

Surgical treatment of osteonecrosis associated with bisphosphonates: a case report

Tratamento cirúrgico da osteonecrose associada a bisfosfonatos: relato de caso

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ABSTRACT

Bisphosphonates (BP) are routinely used in the management of metastatic bone diseases and malignancies neoplasms, but there is an adverse effect of their chronic use called bisphosphonate-related osteonecrosis of the jaw (BRONJ). Treatment for BRONJ is challenging and complex, as there is still no definitive treatment protocols and the various treatments described in the literature have success variables indexes. In this sense, this study aims to emphasize the responsibility of dentist about the knowledge of BRONJ and report a clinical case that the surgical therapy was the best treatment option. Male patient, sixty-nine years old, asked for dental care complaining about bone exposure. On the anamneses, he reported the use of BP due to cancer history. The intra oral examination revealed exposed bone in the lower right molar region extending to retromolar trigon region on lingual side. There was conservative treatment with antibiotic therapy and mouth rinses of chlorhexidine 0.12 %, but not obtaining success. Therefore, we opted for the surgical removal of necrotic bone area and the tooth involved. The postoperative was within normal standard. The knowledge of dentist about this pathology is essential to prevent, diagnose and treat this disease the most appropriate way. Although the treatment of BRONJ remains challenging and complex, surgical therapy is a treatment option for lesions in early clinical stages and resistant to conservative treatment, providing a better prognosis and quality of life for the patient.

KEYWORDS

Bisphosphonate-associated osteonecrosis; Mandible; Oral surgical procedures.

RESUMO

Os bisfosfonatos (BFs) são rotineiramente usados no manejo de patologias ósseas e neoplasias malignas metastáticas, porém há um efeito adverso de seu uso crônico, denominado osteonecrose da mandíbula associada ao uso de bisfosfonatos (OMAB). O tratamento para OMAB é desafiador e complexo, pois ainda não há protocolos definitivos de tratamento e os inúmeros tratamentos descritos na literatura possuem índices variáveis de sucesso. Neste sentido, este estudo objetiva enfatizar a responsabilidade do cirurgião-dentista no conhecimento da OMAB e relatar um caso clínico em que o tratamento cirúrgico foi a melhor opção terapêutica. Paciente do sexo masculino, 69 anos de idade, procurou atendimento odontológico queixando-se de exposição óssea. Na anamnese, relatou fazer uso de BFs devido ao histórico de câncer. O exame intraoral revelou exposição óssea em região de molar inferior direito estendendo-se para região de trigonoretromolar pela face lingual. Fez-se o tratamento conservador com antibioticoterapia e bochechos com clorexidina a 0,12 %, porém não se obteve sucesso. Assim, optou-se pela remoção cirúrgica da área de necrose óssea e do dente envolvido. O pós-operatório ocorreu dentro dos padrões de normalidade. O conhecimento do cirurgião-dentista sobre esta patologia é essencial para prevenir, diagnosticar e tratar esta doença da forma mais adequada. Embora o tratamento de OMAB permaneça desafiador e complexo, o manejo cirúrgico é uma opção terapêutica para lesões em estágios clínicos iniciais e resistentes ao tratamento conservador, proporcionando um melhor prognóstico e qualidade de vida ao paciente.

PALAVRAS-CHAVE

Osteonecrose associada a bisfosfonatos; Mandíbula; Procedimentos cirúrgicos bucais.

INTRODUCTION

Bisphosphonates (BP) are synthetic drugs similar to endogenous pyrophosphate, able to join the bone matrix and to changes in their remodeling [1]. The action mechanism of these drugs is the functional change of osteoclasts and reduction of blood vessels [2]. These drugs are among the ninety most prescribed drugs in the world [3] and they are indicated for treatment of bone diseases and bone metastases associated with soft tissue tumors, providing patients with a significant improvement in quality of life [4].

Despite the undeniable benefit on these patients [4], there is a suggestive adverse effect of their chronic use, so-called the BP-related osteonecrosis of the jaws (BRONJ) [5], which is characterized by spontaneous bone exposure or non-healing wounds, with indolent behavior and difficult to control. For the definitive diagnosis is necessary the simultaneous existence of three factors: use of current or previous BP, presence of necrotic bone in the maxillofacial area, which persists for more than 8 weeks and no local radiotherapy history [6].

