

Osteonecrosis of the Jaws Associated with Medications with Possible Related Sepsis

Osteonecrose dos Maxilares Associada a Medicamentos com Possível Sepse Relacionada

Osteonecrosis de los Maxilares Asociada a Medicamentos con Posible Sepsis Relacionada

Raquel D'Aquino Garcia **CAMINHA**

Master's degree, Applied Dental Sciences Program, Bauru School of Dentistry (FOB), University of São Paulo (USP)
<https://orcid.org/0000-0002-8361-3894>

Vivian Palata **VIOLA**

Master's degree, Applied Dental Sciences Program, Bauru School of Dentistry (FOB), University of São Paulo (USP)
<https://orcid.org/0000-0002-1267-1712>

Flávia Cristina **COSTA**

Bachelor's Degree in Dentistry, Bauru School of Dentistry (FOB), University of São Paulo (USP)
<https://orcid.org/0009-0004-6910-0760>

Ana Livia do **AMARAL**

Master's degree, Applied Dental Sciences Program, Bauru School of Dentistry (FOB), University of São Paulo (USP)
<https://orcid.org/0000-0001-8726-417X>

Gustavo Valerio **MALUF**

PhD, Applied Dental Sciences Program, Bauru School of Dentistry (FOB), University of São Paulo (USP)
<https://orcid.org/0000-0001-5507-1824>

Paulo Sérgio da **SILVA SANTOS**

Full Professor of Department of Surgery, Stomatology, Pathology and Radiology,
Bauru School of Dentistry (FOB), University of São Paulo (USP)
<https://orcid.org/0000-0002-0674-3759>

Abstract

Sepsis is considered a syndrome that occurs as a result of the release of several cytokines and other mediators in response to an infectious process. It develops in a potentially severe way and has a high mortality rate. The diagnosis of medication-related osteonecrosis of the jaw (MRONJ) is becoming more prevalent, and it is a comorbidity that presents a high risk of infection development. Case reports that relate the diagnosis of sepsis to MRONJ are scarce in the literature, and the need for updates for early diagnosis and effective treatments are crucial in these conditions.

Descriptors: Bisphosphonates; Oral Surgery; Osteonecrosis; Sepsis, Platelet-Rich Plasma.

Resumo

A sepse é considerada uma síndrome que ocorre como resultado da liberação de diversas citocinas e outros mediadores em resposta a um processo infeccioso. Ela se desenvolve de forma potencialmente grave e tem uma alta taxa de mortalidade. O diagnóstico de osteonecrose dos maxilares relacionada a medicamentos (OMAM) está se tornando mais prevalente e é uma comorbidade que apresenta um alto risco de desenvolvimento de infecção. Relatos de casos que relacionam o diagnóstico de sepse à OMAM são escassos na literatura, e a necessidade de atualizações para o diagnóstico precoce e tratamentos eficazes é crucial nessas condições.

Descritores: Difosfonatos; Cirurgia Bucal; Osteonecrose; Sepse; Plasma Rico em Plaquetas.

Resumen

La sepsis se considera un síndrome que se produce como resultado de la liberación de varias citocinas y otros mediadores en respuesta a un proceso infeccioso. Se desarrolla de forma potencialmente grave y tiene una elevada tasa de mortalidad. El diagnóstico de la osteonecrosis de mandíbula relacionada con la medicación (MRONJ) es cada vez más frecuente, y es una comorbilidad que presenta un alto riesgo de desarrollo de infección. Los informes de casos que relacionan el diagnóstico de sepsis con MRONJ son escasos en la literatura, y la necesidad de actualizaciones para un diagnóstico precoz y tratamientos eficaces son cruciales en estas afecciones.

Descriptores: Difosfonatos; Cirugía Bucal; Osteonecrosis; Sepsis; Plasma Rico en Plaquetas.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is an increasingly more frequent complication in patients who use antiresorptive and antiangiogenic drugs, with different stages of progression that begins with mild symptoms and can progress to major bone destruction associated with severe infections¹ and significantly worsens the quality of life of the affected patient².

