

Multimodal Therapy for the Management of Drug-Induced Osteonecrosis: Case Report

Terapia Multimodal para o Manejo da Osteonecrose Induzida por Medicamentos: Relato de Caso

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Abstract

Osteonecrosis of the jaws is a complex and debilitating condition, whose characteristic is the gradual destruction of the jaws in patients exposed to predisposing factors, such as tooth extraction. The clinical manifestations vary according to the severity of the lesion, which may culminate in the exposure of necrotic bone. The objective of this study is to discuss therapeutic options in the management of osteonecrosis associated with the use of cancer medication (MRONJ) through a case report, in addition to discourse the topic, discussing the importance of the role of Dentistry in the prevention and management of the condition. A 45-year-old female patient, melanoderma, with malignant left breast neoplasm associated with metastasis in the bone and peritoneum, and using the bisphosphonate Zometa®, was diagnosed with MRONJ after teeth 26 extraction. Multimodal therapy through the use of topical antimicrobials, Antimicrobial Photodynamic Therapy, systemic antibiotic and ozone therapy were adopted to regression of the case. The patient was follow-up for 46 months. In order to update the information regarding MRONJ, cases in maxilla, their repercussions, challenges and therapeutic options, It was carried out additional search in electronic databases. MRONJ is a challenging condition that deserves to be discussed in order to contribute to a better understanding of the disease, prevention and management. That way, the positive result of adjuvant therapies demonstrated in this report may contribute to the structuring of effective protocols for the management of MRONJ, in addition to enabling the development of new questions and, therefore, new studies related to the condition.

Keywords: Osteonecrosis. Maxilla. Bisphosphonate. Bisphosphonates-Related Osteonecrosis of the Jaws. Bone Density.

Resumo

A osteonecrose dos maxilares é uma condição complexa e debilitante, que tem como característica a destruição gradativa dos maxilares em pacientes expostos a fatores predisponentes, como uma extração dentária. As manifestações clínicas variam de acordo com a gravidade da lesão, podendo culminar na exposição de osso necrótico. Este trabalho tem como objetivo discutir opções terapêuticas no manejo da osteonecrose associada ao uso de medicamento (OMAM) oncológico por meio de um relato de caso, além de discorrer acerca do tema, discutindo a importância da atuação da Odontologia na prevenção e manejo da condição. Paciente 45 anos, sexo feminino, melanoderma, portadora de neoplasia maligna em mama esquerda, com metástase em osso e peritônio e sob uso do bisfosfonato Zometa® foi diagnosticada com OMAM após exodontia de unidade 26. Terapia multimodal através do uso de antimicrobiano tópico, Terapia Fotodinâmica antimicrobiana, antibioticoterapia sistêmica e ozonioterapia foram adotadas com vistas à regressão do caso e a paciente foi acompanhada por 46 meses. No intuito de atualizar informações referentes à OMAM, sobretudo casos em maxila, suas repercussões, desafios e opções terapêuticas, foi realizada uma busca adicional em bases eletrônicas. A OMAM é uma condição desafiadora que merece ser discutida a fim de contribuir com um melhor conhecimento, prevenção e manejo. Dessa forma, o resultado positivo das terapias adjuvantes demonstrado no presente relato pode contribuir com a estruturação de protocolos efetivos para o manejo da OMAM, além de possibilitar a elaboração de novos questionamentos e, portanto, novos estudos relacionados à condição.

Palavras-chave: Osteonecrose. Maxila. Bisfosfonato. Osteonecrose Associada a Bisfosfonatos. Conservadores da Densidade Óssea.

1 Introduction

Jaw osteonecrosis is a complex and debilitating condition characterized by the interruption of blood supply or avascular necrosis, which may result in bone exposure, directly impacting the quality of life of affected patients. Its main feature is the gradual destruction of the jawbones in patients exposed to predisposing factors such as local trauma, and despite being rare, it has a high recurrence rate. This condition can be induced by exposure to radiation therapy, high doses of corticosteroids, and also by the use of medications that interrupt blood supply and consequently interfere with bone

remodeling^{1,2}.

