CASE HISTORY REPORT

ABSTRACT

Bisphosphonates have been the first-line treatment option for osteometabolic diseases, such as osteoporosis, hypercalcaemia in malignant bone diseases, and in bone metastasis. It is possible to observe a growing number of cases of osteonecrosis of the jaws in patients using this medication, called bisphosphonate-related osteonecrosis of the jaws. The purpose of this study was to report a conservative treatment for bisphosphonate-related osteonecrosis of the jaws—Stage 2, using antibacterial solution and low-level laser therapy. At the end of the treatment, the patient presented improvement of the lesion with the healing of the mucosa. The literature still lacks successful definite protocols, thus the present case may contribute with another option for conservative management for bisphosphonate-related osteonecrosis of the jaws. More research is necessary in order to develop a good protocol management for bisphosphonate-related osteonecrosis of the jaws.

KEY WORDS: bisphosphonates, osteonecrosis, low-level laser therapy, iodides and hydrogen peroxide

Bisphosphonate-related osteonecrosis of the jaws: Report of a case using conservative protocol

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Spec Care Dentist 36(1): 43-47, 2016

Introduction

Bisphosphonates are very effective to treat benign and malignant conditions involving intense osteoclast bone resorption, for instance osteoporosis, Paget's disease, and multiple myeloma.[1,2] Bisphosphonates are pyrophosphate analog compounds, and are potent osteoclast-mediated bone resorption inhibitors, therefore suppressing bone remodeling.[1,3] When administered, bisphosphonates are rapidly driven towards the bones, due to high affinity for hydroxyapatite, and are accumulated through time.[1] Nitrogen-containing bisphosphonates are the most potent, and are intravenously administered; the ones that do not have nitrogen are less potent, and are orally administered.[2,4,5] One of the most common and serious side effects of this medication is bisphosphonate-related osteonecrosis of the jaws (BRONJ).

BRONJ is an uncommon condition characterized by the exposure of necrotic bone for more than 8 weeks in patients who have used or are using oral or intravenous bisphosphonates and that have not been subjected to radiotherapy.[4,6] This condition has increasing attention since its first reports in 2003.[3,7] Most patients present BRONJ lesions after invasive dental treatments, especially dental extractions, although spontaneous bone exposure has been reported.[8,9] There are also reports of BRONJ related to trauma to the mucosa, implants, and endodontic treatment.[10–13] The most common clinical features are pain, bone exposure, soft tissue swelling, infection, dental mobility, and purulent discharge.[3]

The exact pathogenicity of BRONJ remains unclear, however, some theories have been proposed in order to explain it. One of them says that BRONJ would

DOI: 10.1111/scd.12143

Table 1. BRONJ stages and their respective management according to the American Association of Oral and Maxillofacial Surgeons.[2]

Stages	Management
Risk category: absence of bone exposure in patients treated with oral or intravenous bisphosphonates	Nothing to do; patient advice only
Stage 0: absence of apparent osteonecrosis and presence of unspecific clinical signs and symptoms	Systemic management with antibiotics and/or analgesics
Stage 1: presence of exposed necrotic bone in asymptomatic patient and absence of infection	Mouthwash with oral antibiotics; monthly clinical follow-up; patient advice and review of indications for bisphosphonate administration
Stage 2: presence of exposed necrotic bone and infection, with pain and erythema on affected area, with or without purulent discharge	Mouthwash with oral antibiotics; pain management; use of systemic antibiotics and analgesics; superficial debridement to relieve soft tissue pain
Stage 3: presence of exposed necrotic bone and infection, in addition to one or more of the following: osteonecrosis extending beyond the alveolar bone, resulting in pathological fracture, extraoral fistulae, oroantral or oronasal communication, or osteolisis extending toward the inferior mandibular border or the sinus floor	Mouthwash with oral antibiotics; pain management; use of systemic antibiotics and analgesics; surgical debridement or resection for long-term relief of pain and infection