There is no consensus in the literature as a standard treatment for BRONJ, making the challenging management of these patients [7,8]. In an attempt to guide therapeutic modalities, BRONJ can be classified into three clinical stages: stage 1, patients with asymptomatic exposed necrotic bone; stage 2, exposed necrotic bone associated with pain and infection; and stage 3, exposed necrotic bone associated with pain, infection, pathological fracture, extra oral fistula or osteolysis [9]. Based on these stages, conservative therapies are indicated as chlorhexidine 0.12 % mouthrinses (stage 1), antibiotic therapy associated to chlorhexidine 0.12 % mouthrinses (stage 2) or more aggressive treatments, such as resection of necrotic bone (stage 3) [6]. In this context, for those who do not respond to conservative treatments, even at

early stages, has been recommended surgical treatment [10].

Therefore, the knowledge about the association between BP therapy and the onset of osteonecrosis in gnathic bones is of paramount importance, the health professionals; especially the dentists are responsible to diagnostic and treatment of this disease. This study aims to emphasize the responsibility of health professionals about the knowledge of BRONJ and report a clinical case that the surgical therapy was the best treatment option.

CASE DESCRIPTION

Male patient, 69 years old, reported to dentist a complaining of bone in asymptomatic mouth exposure in the right mandibular region, after making the endodontic treatment of tooth 46. Besides, in anamnesis, he described be in possession of prostate cancer and make use of the drug zoledronic acid 4 mg, via intravenous, administered monthly for approximately one year. Direct oroscopy found exposed bone in the jaw of the right side, accurately on the lingual surface extending from the region of the tooth 46 to trigon retromolar area (Figure 1). The panoramic radiograph analysis showed mild radiolucent area in the mandibular alveolar region distal right to the last tooth (Figure 2).

Considering the reported medical history in the anamnesis and bone exposure observed during the patient clinical examination, the diagnosis was BRONJ at stage 1. In this way, the dentist opted for conservative therapy employing chlorhexidine mouthwash 0.12 % of two to three times a day. With the progression of the disease, systemic antibiotic therapy was added with the prescription of Amoxicillin 500 mg of 8 in 8 hours for 8 weeks, but without success in the BRONJ management. Following, the surgical intervention with the extraction of the tooth 46 and bone lingual board resection in the right mandibular region was the treatment chosen by the dentist. The surgical wound that

still showed necrotic tissue (Figure 3A) was debrided to the onset of bleeding in cancellous bone (Figure 3B). The synthesis was performed using the total closure of the incision (Figure 4) for retail slide in order to promote wound healing by first intention. As adjunctive therapy, in the preoperative period, was used chlorhexidine 0.12 % mouthwash for 1 minute and irrigation of the surgery site with the same solution. In addition, the antibiotic therapy was initiated 2 hours before the procedure with Clindamycin 300 mg, 1 tablet 8 in 8 hours for 4 weeks. Macroscopically, bone lingual board (1.5 x 1.0 x 0.7 cm) was presented, in part, adhered to the dental piece (Figure 5). The collected material was submitted to histopathological evaluation, which showed the presence of numerous bacterial lumpy masses associated with polymorph

nuclear leukocytes and neutrophils in filling small cavities devitalized bone, confirming the process of osteonecrosis (Figure 6).

The process of postoperative healing occurs within the normal range, as evidenced by control in 2 weeks (Figure 7). After three years of monitoring, new clinical examination (Figure 8) and radiographic (Figure 9) was performed, demonstrating bone repair of the affected area by the osteonecrosis. The clinical examination showed a healthy mucosa without bone exposure in the operated area, demonstrating complete repair of the exposed bone injury. The patient is being treated for prostate cancer with pamidronate and abiraterone acetate interspersed administrations. The dentist referred the patient for prosthetic rehabilitation and maintains periodic consultations for dental reviews.



Figure 1 - Bone exposure area in the retromolar trigon region, lingual, reflected in the mirror.



Figure 2 - Soft bone thinning in the distal region of the tooth 46.