In recent years, new drugs have been incorporated into the treatment of disorders of bone metabolism, such as malignant neoplasms, bone metastases, malignant hypercalcemia, and osteoporosis. Concurrently, oral and maxillofacial surgeons began to identify cases of osteonecrosis of the jawbones in patients with a history of treatment with intravenous bisphosphonates. In 2003, Marx reported a series of 36 cases of jaw osteonecrosis in patients using bisphosphonates for anticancer treatment²⁻⁴.

In this context, medication-related osteonecrosis of the jaw (MRONJ) is a rare and serious adverse drug reaction

(ADR) associated with the use of antiresorptive medications commonly used to treat bone disorders^{2,5}. The American Association of Oral and Maxillofacial Surgeons (AAOMS) prepared a report with strategies for managing patients with or at risk of MRONJ in 2007, with the latest revised and updated version in 2022. This document outlines certain requirements that must be present in the patient's history for the lesion to be considered MRONJ: 1. Current or prior treatment with antiresorptive agents alone or in combination with immune modulators or antiangiogenics; 2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for more than eight weeks; and 3. Absence of a history of jaw radiation therapy or local metastatic disease^{2,6}.

Since 2004, the pharmaceutical industry responsible for producing these medications has started to include notifications on their labels regarding the risk of osteonecrosis associated with bisphosphonates and, more recently, with other antiresorptive agents and anticancer drugs. In this regard, drugs with inhibitory function on bone resorption, acting on osteoclasts, such as bisphosphonates, RANK ligand inhibitors (RANK-L), m-TOR inhibitors (a protein involved in cellular growth and metabolism), or those that act on angiogenesis inhibition, have been described as significant risk factors associated with the development of MRONJ⁵.

Based on these diagnostic criteria, adopting the staging of MRONJ assists in establishing appropriate management and facilitates communication among professionals. The staging system advocated by the AAOMS is one of the most commonly used and is based on evidence of necrotic bone, specific clinical findings, as well as radiographic changes and associated symptoms. This system ranges from stage 0 to 3, where the risk of developing the condition is observed at stage 0 and there is a gradual extension and severity in stages 1, 2, and 3^{2,7}.

The treatment of MRONJ is challenging, and therefore, the best option is to prevent osteonecrosis from occurring, with dentists playing a crucial role in preventive measures through preoperative guidance and prophylactic strategies, or alternatively, treating the condition to prevent it from worsening^{1,4}.

In case of diagnostic confirmation, treatment options are diverse and related to the degree of progression, presence or absence of symptoms, and exposure or non-exposure of necrotic bone. In this regard, treatment alternatives are divided into three categories: conservative treatment, surgical treatment (minimally invasive or invasive), and adjuvant therapies^{8,9}.

In light of the above, it is evident that medication-related osteonecrosis of the jaw (MRONJ) is a challenging condition that deserves discussion to contribute to a better understanding of the disease, prevention, management, and treatment options. Thus, the main objective of this work was to discuss

therapeutic options in the management of oncologic MRONJ through a case report, as well as to elaborate on the topic and discuss the importance of Dentistry's role in the prevention and management of this condition.

2 Case Report

This clinical case report was submitted and approved by the Research Ethics Committee of Hospital Santo Antônio/Obras Sociais Irmã Dulce under the Certificate of Presentation for Ethical Appreciation (CAAE) number 51859921.6.0000.0047 and protocol number: 5.026.971.

Patient, 45-year-old female, melanodermic, diagnosed with malignant neoplasm in the left breast with metastasis to bone and peritoneum, presented to the Dentistry Service of the High Complexity Oncology Unit (UNACON) of the Obras Sociais Irmã Dulce (OSID) seven months after extraction of tooth 26, complaining of pain in the region. Upon intraoral physical examination, it was observed that the patient had hydrated and normochromic mucosa without alterations, with an erythematous area compatible with granulation tissue in the region of the ridge corresponding to tooth 26. No signs of bone sequestration or suppuration were observed upon palpation. The responsible oncologist had prescribed pain medication and suspended hormone therapy and intravenous nitrogenous bisphosphonate Zometa® (zoledronic acid) while suspecting MRONJ. A panoramic radiograph of the region was requested, showing slight bone alteration compatible with non-healed socket (Figure 1).

Figure 1 - Panoramic radiograph prior to extraction of tooth 26



Source: Dentistry Service of UNACON.