be induced by an excessive suppression of bone remodeling, due to the accumulation of the medication in the bones, leading to the inhibition of osteoclastic function.[3,14,15] Another one states that BRONJ could be a response to an infection.[16,17] Bisphosphonates act on modulation of immune response of different cell types, which could make it easier for a reaction toward specific biofilm pathogens, such as *Actinomyces* species, which are found on most BRONJ cases.[16,17] A third explanation for BRONJ is that it could be a similar result of ischemia, caused by the antiangiogenic effect of bisphosphonates.[18] The final possible cause is based on the fact that the localized bisphosphonate accumulation and its toxicity could, combined with other antineoplastic medications, lead to damages in the mucosa, which would in turn lead to bone exposure and osteonecrosis.[19,20] Therefore, the management for BRONJ is very complicated, and the well-succeeded treatment includes elimination of infection, controlling symptoms, and stopping progression of the lesion, even if there is still bone exposure.[6]

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has established management strategies toward BRONJ.[5,6] The patients are first classified in stages, according to the gravity of their condition, and for each one there is a specific conduct, displayed on Table 1. According to them, the priority is to prevent the disease, and whenever treatment is initiated, it must be as conservative as possible.[6]

The BRONJ management is still unclear, and there is no gold-standard treatment, although suggested protocols have been accepted.[18,21] It is not always possible to reach mucosal closure, and in these cases, the infection control is considered effective.[2,21] In this context, low-level laser therapy (LLLT) has been used for treatment of BRONJ.[22–25]

The aim of this paper was to report a case of BRONJ in a patient with history of bisphosphonate therapy, successfully treated with a conservative protocol using LLLT and topical iodide-hydrogen peroxide solution, revising the main aspects of this condition.

Case report

A 54-year-old white female patient came to the Stomatology clinic of the Antônio Pedro Fluminense Federal University Hospital, reporting a mandibular lesion with a 7-month progression, which appeared after the introduction of a new lower partial prosthesis. During anamnesis, a diagnosis of multiple myeloma was reported, and the patient was under zolendronate (Zometa) treatment for 2 years and 10 months. General and extraoral physical exams did not demonstrate any other alteration. Intraoral exam showed an area of painful necrotic bone exposure on the lingual surface of the left posterior mandible, with erythema of the surrounding tissue, without purulent discharge, measuring 1.3 cm × 0.5 cm. Panoramic and periapical radiographs were requested (Figure 1A). Based on the clinical information as well as the physical and radiographic exams the diagnosis was BRONJ, Stage 2.

A conservative treatment was initiated, using 0.2% topical chlorhexidine digluconate gel through silicon guard, twice a day, and the patient was advised to interrupt prosthesis use. After 64 days of weekly consultations, there was a discrete enlargement of the exposed bone area, which at that moment measured 2.0 cm × 0.5 cm. Due to this evolution, another topical treatment was weekly added at the Stomatology clinic, which comprised of direct irrigation of a 1:1 solution containing 1% potassium iodate and 10% hydrogen peroxide. A daily 0.12% chlorhexidine digluconate solution mouthwash was also recommended. Between the second and third irrigation appointment, the patient reported a spontaneous fragment bone sequestrum. Intraoral exam revealed a significant decrease in the bone exposure size area. However, two small exposure areas were still present, one at the original lesion's