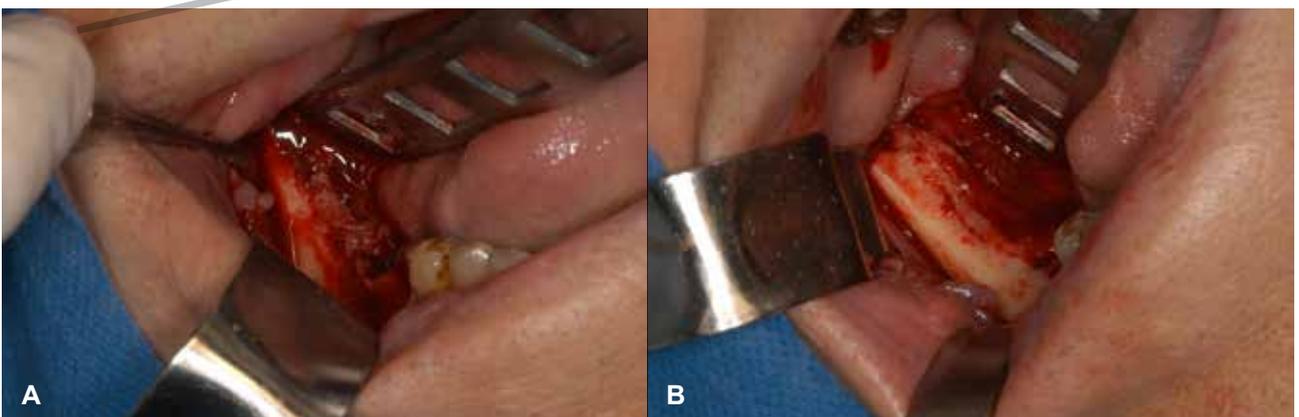


Figure 3 - a) Presence of the necrotic tissue; b) After debridement of the affected area.



Figure 4 - Wound closure with simple stitches and absorbable sutures.



Figure 5 - Bone and tooth board 46 seen from the buccal region.

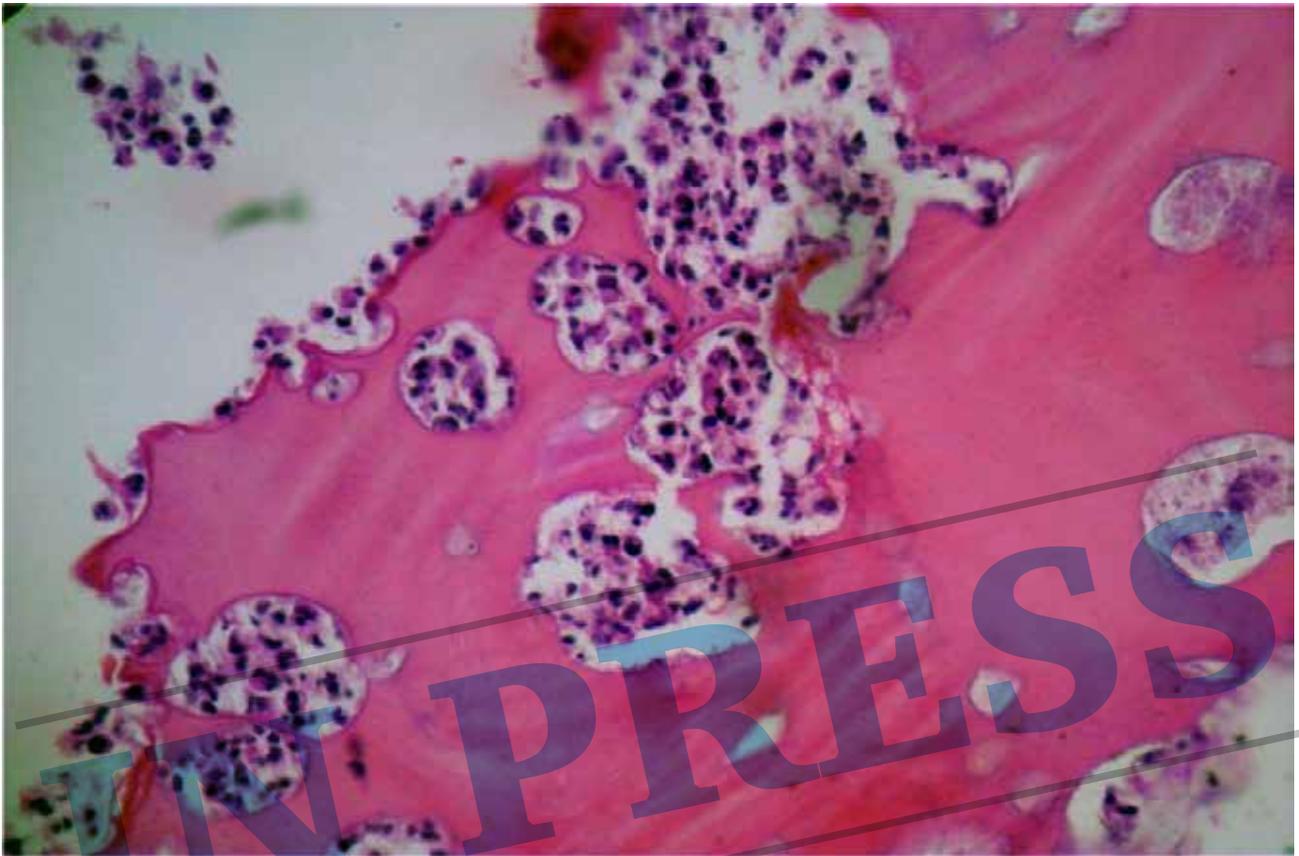


Figure 6 - Neutrophils filling small bone cavities.



