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Medication-induced osteonecrosis of the maxilla, potentiated by fungical infection: Case report

Osteonecrose de Maxila induzida por medicação, potencializada por infecção fúngica: Relato de Caso

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Abstract
Osteonecrosis of the jaws induced using bisphosphonates refers to a condition characterized by the exposure of necrotic bone, usually in the face region and commonly originating from trauma. Osteonecrosis induced by bisphosphonates has its highest prevalence in the mandible and may be initially manifested by ulcerations in the oral mucosa, which expose the underlying bone due to its poor vascularization and the use of bisphosphonates. Bisphosphonates are indicated for the treatment of several comorbidities, such as malignant tumors, bone metastases, osteoporosis. Actinomycosis is rarely a pathological concern due to the low virulence of the organism, but it can manifest itself when associated with other pathologies such as osteonecrosis. The clinical case presents a patient who made prolonged use of bisphosphonates associated with low-intensity trauma evolving to maxillary osteonecrosis potentiated by *actnomyses*. This article aims to demonstrate the connection between actinomycosis and chronic osteonecrosis and the importance of correct diagnosis for correct treatment.
Keywords: Bisphosphonate; Osteonecrosis; Actinomicosis.

Resumo
A osteonecrose dos maxilares induzida pelo uso de bisfosfonatos refere-se a uma condição caracterizada pela exposição de osso necrótico, normalmente em região da face e comumente originaria de um trauma. A osteonecrose induzida por bisfosfonatos tem sua maior prevalência em mandíbula podendo se manifestar inicialmente por ulcerações em mucosa oral, que expõem o osso subjacente devido a sua pobre vascularização e ao uso dos bisfosfonatos. Os bisfosfonatos são indicados para o tratamento de diversas comorbidades, como tumores malignos, metástases ósseas, osteoporose. A actinomicose raramente é uma preocupação patológica devido à baixa virulência do organismo, porém pode se manifestar quando associada a outras patologias como osteonecroses. O caso clínico apresenta um paciente que fez uso prolongado de bisfosfonatos associado a trauma de baixa intensidade evoluindo para osteonecrose de maxila potencializada por *actnomyses*. Este artigo tem por objetivo demostrar a ligação entre a actinomicose e osteonecroses crônicas e a importância do correto diagnostico para correto tratamento.
Palavras-chave: Bisfosfonato; Osteonecrose; Actinomicose.

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1. Introduction

Bisphosphonates are indicated for the treatment of several pathologies, such as malignant tumors, hypercalcemia, Paget's disease, bone metastases and osteoporosis (Marx, 2007).

Bisphosphonate-induced osteonecrosis of the jaws was first described in 2003 by Marx and in 2007 the American Association of Oral and Maxillofacial Surgeons (AAOMS) defined Osteonecrosis of the Mandible Associated with the use of Bisphosphonates as the simultaneous existence of three criteria: treatment with bisphosphonates current or previous; bone necrosis in the maxillofacial region that persists for more than 8 weeks; no history of local radiotherapy (AAOMS, 2016; Marx, 2007).

Clinically, this pathology presents exposed alveolar bone, occurring spontaneously, or becomes evident due to an invasive procedure, such as extraction of a tooth, periodontal surgery, apicectomy, dental implant or high or low intensity trauma. It always originates in the alveolar bone and may extend to the basilar bone or mandibular ramus (Marx, 2007).

Early signs on radiography show sclerosis or loss of the cortical bone around of tooth and/or enlargement of the periodontal ligament (Marx, 2007).

Osteonecrosis associated with the use of bisphosphonates is believed to result from an interconnection between bone metabolism altered by bisphosphonates, local trauma, increased need for bone repair, infection and hypovascularization. Thus, bone necrosis would be the result of the inability of the affected bone tissue to repair and remodel itself in the face of inflammatory conditions triggered by mechanical stress such as chewing, extractions, irritation from prostheses or dental and periodontal infections (Ponte *et al*, 2016; Ruggiero, 2015; Ruggiero *et al*, 2006).