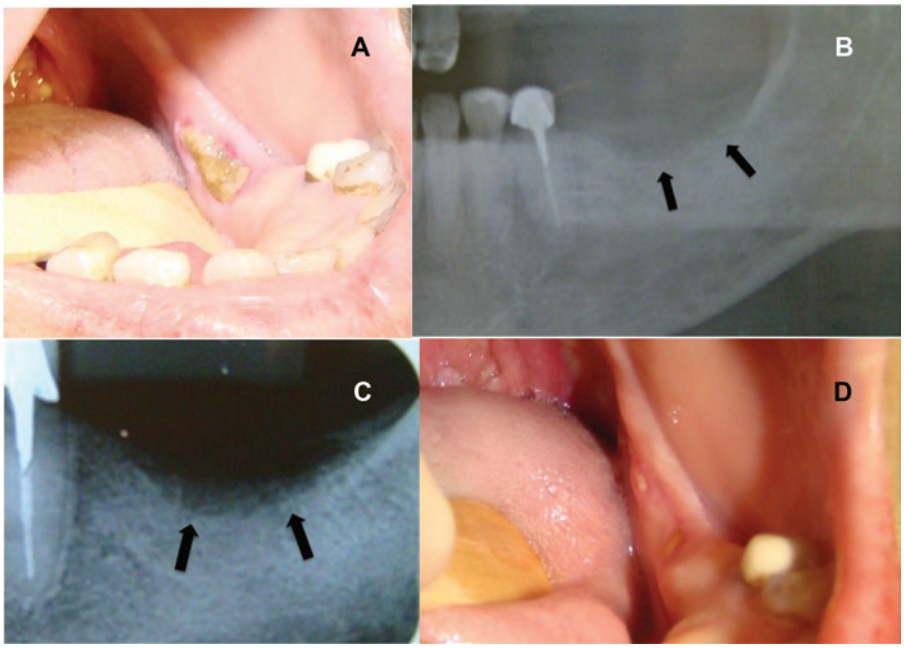

Figure 1. (A) Initial clinical aspect of BRONJ with necrotic bone exposure and erythematous surrounding mucosa. (B) Panoramic radiograph showing osteolysis area (arrows). (C) Periapical radiograph showing osteolysis area (arrows). (D) Clinical aspect after 54 days of LLLT showing partial reepithelization of the lesion.

mesial site, and another on its lower distal edge, depicting small bone spiculae, without signs of infection. A central area compatible with granulation tissue was also observed. Panoramic and periapical radiographic exams showed an approximately 5.0 cm osteolysis area on the left posterior part of the mandible. During the third irrigation session, a significant improvement of the exposed bone area was observed (Figures 1B and C). The patient was asymptomatic, except for a mild discomfort regarding to the bone spiculae with a cutting edge, which was carefully removed with a #15-scalpel blade.

Thirty-five days after the beginning of the irrigation treatment, the lesion remained with two small bone exposure areas, located at the same sites as described earlier, and the adjacent mucosa was still red, with a significant and evident bone loss. The irrigations were interrupted, and the chlorhexidine mouth rinses were maintained. An LLLT protocol was then initiated (*Flash Lase* III, DMC, Brazil). Five weekly sessions were performed, during which punctual applications were carried out, with a 4.0 J dose of infrared light (790 to 830 nm), with 140 J/cm^2 density, and 100 mW potency with 40 seconds per point.

At the end of the 58th day after LLLT began (Figure 1D), an important reduction of bone-exposed areas were observed, with partial reepithelization of the mucosa on the central area of the lesion. Another LLLT was planned, twice a month; however, the patient only returned after 5 months, due to a bone marrow transplant. Physical exam at that moment revealed total remission of the lesion, without bone exposure, and with complete reepithelization of the mucosa, which showed only mild erythema (Figure 2). The patient remains under periodic follow-up, and shows no signs of BRONJ exposure.

Discussion

Considering the possible etiologies, prevention is definitely the best approach towards BRONJ. Therefore, whenever possible, before the bisphosphonate intake, it is important to resolve all conditions that require bone remodeling, or that present risk of breaking mucosa.[18,26] Periodontal pockets must be eliminated, all necessary dental extractions must be performed, as well as restorative and endodontic treatments.[4,18] When the patient is already using bisphosphonates, whether or not BRONJ is established, nonsurgical urgent treatments must be carried out with caution.[18]

Figure 2. Clinical aspect 7 months after the first LLLT session showing complete remission of the lesion with only slight erythema.

