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

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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

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.3,6 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
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 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 Stomatolgy 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 zoledronate (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 prosthetic use. After 64 days of weekly consultations, there was a discreet 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 Stomatolgy 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

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

<table>
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<tr>
<th>Stages</th>
<th>Management</th>
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<tr>
<td>Risk category: absence of bone exposure in patients treated with oral or intravenous bisphosphonates</td>
<td>Nothing to do; patient advice only</td>
</tr>
<tr>
<td><strong>Stage 0:</strong> absence of apparent osteonecrosis and presence of unspecific clinical signs and symptoms</td>
<td>Systemic management with antibiotics and/or analgesics</td>
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<tr>
<td><strong>Stage 1:</strong> presence of exposed necrotic bone in asymptomatic patient and absence of infection</td>
<td>Mouthwash with oral antibiotics; monthly clinical follow-up; patient advice and review of indications for bisphosphonate administration</td>
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<tr>
<td><strong>Stage 2:</strong> presence of exposed necrotic bone and infection, with pain and erythema on affected area, with or without purulent discharge</td>
<td>Mouthwash with oral antibiotics; pain management; use of systemic antibiotics and analgesics; superficial debridement to relieve soft tissue pain</td>
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<tr>
<td><strong>Stage 3:</strong> 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 osteolysis extending toward the inferior mandibular border or the sinus floor</td>
<td>Mouthwash with oral antibiotics; pain management; use of systemic antibiotics and analgesics; surgical debridement or resection for long-term relief of pain and infection</td>
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Figure 2. Clinical aspect 7 months after the first LLLT session showing complete remission of the lesion with only slight erythema.

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/cm² 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. Periodontal pockets must be eliminated, all necessary dental extractions must be performed, as well as restorative and endodontic treatments. When the patient is already using bisphosphonates, whether or not BRONJ is established, nonsurgical urgent treatments must be carried out with caution.

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.

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. Gegler et al. 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. 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. reported only “partial success” in the use of surgical and antibiotic therapies, in addition...
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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. reported two similar cases with the use of infrared laser in continuous scanning mode (0.053 J/cm² 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. and Luomanen and Alaluusua 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. 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. evaluated pain management following LLLT, and concluded that 100% of the patients had significant pain reduction. Manfredi et al. 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. Many studies have shown bone repair, fibroblast, and osteoblast biostimulation, and optimization of calcium transportation following of LLLT. 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. Potassium iodide speeds the hydrogen peroxide decomposition, leading to a much faster release of oxygen. This association was shown to be productive in the elimination of microorganisms, as well as in the mechanical removal of debris and necrotic rests.

The use of 2% sodium iodide and 3% hydrogen peroxide irrigation was more effective than other treatments in cases of osteoradionecrosis and osteorradiomyelitis. The use of this combination of solutions in infected rat alveoli was also reported. 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
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