Iannetti, 2007). We describe its use as the main therapy in the management of a maxillary stage 3 MRONJ, as a conservative treatment modality, for a cardiopathic patient.

## **2. Methodology**

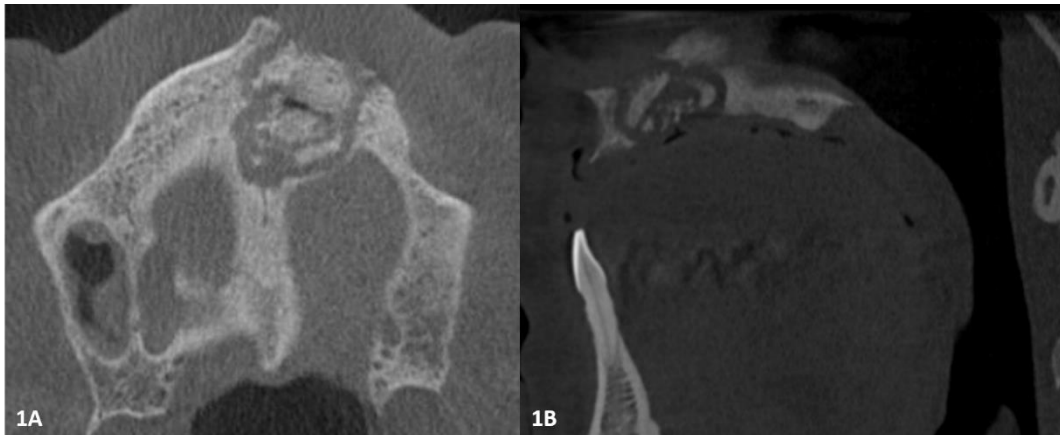
A descriptive observational study was carried out, the objective of which is to present, by means of a highly relevant bibliographic report and scientific and clinical data on the topic addressed, accordingly to Pereira, Shitsuka, Parreira & Shitsuka, (2018). The study has a descriptive and qualitative content, considering that it considers the studied reality and intends to explore the details of the case showed. There was no need for approval by the Research Ethics Committee, given that this is a case report. However, the patient authorized the use of images, clinical and radiographic data for educational and research purposes and signed an informed consent form.

## **3. Case Report**

A 63-year-old man sought treatment for feeding difficulty and oral pain with history of multiple myeloma treated for prolonged period with intravenous bisphosphonate (zoledronic acid). Report of suppuration was also present. The patient wore upper complete denture and presented two areas of bone exposure: one minor in the mandibular body and a large suppurative palatal exposure, which have communication with the buccal side of the maxillary arch, probably caused by prosthetic trauma.

Computed tomography evidenced the presence of a large bone sequestrum in the left anterior maxilla, extending to the hard palate, measuring 21x16mm (Figure 1A and 1B). No bone alteration was seen in the mandibular area. Thus, the mandibular exposure was classified as stage 1 and the maxillary lesion, stage 3.

**Figure 1.** A) Initial axial view of the computed tomography. B) Initial sagittal view of the computed tomography.



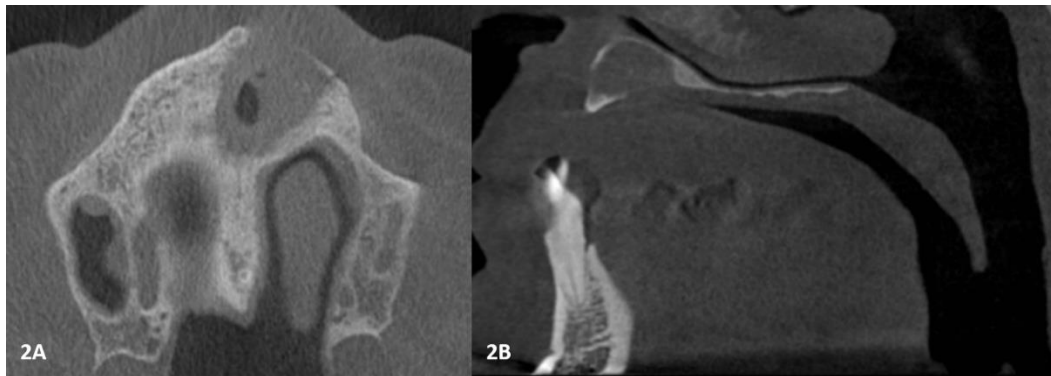
Source: Authors.

In the Figure 1A it is possible to see an axial view of the computed tomography showing an extensive bony sequestrum in the left maxilla, extending to the mid-palatal region. In the Figure 1B it is presented a sagittal view of the computed tomography showing an extensive bony sequestrum in the left maxilla, extending to the mid-palatal region.

Antibiotic (clindamycin 900mg/day/30days), analgesics and chlorhexidine (0,12%) mouth rinse were prescribed. With this initial therapy, suppuration was reduced without regression of bone exposure and pain. Considering that the patient was about to be submitted to a cardiac surgery, due to his cardiac illness, a subsequent conservative treatment with ozone therapy was chosen to avoid surgical risks. The lesions were treated with ozonated water irrigation (20ml syringe) over the lesion and O<sub>3</sub> gas injection (with 1ml syringe with subcutaneous needle) on the border lesion once a week, using the Ozone and Life SSD (Ozone & Life Ind. E Com. E Sistemas LTDA, São José dos Campos-SP), following the manufacturer recommendations.