Our patient presented bone exposure in the mandibular posterior lingual region. Such finding is compatible with the literature reports, which refer to BRONJ prevalence in the milohyoid line area, representing a trauma-prone site, covered by extremely thin mucosa.[8]

BRONJ is very difficult to resolve, and to date there is no treatment that warrants absolute success. Early diagnosis for BRONJ is one of the most important determinants for better disease control.[27] Gegler *et al.*[28] reported two cases of BRONJ in which necrotic areas were still present, even after antibiotic therapy and the use of chlorhexidine mouthwash. Carvalho *et al.*[27] treated case of BRONJ in a multiple myeloma patient with a history of zolendronate use with many antibiotic cycles, and there was only spontaneous sequestrum of a bone fragment, without remission of neither the bone lesion, nor the mucosal ulcer. Furthermore, Merigo *et al.*[29] reported only "partial success" in the use of surgical and antibiotic therapies, in addition

to mouthwashes and Nd:YAG laser in 29 BRONJ patients.

Due to the lack of valid protocols for BRONJ treatment, laser therapy has therefore been recommended for control of this condition. However, the reports using lasers with this purpose vary according to dosimetry, to the form of application, and to the type of laser. In the present report, immediately after spontaneous sequestrum of bone, we chose the use of laser therapy using infrared light as an alternative, with the purpose of stimulating biomodulation of bone and mucosa. Romeo *et al.*[17] reported two similar cases with the use of infrared laser in continuous scanning mode (0.053 J/cm^2 fluence during 15 minutes; five sessions for 2 weeks), in a patient who presented complete repair of the lesion after spontaneous bone *sequestrum*, as well as five other patients, who showed partial healing of mucosa and partial relief of pain.

To date, there are only a few studies reporting the use of LLLT to treat BRONJ, thus more research is needed in order to elucidate a definitive protocol. Vescovi *et al.*[25] and Luomanen and Alaluusua[23] performed five consecutive weekly applications, with 1,064 nm Nd:YAG pulsed laser, with 1.25 W potency, frequency of 15 Hz for 1 minute, in 28 patients, with good long-term results. Da Guarda *et al.*[22] performed punctual laser therapy using 860 nm GaAlAs laser, with 70 mW potency and 4.2 J per point, for 1.5 minutes each, with a 48-hour interval, for a total of 10 days, also attaining success. Romeo *et al.*[17] evaluated pain management following LLLT, and concluded that 100% of the patients had significant pain reduction. Manfredi *et al.*[30] reported partial remission of BRONJ in patients treated with antibiotics in association with laser therapy. LLLT irradiation generates a series of cellular effects, stimulating cell proliferation, tissue repair, angiogenesis, pain relief, and other anti-inflammatory actions.[9] Many studies have shown bone repair, fibroblast, and osteoblast biostimulation, and optimization of calcium transportation following of LLLT.[31–33] It is therefore an excellent alternative for BRONJ management.

A conservative management before LLLT seems to be another option to deal with BRONJ. In our case, we chose a topical therapy, with the association of chlorhexidine digluconate, 1% potassium iodide, 10% hydrogen peroxide, and LLLT. The patient demonstrated a good recovery with resolution of the signs and symptoms of BRONJ. Hydrogen peroxide releases oxygen when in contact with the tissue, causing an antimicrobial effect. This mechanism promotes antisepsis of wounds and aids in the removal of debris, and the reactions involved may be catalyzed by adding iodide.[34] Potassium iodide speeds the hydrogen peroxide decomposition, leading to a much faster release of oxygen.[34] This association was shown to be productive in the elimination of microorganisms, as well as in the mechanical removal of debris and necrotic rests.[34]

The use of 2% sodium iodide and 3% hydrogen peroxide irrigation was more effective than other treatments in cases of osteorradionecrosis and osteorradiomyelitis.[35,36] The use of this combination of solutions in infected rat alveoli was also reported.[34]

Studies using iodide and hydrogen peroxide solution are scarce. A search in the PUBMED database for "BRONJ," "iodide," and "hydrogen peroxide" in association, and without "BRONJ" did not present any results in 2014/10/08, demonstrating the need for future investigations of this solution, especially regarding clinical trials.