Risk factors associated with the development or the aggravation of MRONJ are smoking, decompensated diabetes, renal failure, rheumatoid arthritis, advanced age, continuous use of corticosteroids, and others³⁻⁶. In this context, MRONJ associated with individual systemic conditions has the possibility of evolving into sepsis condition, putting patients' lives at risk.

By definition, sepsis is the host response to infection, and is considered a syndrome that results

from the release of multiple cytokines and other mediators. It develops in a potentially severe form, has a mortality rate of 50% of cases, and represents a means of defending the host against an invasive organism, so the septic response can quickly become injurious to the host, resulting in damage, multiple organ failure, and consequently death.⁷ Clinical and laboratory evaluation is essential for the diagnosis and treatment of sepsis, considering that the earlier the diagnosis is made, the better the patient's prognosis will be⁸.

Literature is limited in relation to case reports of sepsis associated with MRONJ^{4,5,9,10}. Therefore, the purpose of this article is to present the case of a patient who developed severe sepsis possibly associated with MRONJ in the mandible.

CASE REPORT

Male patient, 78 years old, smoker, with history of chronic obstructive pulmonary disease

(COPD), prostate cancer and bone metastases, using prednisone and antibiotic sodium sulbactam + sodium ampicillin (Unasyn: Haupt Pharma Latina, Borgo San Michele, Latina – Italy), and zoledronic acid (Zometa: Novartis Pharma Stein AG, Stein, Switzerland) 4mg every 3 weeks - used 32 doses. In the initial dental examination, the main complaint was jaw pain and the clinical examination identified exposed necrotic bone in the region of the premolars and lower molars on the left side, erythema, significant mucosal edema and the presence of purulent secretion (Fig 1.A). Cone-Beam Computed Tomography (CBCT) revealed hypodense areas interspersed with hyperdense areas in the left mandibular body extending from the alveolar ridge to the mandibular canal and in width from premolars to molars, compatible with areas of bone osteolysis (Fig 1.B). Based on clinical and tomographic examination, a presumptive diagnosis of MRONJ stage 2 (AAOMS, 2022) was established.

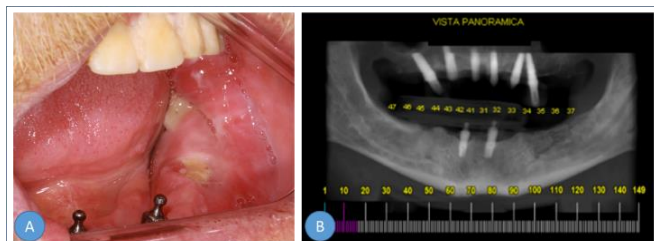


Figure 1: (A): Intra-oral appearance of the OMAM (Stage 3), (B): CBCT showing an area of osteolysis in the region of the left posterior mandible.

The patient was admitted to the Intensive Care Unit (ICU) due to sepsis associated with MRONJ. In the initial examination the patient presented body temperature of 40°C, O2 saturation of 85%, 124bpm, blood pressure 185x74mmHg and respiratory rate of 31rpm. Clinically, he presented spontaneous pain and on touch, drainage of purulent secretion, bone exposure and edema. The complementary laboratory tests identified: red blood cells = 4.28 million/mm³; hematocrit = 38.8%; leukocytes = 16.2%; rods = 1.251/mm³; segmented = 11.935/mm³ and CRP = 14.51mg/dL. Due to the unstable systemic condition, a conservative approach was chosen at this moment, by prescribing the intravenous antibiotic meropenem (Meronem: ACS Dobfar S.p.A. Tribiano, Milan, Italy) associated with local decontamination with 0.12% chlorhexidine in the region of the exposed bone. After 11 days, the patient was dismissed from hospital with significant improvement in the systemic condition (body temperature of 36.2°C, O2 saturation of 94%, 72bpm, blood pressure 140x60mmHg and respiratory rate of 18rpm, red blood cells=4.58million/mm³; hematocrit=40%; leukocytes=12.19%; rods=188 /mm³; segmented=5264 /mm³; CRP=2.56 mg/dL).

