

Ozonotherapy for Treatment of Radiation Therapy-induced Jaw Osteonecrosis and Bisphosphonates: Case Report

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Ozonioterapia para o Tratamento de Osteonecrose em Mandíbula Induzida pela Radioterapia Associada com Bisfosfonato: Relato de Caso

Ozonoterapia para el Tratamiento de la Osteonecrosis de la Mordaza Inducida por Terapia de Radiación y Bisfosfonatos: Relato de Caso

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ABSTRACT

Introduction: The inhibition of osteoclastic activity, associated with different treatment modalities in patients with head and neck cancer, make bones unable to respond to repair processes related to physiological traumas or infection and may result in bone necrosis. The present study aims to report a clinical case of osteoradionecrosis in mandible, and how its sequelae were controlled by ozonotherapy. **Case report:** A 73-year-old female patient with infiltrative ductal breast carcinoma with mandibular metastasis was submitted to chemo and radiotherapy at head and neck region associated with bisphosphonate. Three years later, she was diagnosed with hemimandibular osteoradionecrosis that exhibited communication with oral cavity and with a chronic, suppurative and persistent associated infection. It was applied adjuvant therapy with ozone through the cutaneous fistula and the exposed and necrotic bone. Additionally, non-vital bone debridement was proceeded in two surgical steps. The patient is after a 1-year follow-up non-symptomatic. **Conclusion:** It is supposed that ozonotherapy, due to its antibacterial and immunoregulatory mechanism of action, was an important therapeutic agent for improving the patient's quality of life.

Key words: Bisphosphonate-Associated Osteonecrosis of the Jaw/radiotherapy; Bisphosphonate-Associated Osteonecrosis of the Jaw/drug therapy; Osteonecrosis/radiotherapy; Ozone/therapeutic use; Neoplasms.

RESUMO

Introdução: A inibição da atividade osteoclástica, associada a diversas modalidades de tratamento utilizadas em pacientes com câncer de cabeça e pescoço, torna o osso incapaz de responder aos processos de reparo relacionados a traumas fisiológicos ou à infecção, e pode resultar em necrose óssea. O presente estudo tem como objetivo relatar um caso clínico de osteonecrose em mandíbula como consequência do uso de bisfosfonato associado à quimioterapia e à radioterapia para tratamento de câncer de mama com metástase para mandíbula, tendo suas sequelas controladas por meio do uso da ozonioterapia. **Relato do caso:** Paciente do sexo feminino, 73 anos, com história de carcinoma ductal infiltrante de mama com metástase óssea em mandíbula, a qual foi submetida ao tratamento de quimioterapia e radioterapia em região de cabeça e pescoço; três anos depois, foi diagnosticada com osteonecrose da hemimandíbula direita com exposição completa para a cavidade bucal e infecção crônica, supurativa e persistente. Foi realizada terapia adjuvante com aplicação de ozônio nas fistulas cutâneas e no remanescente ósseo exposto e necrosado, além do desbridamento dos sequestros ósseos em duas etapas cirúrgicas. Paciente encontra-se em acompanhamento há 1 ano, sem sintomatologia associada. **Conclusão:** Observou-se que a ozonioterapia, em razão da sua ação antibacteriana e cicatrizante, foi um importante agente terapêutico para a melhora da qualidade de vida da paciente.

Palavras-chave: Osteonecrose da Arcada Osseodentária Associada a Difosfonatos/radioterapia; Osteonecrose da Arcada Osseodentária Associada a Difosfonatos/tratamento farmacológico; Osteonecrose/radioterapia; Ozônio/uso terapêutico; Neoplasias.