Conclusion

Since the first clinical reports of BRONJ, the knowledge about the disease has increased, however the exact pathogenesis is not clear. It is important to point out that despite the reported cure for some cases in the literature, treatment is very difficult, and there are still no well-established treatment protocols. Professionals should understand that prevention is the key to BRONJ management. Health care professionals must be aware of BRONJ, avoiding predisposing factors and whenever possible, should perform all dental procedures before the beginning of bisphosphonate intake. The therapeutic protocol presented in this report using direct irrigation of a 1:1 solution containing 1% potassium iodide and 10% hydrogen peroxide for microbiological control with subsequent LLLT application was successful, resulting in complete remission of the clinical picture. However, future clinical studies evaluating the effects of the association between the solution and LLLT for BRONJ are required.

References

1. Rogers MJ, Gordon S, Benford HL, et al. Cellular and molecular mechanisms of action of bisphosphonates. *Cancer* 2000;88(12 Suppl):2961-78.
2. Woo S-B, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-61.
3. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-7.
4. Janovská Z. Bisphosphonate-related osteonecrosis of the jaws. A severe side effect of bisphosphonate therapy. *Acta Medica (Hradec Kralove)* 2012;55:111-5.
5. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2007;65:369-76.
6. Ruggiero SL, Dodson TB, Assael LA, et al. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw—2009 update. *Aust Endod J* 2009;35:119-30.
7. Migliorati CA. Bisphosphanates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003;21:4253-4.
8. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg O* 2005;63:1567-75.