Considering the local and systemic

complications presented by the patient, the multidisciplinary team (dental surgeon, oncologist and cardiologist) opted for a surgical approach to the MRONJ under general anesthesia 6 months after the resolution of the sepsis. In this moment, an increase in the area of exposed bone tissue was observed (Fig 2. A) and surgical resection of the necrotic bone was made, until exposure of the bleeding bone tissue (Fig 2. B - C), leukocyte and platelet rich fibrin (L-PRF) membranes (Fig 2. D). The antibiotics ciprofloxacin and clindamycin were prescribed orally for 21 days.



Figure 2: (A): Preoperative intraoral aspect (1st surgery), (B): Fragment of necrotic bone removed, (C): Sound remaining bone tissue, (D): LPRF membranes in position.

There was complete healing of the surgical site 6 months after the procedure (Fig 3. A). At the 10 month late postoperative control, a fistula was observed in the previously operated region, associated with the presence of purulent secretion, edema and mild discomfort (stage 3 AAOMS) (Fig 3. B). At CBCT, bone lysis was observed extending from the inferior alveolar ridge at the premolar level to the region of the left coronoid process (Fig 3. C).

Therefore, it was decided to perform a new surgical approach under general anesthesia, where resection of the necrotic bone (Fig 4. A) was made in the posterior region of the left mandible, with an association of 6 L-PRF membranes (Fig 4. B). In the late postoperative control (9 months) of the second surgical approach, we observed healing of the region, with no signs of bone exposure or infection (Fig 4. C), no associated symptoms and no osteolysis in the surgical area on the CBCT (Fig 4. D), demonstrating the resolution and stability of the condition for 9 months of follow-up. Figure 5 shows case chronology.

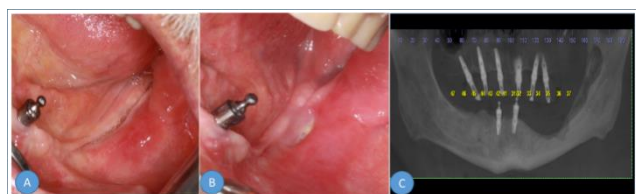


Figure 3: (A): Postoperative control 6 months (1st surgery), (B): Postoperative control 10 months (1st surgery) (OMAM Stage 3), (C): CBCT showing an area of osteolysis in the mandible region rear left.

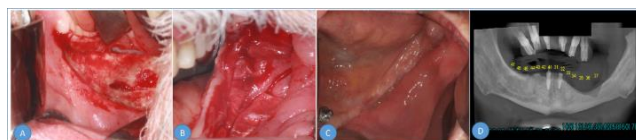


Figure 4: (A): Healthy remaining bone tissue, (B): LPRF membranes in position, (C): Postoperative control 19 months (2nd surgery), (D): CBCT showing absence of osteolysis in the left posterior mandible.

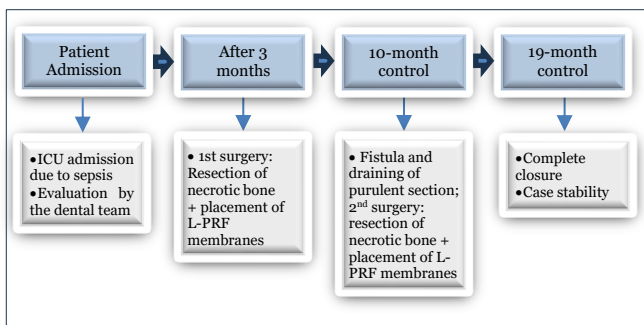


Figure 5: Case chronology

DISCUSSION

In the case report cited in this paper, the patient received 32 doses of zoledronic acid over a 54-month period. This would be a relatively extensive period, since, according to the literature, 38.2 months of average treatment duration with this drug would be a crucial factor for the development of MRONJ.¹¹ Oncology patients and patients with bone diseases commonly make use of this medication as they usually present complications such as pain, pathological fracture, spinal cord compression and hypercalcemia, mostly as a result of metastases. This occurs as a result of osteoclast activation, mediated by different cytokines produced by tumor cells, generating bone resorption and allowing tumor growth.¹²

It is known that oncologic patients with bone metastases have greater osteoclastic inhibition and therefore have a higher chance of developing osteonecrosis, especially when receiving high doses of zoledronic acid.^{13,14} Associating this with risk factors that can favor the development and/or worsen MRONJ, such as smoking, uncontrolled diabetes, renal failure, advanced age, continuous use of corticosteroids, among others, when associated with individual systemic conditions can progress to sepsis condition, putting patients' lives at risk.^{1,4-6}