The mandibular lesion healed in 12 weeks and after 8 months of treatment, the maxillary sequestrum spontaneously exfoliated, resulting in absence of bone exposure and full coverage of the bone with mucosal tissue without suppuration and pain, for the twelve months of follow-up. (Figure 2A and 2B and Figure 3A and 3B)

**Figure 2.** A) Axial view of the computed tomography after 8 months of Ozone therapy. B) Sagittal view of the computed tomography after 8 months of Ozone therapy.



Source: Authors.

In the Figure 2A is demonstrated an axial view of the computed tomography after 8 months of Ozone therapy, showing a maxillary bone defect afterward spontaneous exfoliation of the sequestrum, recovered by mucosa. The Figure 2B presents the sagittal view of the computed tomography after 8 months of Ozone therapy, showing the maxillary bone defect afterward spontaneous exfoliation of the sequestrum.

**Figure 3.** A) Clinical oral aspect of palate after Ozone therapy. B) Clinical oral aspect after Ozone therapy.



Source: Authors.

In the images above is possible to observe the clinical aspect of palatal area (Figure 3A) evidencing complete epithelization of the previously bone exposure area and the buccal side of maxilla (Figure 3B) showing absence of suppuration and complete epithelization of the area.

#### 4. Discussion

Bisphosphonates are extremely effective in reducing the symptoms and complications of bone lesions such as multiple myeloma by inhibition of osteoclast activity. Mostly, its intravenous forms are used in treatment of malignant diseases with monthly intervals (Petrucci, Gallucci, Agrillo, Mustazza & Foà, 2007). The American Association of Oral and Maxillofacial Surgeons (AAOMS) suggests that these BP are more related to MRONJ development and the longer the treatment the greater the risk of develop lesions (Ruggiero et al, 2014).

Once established the MRONJ, its staging seems to have influence on treatment success (Ruggiero et al, 2014; Momesso et al, 2020; Coropciuc et al, 2017). The recommendation is that stages 0 and 1 could be treated with non-invasive therapies, like antibiotics, pain killers and mouth rinses. The stages 2 and 3 diseases may require invasive procedures like debridement or even bone resection (Ruggiero et al, 2014). It is important to establish that treatment goals for MRONJ does not involve the absence of bone alterations, but the preservation of the quality of life by pain reduction, infection control and prevention of lesion increase or appearance of new necrotic areas (Ruggiero et al, 2014; Jarnbring et al, 2015), which was achieved in this case with total epithelization of the areas.

Ozone therapy has been used for different purposes in dentistry since the twentieth century (Suh et al, 2019) and the efficacy on management of MRONJ has been demonstrated by several authors (Ripamonti et al, 2012; Agrillo et al, 2007; Petrucci et al, 2007; Suh et al, 2019). O<sub>3</sub> gas insufflations had been used alone or in conjunct with surgery to treat MRONJ lesions and no relapse was seen during a mean follow-up pf 18 months (Ripamonti et al, 2012). Other authors employed OZONYTRON® GmbH (MIO International Ozonytron GmbH, Germany) as adjunct of other therapies to improve healing in osteonecrosis areas (Agrillo et al, 2007).

Apparently, ozone therapy efficacy is due to the potential of stimulate the endogen antioxidant system and tissue oxygenation processes, activate blood circulation, stimulate calcium, phosphorous and iron metabolism, besides the antimicrobial activity (Agrillo et al, 2007). Other study (Xiao et al, 2017) found that ozone therapy with oil suspension could promote would healing with the activation of fibroblasts and improving the migration process of fibroblasts to the injured tissue.

In the present reported case, the ozone effects on angiogenesis and immune system led to spontaneous exfoliation of the bone sequestrum due to formation of granulating tissue from

the mucosa that recovered the area (Agrillo et al, 2012). A similar occurrence was reported by some authors that used O<sub>3</sub> gas insufflations on MRONJ areas, which responded with spontaneous expulsion of the necrotic bone (Ripamonti et al, 2012). Other study (Ripamonti, Cislighi, Mariani & Maniezzo, 2011) reported that some of their patients showed complete repair of the bone lesions with full recover of the mucosal tissue, after the ozone therapy with oil suspension.

Finally, surgeons should have in mind the patient's medical state or condition, especially oncologic patients, who generally have systemic alterations that may bring more risks to the surgical procedure (Argilés, Stemmler, López-Soriano & Busquets, 2018). Thus, it is up to the professional to decide the best treatment option for the patient: surgical or conservative, being the ozone therapy, a viable option as presented, which prevented the surgery in a cardiopathic patient.

## 5. Conclusion

Ozone therapy may be considered a good conservative treatment for MRONJ due to its healing adjuvant characteristics and it is suggested as an option for advanced lesions when resection could bring risks and disfigurement for the patient.

Finally, the authors suggest more clinical studies about this subject, because there is still lack of consolidated information on the treatment protocol to MRONJ lesions and also the Ozone therapy needs to be more explored with the aim of determine all the benefits which this therapy could bring to that kind of lesions.

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