The patient was followed by the Dentistry Service of UNACON for 46 months, from June 2019 to March 2023. In this regard, part of the follow-up occurred during the COVID-19 pandemic, which resulted in the temporary suspension of dental care at the institution. The patient's progress was summarized to facilitate the understanding of the case in each distinct period (pre-pandemic, during the suspension of in-person care, and after the team's return) and the therapeutic management thereof.

In the pre-pandemic period, after the patient returned with the previously described imaging exams, she was followed by the team for three months, during which she experienced two episodes of remission and recurrence of pain and suppuration,

occurring at intervals of 30-45 days. At these times, she was prescribed Clavulin® (Amoxicillin + Clavulanic acid: 1 tablet 500mg + 125 mg, every 8 hours for 7 days) and rinsing with Periogard® (0.12% Chlorhexidine Gluconate mouthwash, two or three times a day for 14 days) for infection control. The patient was then referred for ozone therapy at another institution.

In the following two months, the patient returned for follow-up appointments and did not present any symptoms. Upon intraoral physical examination, there was no evidence of suppuration or erythema. She reported that ozone therapy would be suspended for two months due to the institution where the treatment was offered being closed. At the beginning of the 3rd month, however, the patient presented with painful symptoms and suppuration in the gingival sulcus. Amoxicillin was prescribed at a dose of 500 mg every 8 hours for seven days, and after one week, antimicrobial Photodynamic Therapy (aPDT) was initiated using 0.05% methylene blue applied with a syringe and insulin needle for five minutes (pre-radiation time) at the site with necrosis, followed by irradiation with a low-power laser device (LBP) from Twin Flex® (MMOptics, São Carlos, Brazil), with a maximum output power of 100 mW, active tip area of 0.1256 cm², red wavelength (660 nm), and irradiation with 9J (90 s) in the affected gingival sulcus. The aPDT sessions were performed at weekly intervals for a month and a half, with control of symptoms, until there was a recurrence of purulent secretion drainage from the gingival sulcus, leading to an adjustment of the aPDT protocol (application of 9J at 2 distinct points - buccal and lingual sides of the gingival sulcus, totaling 18J), which was maintained for four weeks until there was a recurrence of pain and drainage of purulent secretion. Again, Clavulin® was prescribed and Periogard® mouthwash was recommended, according to the previously described protocol, in addition to maintaining the aPDT protocol. After 15 days of prescription, with still discreet purulent secretion in the gingival sulcus, the patient informed that she would return to treatment with ozone therapy at the institution where she was being treated. Up to this point, 13 sessions of aPDT had been performed. Figure 02 shows the panoramic radiograph control after seven months of follow-up by the UNACON dentistry team.

Figure 2 - Panoramic radiograph after 7 months of follow-up



Source: UNACON Dentistry Service.

Due to the COVID-19 pandemic, the patient did not resume treatment with ozone therapy and remained without follow-up or complaints for three months until she reached out to the team through social media, reporting discomfort in the area. It is worth noting that during this period, the dentistry team was not working due to the pandemic, so the aPDT protocol could not be resumed. Therefore, the PENTO protocol was established (Pentoxifylline 400 mg, one tablet every 12 hours for 30 days; Tocopherol (Vitamin E) 1 capsule orally once a day for 30 days). Two months later, the patient contacted the team again reporting the observation of bone exposure in the oral cavity, and the following day, she informed that there was bone sequestration expulsion (Figure 3).

Figure 3 - Bone sequestration. Recorded by the patient



Source: UNACON Dentistry Service.

Two months later, after the resumption of dental team activities, the patient returned for a consultation complaining of pain and purulent exudate production. The team decided to maintain the PENTO protocol and reinstate aPDT using the same parameters as before the pandemic. After one week, the patient returned with local swelling and suppuration. At this point, the team initiated the 3rd aPDT session and prescribed Clavulin BD®. Subsequently, seven more APDT sessions were conducted over a period of approximately one month until a new episode of suppuration occurred, and another cycle of Clavulin BD® was prescribed, followed by two additional weekly APDT sessions. After 20 days, the patient returned without complaints and no changes were observed on physical examination. The PENTO protocol and aPDT were discontinued, and for 73 days, the patient remained asymptomatic. During this period, there was a tumor recurrence, and the patient underwent surgery in the abdominal cavity and started a new cycle of chemotherapy with Taxol and Doxorubicin. Upon her return, she presented with purulent drainage in the region. Clavulin BD® was prescribed for seven days, resulting in improvement of the condition. Seven months later, the patient returned reporting painful sensations at the site of the lesion, sometimes radiating, with no visual changes upon physical examination. However, during palpation, the patient complained of pain. Analgesia was prescribed for comfort, and close monitoring was advised. The following week, the patient returned stating

she had expelled a bone fragment and continued to experience discomfort in the region. Clinically, there were no signs of inflammation or infection. After 13 months, the patient returned for evaluation without any complaints or infectious or inflammatory signs.