RESUMEN

Introducción: La inhibición de la actividad osteoclástica, asociada con las diversas modalidades de tratamiento utilizadas por los pacientes con cáncer de cabeza y cuello, hace que el hueso no pueda responder a los procesos de reparación relacionados con traumas o infecciones fisiológicas y puede provocar necrosis ósea. El presente estudio tiene como objetivo informar un caso clínico de osteonecrosis mandibular como consecuencia del uso de bisfosfonato asociado con quimioterapia y radioterapia para tratar el cáncer de mama con mandíbula metastásica, controlando sus secuelas mediante el uso de la terapia con ozono. **Relato del caso:** Paciente de 73 años con antecedentes de carcinoma ductal mamario infiltrante con metástasis en la mandíbula ósea fue sometida a quimioterapia y radioterapia en la región de la cabeza y el cuello. Tres años después, le diagnostica con osteonecrosis hemimandibular derecha con exposición completa a la cavidad oral e infección crónica, supurativa y persistente. La terapia adyuvante se realizó con la aplicación de ozono en las fistulas cutáneas y en el remanente óseo expuesto y necrótico, además del desbridamiento de los sequestros óseos en dos etapas quirúrgicas. El paciente ha estado bajo seguimiento durante 1 años in síntomas asociados. **Conclusión:** Debido a su acción antibacteriana y curativa, la ozonioterapia fue un importante agente terapéutico para mejorar la calidad de vida del paciente.

Palabras clave: Osteonecrosis de los Maxilares Asociada a Difosfonatos/radioterapia; Osteonecrosis de los Maxilares Asociada a Difosfonatos/tratamiento farmacológico; Osteonecrosis/radioterapia; Ozono/uso terapéutico; Neoplasias.

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INTRODUCTION

The bone metabolism occurs continuously by osteoclastic and osteoblastic activity. When there is a profound inhibition of osteoclasts associated with medications or an insufficient blood irrigation, the bone may become unable to respond to the repair processes, resulting in bone necrosis¹. Osteonecrosis of the jaws is a condition of exposed, necrotic bone tissue, which varies in size, and may be flat or irregular. Drainage of purulent secretion with formation of intra or extraoral fistula is common². Radiographic changes are evident in cases with extensive bone involvement and can help in determining the bone necrosis degree, with adequate therapeutic targeting³.

In recent years, special attention has been directed to bisphosphonates (BP) induced osteonecrosis. BP has fundamental biological effects on calcium metabolism. They are indicated for the prevention of bone metastasis, bone neoplasms and osteoporosis⁴. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS)⁵, medication-related osteonecrosis of the jaw (MRONJ) has been defined as current or previous treatment with antiresorptive agents, exposed bone or bone that can be probed by an intra or extra-oral fistula in a maxillofacial region that persists for more than 8 weeks, and negative history of radiotherapy in the mandibular region or local metastatic disease⁵.

Another form of osteonecrosis of the jaw is radiotherapy-induced osteoradionecrosis (ORN), causing osteoblast reduction activity and blood supply changes immediately after the treatment or even years after it. The degree of damage to the bone tissue depends on the total dose of radiotherapy, irradiated size field, number, and interval between sessions, surgical and/or trauma to the irradiated tissue^{6,7}.

Currently, ozonotherapy has been used to treat many conditions. The ozone molecule consists of three oxygen atoms (O₃). The ozone can be conveyed in water and unsaturated vegetable oil, in addition to being able to be used in gas form itself⁸. This molecule causes local peripheral vasodilation, increased blood flow, oxygenation, and cellular metabolism, promoting acceleration of the healing process. Recent studies have shown that ozonotherapy reduces considerably the growth of *A. actinomycetemcomitans* and *Tannerella forsythia*^{9,10}.

The goal of this study was to report a clinical case of a patient with severe mandibular ORN, in which ozonotherapy proved to be an important adjuvant therapeutic agent, together with surgical debridement.

The Institutional Review Board of the Institute of Health Sciences (ICS) of the Federal University of Bahia

(UFBA) reviewed and approved the clinical case, with number CAAE: 34306720.6.0000.5662.

CASE REPORT

A 73-year-old female patient, melanoderma, sought the service of Oral and Maxillofacial Surgery of the Bahia School of Medicine and Public Health (EBMSP)/General Hospital Roberto Santos (HGRS), Salvador, Bahia, Brazil, complaining of pain in the jaw region, difficulties to feed and intense halitosis.

In February 2007 the patient had been diagnosed with infiltrative ductal breast carcinoma, with staging T3N1M0. In April 2007, a surgery removed the tumor associated with right breast radical mastectomy. After surgery, the adjuvant treatment included 6 cycles of chemotherapy (500 mg/m² 5-fluorouracil, 50 mg/m² doxorubicin and 500 mg/m² cyclophosphamide) with radiotherapy.