A case report of MRONJ and sepsis was described by Viviano⁵ where a 59-year-old, diabetic, heart disease patient who took zoledronic acid developed severe MRONJ with recurrent abscesses after oral osteoporosis therapy with zoledronic acid, whose progression led to a subsequent submandibular abscess, bacterial embolism of the left internal jugular vein, sepsis, and death. The author emphasizes in his case report that systemic comorbidities may aggravate cases of MRONJ.

The choice of the best MRONJ treatment should be based on the staging of osteonecrosis and the systemic conditions of the individual affected.³ It is known that the resolution of MRONJ lesions can be refractory and so the literature reports adjuvants such as the use of L-PRF membranes in the surgical site after resection of the necrotic bone. These membranes are rich in

platelets, natural autologous fibrin matrix, and is able to regulate inflammation and stimulate the immune response, favoring bone healing, as well as providing a protective barrier.¹⁵⁻¹⁷

In case reports of MRONJ and sepsis, it is observed that in all cases the patients had comorbidities, among them it is worth mentioning diabetes and autoimmune diseases, as well as the use of corticoids. In the present case, the patient was on corticoids and had COPD. There are rare cases in the literature of MRONJ associated with sepsis, but they exist and should not be underestimated.

Table 1 describes the cases of MRONJ and sepsis found in the PUBMED database through December 2022.

Table 1. Sepsis-associated MRONJ cases present in PUBMED

Kachling et al., 2014	
Sex/age (years)	Female/59
Related medication	Alendronate 70 mg per week/ for 6 months, orally
Site of the lesion MRONJ	Generalized mandibular bone
Comorbidities	Generalized osteoporosis, fibrous dysplasia, corticosteroid-dependent psoriatic arthritis, chronic maxillary sinusitis
Case Report	MRONJ-induced submandibular abscess, with evolution to bacterial embolism of the internal jugular vein and bacterial sepsis, multiple organ failure syndrome and death
Yamashiro et al. 2016	
Sex/age (years)	Male/59
Related medication	Alendronate 35 mg / week for 7 weeks, orally
Site of the lesion MRONJ	Right posterior mandible
Comorbidities	Diabetes, cirrhosis, interstitial pneumonia
Case Report	Right mandibular cellulitis with evolution to sepsis and lethal disseminated intravascular coagulation
Qaisi et al., 2016	
Sex/age (years)	Female/65
Related medication	Risedronate (Actonel), for 4 years; annual injections of zoledronic acid (Reclast) for 2 years; denosumab (Prolia), subcutaneously started one week before the dental procedure
Site of the lesion MRONJ	Diffuse sclerotic changes in the left mandible with extraoral fistula and bone exposure
Comorbidities	Hypertension, gastroesophageal reflux, iron deficiency anemia, and rheumatoid arthritis
Case Report	Four areas of clinical bone exposure associated with changes on imaging examination throughout the mandible, with rapid evolution to extra-oral bone exposure, fistula in cervical region and sepsis
Viviano et al., 2017	
Sex/age (years)	Female/59
Related medication	Zoledronic acid, intravenous
Site of the lesion MRONJ	Right mandible
Comorbidities	Diabetes and atrial fibrillation
Case Report	Submandibular abscess; bacterial embolism of the left internal jugular vein; sepsis and death

Source: Survey Data

CONCLUSION

Considering the severity of the case reported in this study and the few other reports of sepsis-related MRONJ found in the present literature, we can see the need for rapid diagnosis and management of MRONJ to optimize the patient's treatment and consequently minimize the severe complications caused by this condition.

From the cited considerations, it is important to understand how the antiresorptive and

antiangiogenic drugs work, and to evaluate the systemic and oral condition of the patient.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

CORRESPONDING AUTHOR

Paulo Sérgio da Silva Santos

Department of Surgery, Stomatology, Pathology and Radiology
Bauru School of Dentistry (FOB)
University of São Paulo (USP)
17012-901 Bauru – SP, Brasil

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