3 Discussion

It is known that the use of intravenous antiresorptive agents inhibits osteoclastic activity, and when associated with dental trauma, especially tooth extraction, it prolongs the exposure time of the alveolar bone to the inflammatory and infectious environment, which may favor the development of MRONJ¹⁰. This risk varies depending on the type of drug used, the duration of exposure¹, and frequency⁹, being even higher in patients exposed to zoledronic acid - Zometa®, as it is a nitrogen-containing antiresorptive agent¹.

In the present case, the diagnosis was established by combining clinical aspects with the data from the medical history, and confirmed by radiographic findings of the lesion, meeting the criteria for stage 2 as proposed in the AACOM report. This stage is characterized by the presence of exposed and necrotic bone or bone that can be probed through a fistula, associated with infection evidenced by pain and erythema in the region of exposed bone, with or without suppuration⁶. Similarly, Zisis et al.¹¹ and Kinoshita et al.¹² demonstrated that the use of Denosumab, also considered an antiresorptive drug, triggered MRONJ in a 78-year-old and a 74-year-old patient, respectively, for the treatment of tumor recurrence in bone tissue.

Although there is no established protocol for managing MRONJ, AACOM recommends that cases diagnosed at stage 2 be treated with conservative strategies aimed at controlling infection and associated symptoms¹, as well as promoting the healing process¹³. In this regard, the team opted for a conservative therapeutic approach, combining systemic antibiotic use (Clavulin®) with 0.12% Chlorhexidine Gluconate to attempt to control the associated infectious focus, and the use of aPDT as an adjuvant therapy, aiming at microbial control associated with accelerated local tissue repair.

The reported case also included ozone therapy as a therapeutic approach. The use of ozone over a two-month period showed promising results, with nearly complete closure of the alveolar ridge and absence of erythema, suppuration, and pain. Ozone has the ability to aid tissue healing, local oxygenation, antimicrobial action, and induction of bone sequestration formation¹⁴. Additionally, it contributes to increased vascularization, stimulates granulation tissue formation, improves pain symptoms, and controls lesion progression, albeit partially, without contraindicating its association with other therapies, such as surgical debridement^{14,15}.

In a study conducted by Agrillo et al.¹⁴, the authors performed sequestrum removal followed by ozone application twice a week for three minutes. Patients also used antibiotics,

antifungal agents, and oral antiseptics as part of the protocol. Results showed that ozone therapy completely alleviated symptoms in 60% of cases, while 30% experienced significant reduction in lesion size and symptom improvement. Only 10% of individuals showed partial regression of symptoms. Similarly, in a study by Oliveira et al.¹⁵, conservative mandibular debridement was possible after two months of weekly ozone therapy, leading to subsequent control of the infectious process, healing of fistulas, and symptom remission. In a meta-analysis by Di Fede et al.¹⁶, the effects of conservative or aggressive surgical treatment alone were compared with surgery combined with ozone therapy for MRONJ treatment. The study revealed that the combination of therapies had a superior effect across all stages of osteonecrosis.

In the present case, after one month of interruption of ozone therapy due to the institution's recess, the lesion resumed purulent drainage associated with painful symptoms. Given the progression of the condition and the circumstances, infection control was necessary through systemic antibiotic administration combined with aPDT. In this regard, photobiomodulation has shown favorable outcomes, particularly in photobiostimulation and decontamination through the addition of a photosensitizing dye, which aids in soft tissue healing^{2,12}. Furthermore, the use of aPDT is important in a scenario where the use of local and/or systemic antibiotics may not be sufficient to eradicate the microorganisms present in the biofilm on the exposed bone region¹³. In a case study published by Epstein et al.¹⁷, three patients diagnosed with MRONJ underwent aPDT and PENTO protocol, in addition to photobiomodulation. The patients achieved excellent results throughout the treatment and did not require surgical intervention.