In 2011, the disease returned, with mandible metastases. The treatment resumed with radiotherapy at the mandible and chemotherapy (7 cycles of docetaxel 80 mg), and a palliative amount of pamidronate disodium 90 mg was administered, an intravenous bisphosphonate infusion.

In 2014, she was diagnosed with ORN in the mandible. The medical team prescribed Ciprofloxacin 250 mg and metronidazole 250 mg for 2 years. Patient continued in outpatient/clinical follow-up, but without improvement of the condition.

In December 2016, the patient sought the service with intense pain in the mandible. At the physical examination, there was an extensive area of bone exposure with symphysis involvement, body, and right mandibular branches, as well as three facial fistulas located in the retromandibular and pre-auricular regions, with drainage of purulent secretion (Figure 1).

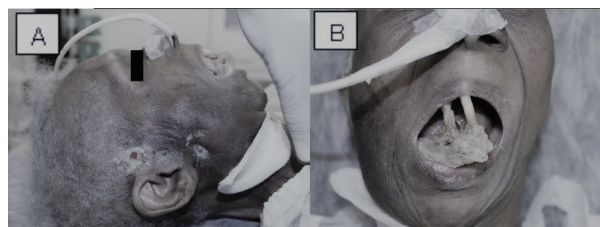


Figure 1A. Fistulas on the right side, with purulent secretion drainage; **1B.** Pathological fracture and extensive mandibular bone exposure

Panoramic radiography (Figure 2A) and contrast face tomography revealed an extensive lytic area in the right hemi-mandible, with a pathological fracture in the symphysis region (Figure 2B, 2C and 2D). After complementary exams, antibiotic therapy due to its

ineffectiveness was withdrawn, and the treatment with local application of ozone was initiated with injection of the gas generated by a device of the Philzon® brand with a concentration of 30 ug/ml, in weekly injections in the dermal fistulae region and remnant of the right mandible (Figure 3A).

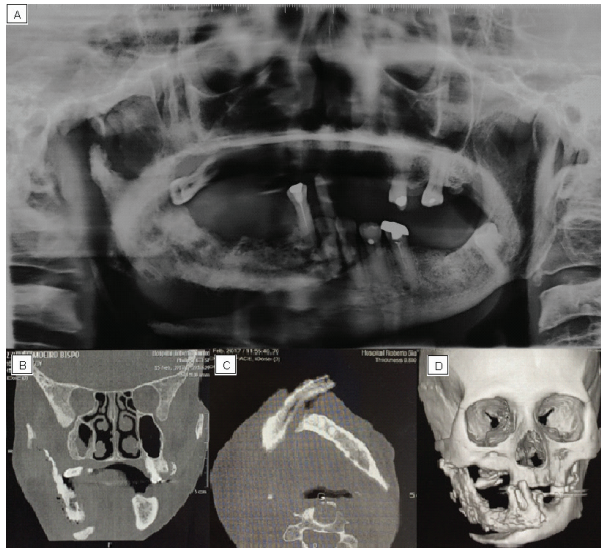


Figure 2A. Panoramic radiography with extensive lytic area in right hemi-mandible associated with pathological fracture in symphysis region; **2B.** Face tomography with extensive bone involvement and pathological fracture in the symphysis region - Coronal view; **2C.** Axial view; **2D.** 3D Reconstruction



Figure 3A. Ozonotherapy in extra oral fistulas; **B.** Removal of the right mandible and condyle; **C.** Bone fragments

After two months of weekly treatment with ozonotherapy, the patient was admitted to the HGRS for the bone sequestration debridement, but the surgery was aborted due to the radiotherapy caused airways

stenosis. The second option would be tracheostomy, but the patient was too weak. In this way, she was submitted to conservative mandible debridement, with local anesthesia, using 2% lidocaine with 1:100,000 epinephrine. Due to the difficulties inherent to anesthesia, only the region of the right mandibular angle and symphysis were removed (Figure 3B and 3C).

The patient returned to the routine postoperative appointments and reported nutritional improvement status and quality of life. Ozone applications remained weekly with the same protocol, in order to control any possible infection.