9. Pereira AN, Eduardo C de P, Matson E, Marques MM. Effect of low-power laser irradiation on cell growth and procollagen synthesis of cultured fibroblasts. *Lasers Surg Med* 2002;31:263-7.
10. Pires FR, Miranda A, Cardoso ES, et al. Oral avascular bone necrosis associated with chemotherapy and biphosphonate therapy. *Oral Dis* 2005;11:365-9.
11. Lazarovici TS, Yahalom R, Taicher S, Schwartz-Arad D, Peleg O, Yarom N. Bisphosphonate-related osteonecrosis of the jaw associated with dental implants. *J Oral Maxillofac Surg* 2010;68:790-6.
12. Sarathy AP, Bourgeois SL Jr, Goodell GG. Bisphosphonate-associated osteonecrosis of the jaws and endodontic treatment: two case reports. *J Endod* 2005;31:759-63.
13. Cheng A, Mavrokokki A, Carter G, et al. The dental implications of bisphosphonates and bone disease. *Aust Dent J* 2005;50 (4 Suppl 2):S4-13.
14. Orriss IR, Key ML, Colston KW, Arnett TR. Inhibition of osteoblast function in vitro by aminobisphosphonates. *J Cell Biochem* 2009; 106:109-18.
15. Walter C, Klein MO, Pabst A, Al-Nawas B, Duschner H, Ziebart T. Influence of bisphosphonates on endothelial cells, fibroblasts, and osteogenic cells. *Clin Oral Investig* 2010; 14:35-41.
16. Hansen T, Kunkel M, Weber A, James Kirkpatrick C. Osteonecrosis of the jaws in patients treated with bisphosphonates—histomorphologic analysis in comparison with infected osteoradionecrosis. *J Oral Pathol Med* 2006;35:155-60.
17. Romeo U, Galanakis A, Marias C, et al. Observation of pain control in patients with bisphosphonate-induced osteonecrosis using low level laser therapy: preliminary results. *Photomed Laser Surg* 2011;29:447-52.
18. Brozoski MA, Traina AA, Deboni MCZ, Marques MM, Naclério-Homem Mda G. Bisphosphonate-related osteonecrosis of the jaw. *Rev Bras Reumatol* 2012;52:265-70.
19. Reid IR, Bolland MJ, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone* 2007;41: 318-20.
20. Landesberg R, Cozin M, Cremers S, *et al*. Inhibition of oral mucosal cell wound healing by bisphosphonates. *J Oral Maxillofac Surg Off* 2008;66:839-47.
21. Rugani P, Acham S, Truschnegg A, Obermayer-Pietsch B, Jakse N. Bisphosphonate-associated osteonecrosis of the jaws: surgical treatment with ErCrYSGG-laser. Case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:e1-6.
22. Da Guarda MG, Paraguassú GM, Cerqueira NS, Cury PR, Farias JG, Ramalho LMP. Laser GaAlAs (λ860 nm) photobiomodulation for the treatment of bisphosphonate-induced osteonecrosis of the jaw. *Photomed Laser Surg* 2012;30:293-7.
23. Luomanen M, Alaluusua S. Treatment of bisphosphonate-induced osteonecrosis of the jaws with Nd:YAG laser biostimulation. *Lasers Med Sci* 2012;27:251-5.
24. Scoletta M, Arduino PG, Reggio L, Dalmasso P, Mozzati M. Effect of low-level laser irradiation on bisphosphonate-induced osteonecrosis of the jaws: preliminary results of a prospective study. *Photomed Laser Surg* 2010;28:179-84.
25. Vescovi P, Merigo E, Manfredi M, *et al*. Nd:YAG laser biostimulation in the treatment of bisphosphonate-associated osteonecrosis of the jaw: clinical experience in 28 cases. *Photomed Laser Surg* 2008;26: 37-46.
26. Wong PK, Borromeo GL, Wark JD. Bisphosphonate-related osteonecrosis of the jaw in non-malignant bone disease. *Rheumatol Int* 2013;33:2189-98.
27. Carvalho A, Mendes RA, Carvalho D, Carvalho JFC. Osteonecrose da mandíbula associada a bifosfonatos intravenosos em doentes oncológicos. *Acta Med Port* 2008;21:505-10.
28. Gegler A, Cherubini K, Figueiredo MAZ, Yurgel LS, Azambuja AA. Bisfosfonatos e osteonecrose maxilar: revisão da literatura e relato de dois casos. *Revista brasileira de cancerologia* 2006;52:25-31.
29. Merigo E, Manfredi M, Meliti M, *et al*. Bone necrosis of the jaws associated with bisphosphonate treatment: a report f twenty-nine cases. *Acta Biomed* 2006;77:109-17.
30. Manfredi M, Merigo E, Guidotti R, Meleti M, Vescovi P. Bisphosphonate-related osteonecrosis of the jaws: a case series of 25 patients affected by osteoporosis. *Int J Oral maxillofac Surg* 2011;40:277-84.
31. Merli LA, Santos MT, Genovese WJ, Faloppa F. Effect of low-intensity laser irradiation on the process of bone repair. *Photomed Laser Surg* 2005;23:212-5.
32. Saygun I, Nizam N, Ural AU, Serdar MA, Avcu F, Tözüm TF. Low-level laser irradiation affects the release of basic fibroblast growth factor (bFGF), insulin-like growth factor-I (IGF-I), and receptor of IGF-I (IGFBP3) from osteoblasts. *Photomed Laser Surg* 2012;30:149-54.
33. Nissan J, Assif D, Gross MD, Yaffe A, Binderman I. Effect of low intensity laser irradiation on surgically created bony defects in rats. *J Oral Rehabil* 2006;33:619-924.
34. Rodrigues MTV. Análise microscópica e histometrica comparativa da aplicação de uma pasta à base de metronidazol e da irrigação com iodeto de sódio e peróxido de hidrogênio para tratamento de alvéolos dentários infectados de ratos. 2007. Dissertação (Mestrado em odontologia). Faculdade de odontologia de Bauru, Universidade de São Paulo, 2007.
35. Biazolla ER, Castro AL, Pinto DS. Osteorradiomielite de mandíbula: incidência e avaliação clínica de sua terapêutica. *RGO* 1996;44:362-4.
36. Souza EW, Albergaria Barbos JR. Procedimentos odontologicos em pacientes submetidos a radioterapia de cabeça e pescoço. *Odonto Mod* 1991;18:23-5.