The classification of medication-induced osteonecrosis was established by the AAOMS where it is divided into 04 stages: Stage 0: Patients without evidence of necrotic bone, but with non-specific symptoms and clinical findings; Stage 1: Asymptomatic bone exposure/necrosis without signs of infection; Stage 2: Bone exposure/necrosis with painful symptoms and signs of infection; Stage 3: Bone exposure/necrosis with signs of infection and containing at least one of the symptoms: pathological fracture, extraoral fistula, osteolysis involving the base of the mandible (AAOMS, 2016; Marx, 2007; Ruggiero, 2015).

Actinomycosis of the jaws is a bacterial infection, which can produce abscesses, bone necrosis, and when it reaches the maxilla it can maintain a process of chronic sinusitis, being a theme discussed in congresses since 1911 (Sezer *et al*, 2017).

Actinomycosis is rarely a pathological concern due to low virulence and does not appear to be an opportunistic disease because there is no specific predisposition for immunocompromised individuals where the prerequisite for disease development is the transport of pathogens to tissue layers with an anaerobic environment. (Haggerty & Tender, 2012; Sezer *et al*, 2017).

Comorbidities such as immunosuppression, osteoradionecrosis, osteonecrosis induced by medication and leukemia are systemic factors that favor infections by actinomyces mainly in patients with lesions in the oral mucosa (Agarwal *et al*, 2019; McCann *et al*, 2019).

Bacteria associated with *Actinomyces* increase its effectiveness, since they have a relatively low invasive power when not associated with other bacteria and may cause an early manifestation of the infection. The involvement of bone tissue in infections by Actinomycosis is rare, usually osteomyelitis occurs secondary to the primary infection where the infection progresses by direct extension into adjacent tissues, but in rare cases bone infections may occur concomitantly with other lesions (Gannepalli *et al*, 2015; Meethal *et al*, 2016; Sezer *et al*, 2017).

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2. Methodology

This clinical case report aims to discuss the proposed treatment and discuss the topic through the bibliographic survey carried out and thus contribute to the scientific production on the subject, thus representing a descriptive and qualitative content.

The case was conducted in accordance with clinical and professional ethics. The patient reported in the study has a personal data sheet and anamnesis, where he authorized the use of images, clinical and radiographic data for educational and research purposes, following the Declaration of Helsinki.

3. Case Report

Patient JS, 73 years old, Caucasian, being treated for colon adenocarcinoma, had used Zometa for 04 years, and frequent use of oral alendronate.

Patient attended the outpatient clinic of Grup Leforte/DASA due to poor adaptation of complete dentures, with greater discomfort in the anterior region of the maxilla.

During the physical examination, the patient presented a total edentulous upper and lower jaw, bone exposures in the anterior region of the maxilla with a necrotic appearance, probably due to a poorly adapted prosthesis and prolonged use of oral bisphosphonates (VO), exposure of a large anterior area of the maxilla with the presence of suppurative secretion, preserved mouth opening and no edema, characterizing it as Stage 2 osteonecrosis induced by bisphosphonates.

Figure 1 - Maxilla with exposure of necrotic bone tissue.

Source: Private Collection.

Because the patient had motor and cognitive sequelae from a stroke, the team opted for excision of the lesion in a surgical center under general anesthesia, also considering the size of the lesion.

An intraoral approach was chosen, a Neumann incision was made and mucoperiosteal detachment to expose the anterior region of the maxilla and necrotic tissue.

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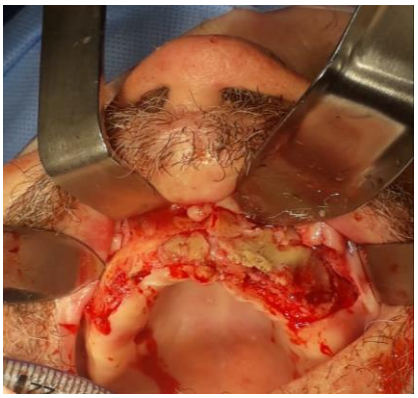
Figure 2 - Exposure of the maxilla and necrotic tissue showing the extent of the lesion.



Source: Private Collection.