After 5 postoperative months, it was noticed that the proximal stump of the right mandibular branch, which had been left in the first surgery, had moved to the medial region, resulting in parasymphysis. A second surgical procedure under local anesthesia removed all the remaining necrotic bone tissue (Figure 4A and 4B). At the postoperative image exam, a bone fragment in the right palpable right mandibular angle could be verified at the examination (Figure 4C).

The patient exhibited remission of the infectious process and healing of the skin fistulas and returned to weekly follow-up for ozonotherapy in order to accelerate the healing process. Figure 4D shows the patient in 1-year non-symptomatic follow-up.



Figure 4A: Removal of right mandibular branch and condyle. **Figure 4B:** Bone fragment. **Figure 4C:** Postoperative image with presence of necrotic bone in right mandibular angle region. **Figure 4D:** 1-year follow-up after treatment initiation.

DISCUSSION

Osteonecrosis in the jaw is a complication associated with several factors, including head and neck radiotherapy, corticosteroids, antiresorptive and anti-angiogenic agents. The chosen therapeutic modality or different associations will depend on the location and type of the tumor, the staging and the individual's health condition¹¹. For this case report, the patient underwent several treatment modalities of breast cancer and bone metastases, including: locoregional radiotherapy, chemotherapy and use of bisphosphonates. The diagnosis of BP-induced maxillary osteonecrosis is exclusive for patients who did not undergo radiotherapy⁵, thus the diagnosis of the case presented is ORN.

The ORN classification was proposed by Lyons et al.¹², based on the combination of clinical and radiographic findings, symptoms, and oral and/or cutaneous fistulas, in patients with mandibular ORN. In more advanced stages, there may be an intense pain complaint, pathological fracture, and oral and/or cutaneous fistula. The patient in the present case was in stage 4, where she presented an extensive ORN area (> 2.5 cm) in the right mandible region, pathological fracture in the symphysis region, intraoral bone exposure, secretory cutaneous fistulas, and pain. Such signs and symptoms justified the need of surgical approach.

Osteonecrosis, both induced by radiotherapy, and use of BP, affects the mandible preferentially. This occurs because of its greater corticalization and less vascularization. This association could be evidenced in a study carried out in 2003 by Ruether et al.¹³, where of the 68 patients diagnosed with ORN of the jaws, 67 (98.5%) were in the mandibular region¹³. A similar aspect was observed in the present case.

According to Marx¹⁴, the pathophysiology of ORN is directly related to hypoxia, hypocellularity and hypovascularity. New concepts have demonstrated that radiotherapy promotes increased fibrosis and tissue atrophy, with micro vessels lesion and increased local inflammatory activity, with the reactive oxygen species (ROS), tumor necrosis factor α (TNF- α) and fibroblast growth factor (FGF) production^{7,15,16}.

Potential applications of ozone in clinical practice in dentistry are based on antimicrobial, anti-inflammatory, immunomodulatory, anti-hypoxic and analgesic actions. Ozone stimulates the proliferation of immunocompetent cells and production of immunoglobulins. It also activates macrophages and stimulates the production of interleukins, leukotrienes and prostaglandins^{8,17}.

Despite being well tolerated by the body, to date, there is no internationally established protocol for the

management of ORN with ozonotherapy due to lack of controlled and randomized studies. However, preliminary studies have shown promising results of this therapy in the management of ORN and osteonecrosis associated with the use of medications^{18,19}, and without contraindication of concomitant use with surgery or even with antibiotic therapy¹⁹.

CONCLUSION

ORN is a serious complication of radiotherapy, which can lead the patient to poor prognosis. Associated with this fact, the patient had bone metastasis with prolonged use of BF, and underwent chemotherapy, which further aggravated the condition of bone necrosis. Ozonotherapy has been shown to be a supportive and less invasive treatment and improving the quality of life of cancer patients. It is strongly recommended controlled and randomized studies to confirm this statement definitively.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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REFERENCES