Therefore, the use of aPDT proved effective in controlling the infection, with a reduction in purulent drainage and painful symptoms after 13 sessions, allowing the patient to be managed until the return to ozone therapy. However, this return was not possible due to the restrictions imposed by the COVID-19 pandemic scenario. It is worth noting that the patient did not show microbial resistance with this therapeutic approach, corroborating with a case report where 37 sessions of aPDT were performed for the same purpose, and as a result, complete healing of the necrotic site occurred, without resistance to this therapeutic¹⁸ modality. This fact reinforces the positive contribution of adjuvant therapies combined with a conservative approach as effective methods that can be used long-term without presenting adverse effects.

However, faced with the recurrence of pain associated with the critical period of the pandemic, when there was a temporary suspension of dental care at UNACON, the team opted for prescribing pentoxifylline associated with tocopherol. The PENTO protocol, in addition to having beneficial effects in reducing osteoradionecrosis, as previously reported in the literature^{15,16}, it is systemic and administered orally, which allows patient care for prolonged periods, as

occurred during the pandemic, especially as there is no need for regular periodic hospital visits.

Pentoxifylline is a peripheral vasodilator derived from dimethylxanthine, which improves blood flow in compromised areas. Tocopherol, on the other hand, is a potent antioxidant that combats oxygen free radicals by inhibiting platelet aggregation¹⁵. Although it has been described in the literature as an effective treatment in cases of osteoradionecrosis^{15,16}, although there is still a shortage of studies validating the effectiveness of pentoxifylline and tocopherol combined in the management of MRONJ. Recently, Magalhães et al.¹⁹ published data from a randomized clinical trial with 114 patients using intravenous bisphosphonates and requiring dental extractions. As a prophylactic measure to prevent osteonecrosis, individuals used the PENTO protocol combined with vitamin E.

At the end of the study, 32 dental extractions were performed, with MRONJ diagnosed in only 3 patients (17.6%). The authors concluded that the protocol used reduced the incidence of MRONJ. Additionally, the use of the PENTO protocol combined with antimicrobial therapy has shown positive results in the total or partial resolution of cases and in the safe elimination of bone sequestration without significant adverse effects^{20,21}.

Similarly to the study by Owosho et al.²⁰, which combined the use of PENTO with Clavulin BD® for six months, in the present case, the combination of these approaches showed success in symptom regression after one month, and in the following months, there was subsequent expulsion of bone sequestration without the need for a more invasive surgical approach. The condition remained stable for the subsequent seven months of follow-up, even after the discontinuation of the PENTO protocol and aPDT. Additionally, no adverse effects related to the protocol were observed. In a systematic review published by Calvacante and Tomasetti²², the use of PENTO for the treatment of MRONJ has great potential in terms of favorable patient prognosis.

Therefore, it can be concluded that, similar to findings in the literature, the combination of antimicrobial therapy with PENTO administration led to a significant improvement in the MRONJ condition in the reported case. This finding reinforces what the available literature suggests and underscores the need for further studies to generate evidence validating the efficacy of protocols in the challenging treatment of MRONJ.

The present case presents a certain degree of difficulty in controlling the infection over a prolonged period. In this context, ozone therapy showed positive results, and the interruption of it had a negative impact on the resolution of the case. Furthermore, the unavailability of well-established therapeutic options in the public service, combined with the absence of a gold-standard management, limits the practitioner's ability to intervene effectively. Thus, the search for available alternatives that can promote a positive outcome

within the limitations of the units becomes an even greater challenge. In this case, the decision was made to use local and systemic antibiotic therapy, along with aPDT as an adjunctive therapy, followed by the PENTO protocol.

4 Conclusão

Thus, it can be inferred that MRONJ is a challenging condition to control. The 46-month follow-up described in this case report illustrates the challenge faced by oral and maxillofacial surgeons in containing the infectious process in bone tissue whose healing capacity is compromised due to the use of nitrogen-containing bisphosphonates. This microbial proliferation hinders lesion healing, leading to episodes of infection and associated symptoms remission and recurrence, even with different therapeutic approaches. It can also be inferred that within conservative treatment, adjuvant therapies were crucial in containing the progression of the condition and reducing symptoms, thus avoiding surgical intervention, which suggests the possibility of developing more effective conservative protocols in the future.

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