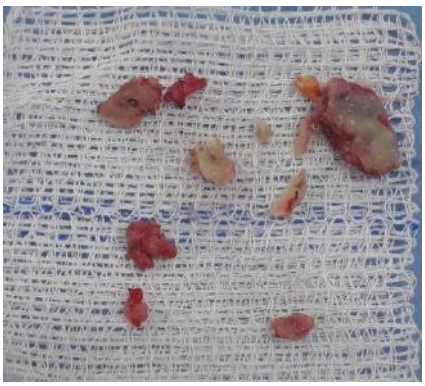
A total surgical removal of the lesion was performed, preserving the healthy tissue as much as possible and not injuring the adjacent tissues.

Image 3 - Clinical appearance after removal of necrotic bone tissue and osteoplasty.

Source: Private Collection.

The lesion was sutured with the edges coapted. All bone tissue removed was submitted to anatomopathological examination.

Figure 4 - Necrotic bone tissue removed.



Source: Private Collection.

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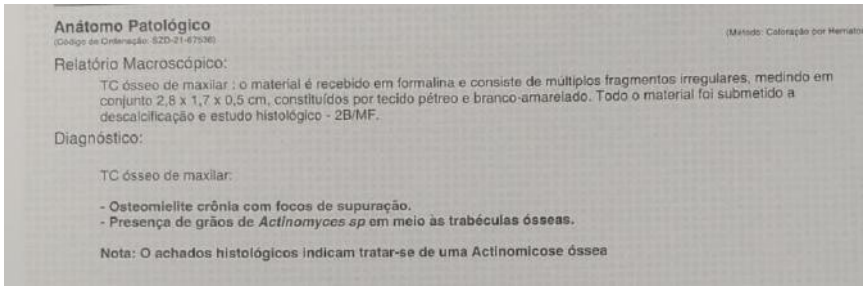
Figure 5 - Anatomopathological examination report.



Anátomo Patológico

Relatório Macroscópico:

TC ósseo de maxilar : o material é recebido em formalina e consiste de múltiplos fragmentos irregulares, medindo em conjunto 2,8 x 1,7 x 0,5 cm, constituídos por tecido pétreo e branco-amarelado. Todo o material foi submetido a descalcificação e estudo histológico - 2B/MF.

Diagnóstico:

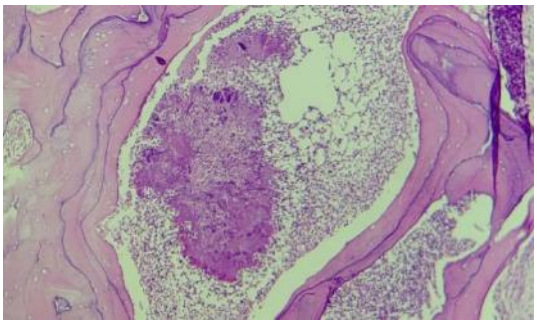
TC ósseo de maxilar:

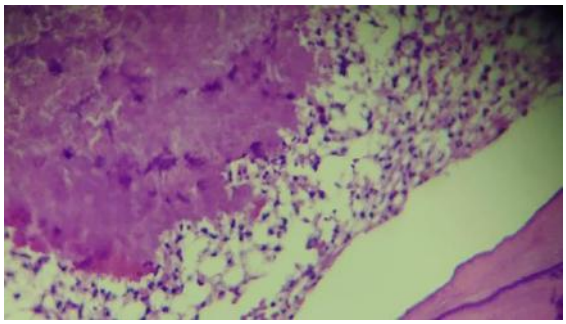
- Osteomielite crônia com focos de supuração.
- Presença de grãos de *Actinomyces sp* em meio às trabéculas ósseas.

Nota: O achados histológicos indicam tratar-se de uma Actinomicose óssea

Source: Private Collection.

Figures 6 and 7 - Microscopic examination showing necrotic bone with granules of *Actinomyces sp*.





Source: Private Collection.

The microscopic slides of the anatomopathological examination obtained from the material collected during the surgical intervention show absence of osteogenic activity and necrotic bone containing granules of *Actinomyces sp*.

According to the anatomopathological report, Chronic Osteomyelitis with suppuration is concluded, confirming the diagnosis, and grains of *Actinomyces sp*, closing the diagnosis as Osteonecrosis of the Maxilla induced by bisphosphonate potentiated by actinomycosis.