1. Fliefel R, Tröltzsch M, Kühnisch J, et al. Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. *Int J Oral Maxillofac Surg.* 2015;44(5):568-85. doi: <https://doi.org/10.1016/j.ijom.2015.01.026>
2. Corsi A, Ungari C, Riminucci M, et al. Bisphosphonate-related osteonecrosis and metastasis within the same site of the jaw. *J Oral Maxillofac Surg.* 2017;75(8):1679-84. doi: <https://doi.org/10.1016/j.joms.2017.01.008>
3. Klingelhöffer C, Klingelhöffer M, Müller S, et al. Can dental panoramic radiographic findings serve as indicators for the development of medication-related osteonecrosis of the jaw? *Dentomaxillofac Radiol.* 2016;45(5):20160065. doi: <https://doi.org/10.1259/dmfr.20160065>

4. Shintani T, Hayashido Y, Mukasa H, et al. Comparison of the prognosis of bisphosphonate-related osteonecrosis of the jaw caused by oral and intravenous bisphosphonates. *Int J Oral Maxillofac Surg.* 2015;44(7):840-4. doi: <https://doi.org/10.1016/j.ijom.2015.03.013>
5. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw -- 2014 update. *J Oral Maxillofac Surg.* 2014;72(10):1938-56. doi: <https://doi.org/10.1016/j.joms.2014.04.031>
6. Grisar K, Schol M, Schoenaers J, et al. Osteoradionecrosis and medication-related osteonecrosis of the jaw: similarities and differences. *Int J Oral Maxillofac Surg.* 2016;45(12):1592-9. doi: <https://doi.org/10.1016/j.ijom.2016.06.016>
7. McLeod NMH, Pratt CA, Mellor TK, et al. Pentoxifylline and tocopherol in the management of patients with osteoradionecrosis, the Portsmouth experience. *Br J Oral Maxillofac Surg.* 2012;50(1):41-4. doi: <https://doi.org/10.1016/j.bjoms.2010.11.017>
8. Srinivasan K, Chitra S. The application of ozone in dentistry: a systematic review of literature. *Sch J DentSci.* 2015;2(6):373-7.
9. Rupel K, Ottaviani G, Gobbo M, et al. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). *Oral Oncol.* 2014;50(11):1049-57. doi: <https://doi.org/10.1016/j.oraloncology.2014.08.016>
10. Huth KC, Jakob FM, Saugel B, et al. Effect of ozone on oral cells compared with established antimicrobials. *Eur J Oral Sci.* 2006;114(5):435-40. doi: <https://doi.org/10.1111/j.1600-0722.2006.00390.x>
11. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol.* 2005;23(34):8580-7. doi: <https://doi.org/10.1200/JCO.2005.02.8670>
12. Lyons A, Osher J, Warner E, et al. Osteoradionecrosis--a review of current concepts in defining the extent of the disease and a new classification proposal. *Br J Oral Maxillofac Surg.* 2014;52(5):392-5. doi: <https://doi.org/10.1016/j.bjoms.2014.02.017>
13. Reuther T, Schuster T, Mende U, et al. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review. *Int J Oral Maxillofac Surg.* 2003;32(3):289-95. doi: <https://doi.org/10.1054/ijom.2002.0332>
14. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg.* 1983;41(5):283-8. doi: [https://doi.org/10.1016/0278-2391\(83\)90294-x](https://doi.org/10.1016/0278-2391(83)90294-x)
15. Delanian S, Depondt J, Lefaix JL. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. *Head Neck.* 2005;27(2):114-23. doi: <https://doi.org/10.1002/hed.20121>
16. Dantas JBL, Reis JVNA. New therapeutic approaches to osteoradionecrosis: Literature Review. *J Health Sci.* 2019;21(3):243-9. doi: <https://doi.org/10.17921/2447-8938.2019v21n3p243-249>
17. Indhuja RS, Sadasivan A, Koshi E. Application of ozone therapy in dentistry. *Int J Sci Res.* 2016;5(8):21-25. doi: <https://doi.org/10.36106/ijrs>
18. Batinjan G, Zore IF, Vuletić M, et al. The use of ozone in the prevention of osteoradionecrosis of the jaw. *Saudi Med J.* 2014;35(10):1260-63.
19. Agrillo A, Filiaci F, Ramieri V, et al. Bisphosphonate-related osteonecrosis of the jaw (BRONJ): 5 year experience in the treatment of 131 cases with ozone therapy. *Eur Rev Med Pharmacol Sci.* 2012;16(12):1741-7.

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