After hospital discharge, cephalexin was prescribed at home for 10 days, as well as non-steroidal anti-inflammatory drugs and analgesics to control postoperative pain. Outpatient follow-up was provided for the case, with no recurrence of the pathology.

4. Discussion

Bisphosphonates are indicated for the treatment of several pathologies, such as malignant tumors, hypercalcemia, Paget's disease, bone metastases and osteoporosis (Marx, 2007).

In the literature, we see a higher incidence of osteonecrosis associated with the use of bisphosphonates occurring in the mandible, mainly in the lingual wall of the posterior region, with few descriptions in the maxilla or both, reaffirming the importance of the case described in this article (Motta *et al*, 2015).

It is believed that the higher concentration of bisphosphonates in the maxillary bones occurs due to the greater blood supply and faster bone turnover as a result of the presence of teeth, requiring daily bone remodeling around the periodontal ligament. This fact associated with invasive dental treatments, the presence of thin gun covering these bones and possible low-impact trauma can explain the almost exclusive occurrence of osteonecrosis associated with the use of bisphosphonates in these bones (Motta *et al*, 2015; Ponte *et al*, 2016).

In rare cases, patients undergoing chemotherapy associated with the use of bisphosphonates may present a severe phase of immunosuppression that inhibits the immune-cellular response and leads to bone marrow degeneration, altering bone

cell activity, vasculitis, and reduced blood supply, causing an osteonecrosis, which due to immunosuppression may be related to actinomycosis as described in the case above (Infante-Cossio *et al*, 2012).

The incidence of *Actinomyces* infection in the mandible is 53.6%, followed by the jugal mucosa (16.4%), chin (13.3%), maxilla (5.7%) and TMJ (0.3%). thus, making the case described as unusual in view of the involvement of the maxilla (Gannepalli *et al*, 2015; Suzuki *et al*, 2021).

Actinomyces produces chronic infections of slow development, granulomatous lesions, particularly when normal mucosal barriers are breached by trauma, surgery or previous infection as reported in the case, and may present in an acute or chronic form. (Gannepalli *et al*, 2015; Hirshberg *et al*, 2003; Sezer *et al*, 2017; Steven-Fergus & Savord, 1980).

Due to the decreased vascular supply, the penetration of antibiotics in actinomycosis is also significantly reduced, which explains the need for surgical excision of the lesion and long-term antibiotic coverage, thus demonstrating the correlation of the treatment of osteonecrosis induced by bisphosphonates (Agarwal *et al*, 2019; Haggerty & Tender, 2012).

Some authors discuss the need for removal of bisphosphonates in patients who have progressed with osteonecrosis to help in the treatment of the pathology, not observing a great improvement in the clinical conditions due to the high rate of bioavailability of the medication (Dimitrakopoulos & Magopoulos, 2006; Migliorati *et al*, 2005; Senturk *et al*, 2017).

Some studies demonstrate the possibility of treating medication-induced osteonecrosis in the early stages with low-power laser therapy, as laser therapy has a bio-stimulating effect and antimicrobial potential, and the proposed treatment was not proposed for this case because the patient was already in a more advanced stage. advanced stage of the disease (Crossman & Herold, 2009; Vescovi *et al*, 2008).

The proposed treatment for the case is in line with the treatment proposed in the literature for actinomycosis and osteonecrosis induced by stage 2 medication. According to the literature, the most commonly used antibiotics for the treatment are penicillin, erythromycin, vancomycin, cephalosporins, chloramphenicol, clindamycin and tetracyclines, having a higher success in the treatment of cases using clindamycin or cephalosporins, where long-term follow-up is necessary to prove its effectiveness (Crossman & Herold, 2009; Haggerty & Tender, 2012).

5. Conclusion

Actinomyces infections are rare and are usually opportunistic infections associated with periodontal and endodontic disease. With this article we can evaluate the opportunistic actinomycosis resulting from osteonecrosis induced by bisphosphonates and the importance of diagnosis, for the correct treatment and to avoid recurrences, thus obtaining the cure of the patient, being necessary new studies on the relationship of the two pathologies.

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