Figure 7 - Wound healing aspects in period of 2 weeks.

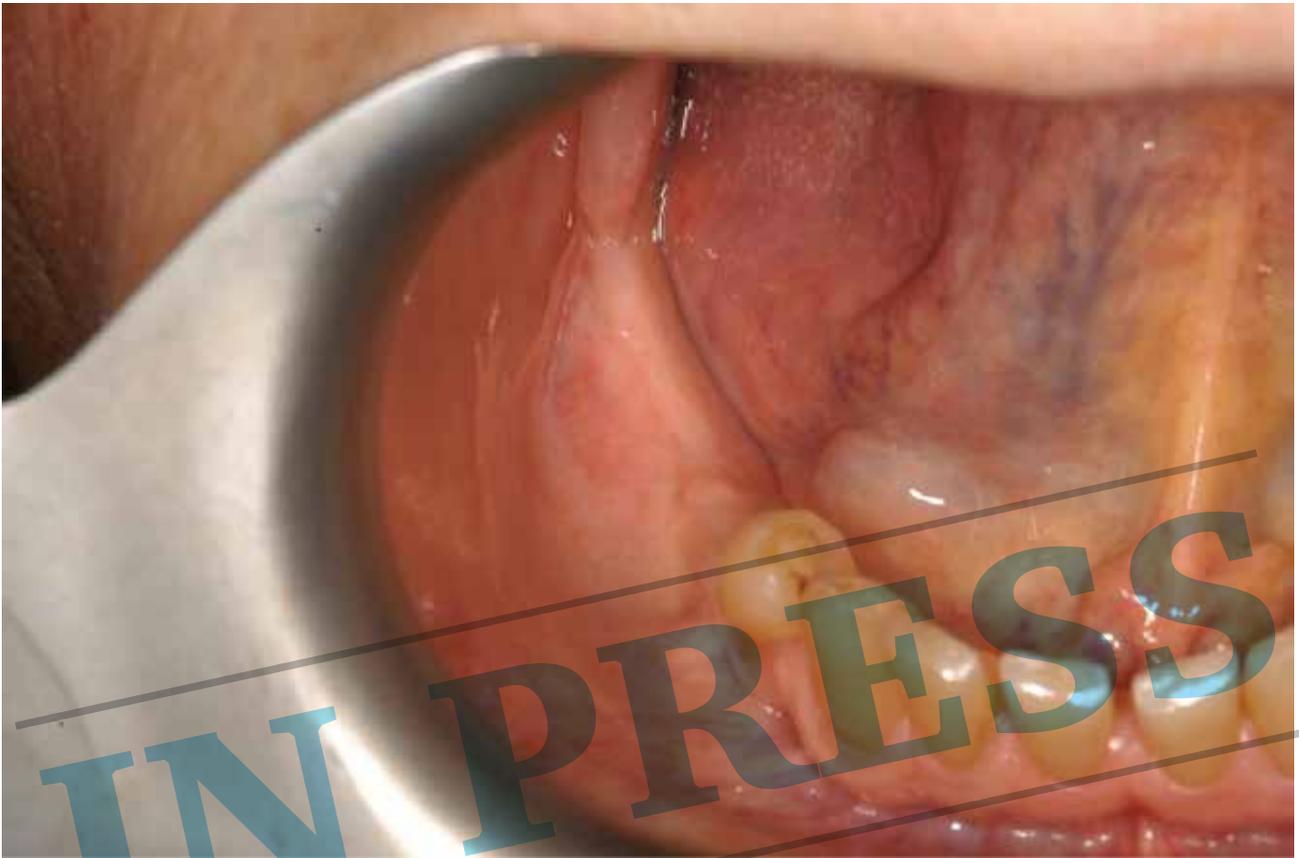


Figure 8 - Region mucosa after 3 years of follow-up.



Figure 9 - Radiographic control 3 years of age surgical intervention.

DISCUSSION

The literature suggests that BP chronic use can raise in a serious adverse effect: BRONJ [5]. Its occurrence is almost exclusive to gnathic bones, possibly because the oral cavity is subject to constant trauma from jaw movements, and by direct contact with several pathogenic microorganisms [11]. Added to this fact, there is still inadequate bone response to metabolic demands due to the presence of BP, which alters the bone remodeling and favors avascular necrosis, culminating in the appearance of osteonecrosis [1,2].

There is an important discussion about the causal association between the use of BP and the onset of osteonecrosis in patients previously submitted to extractions. This dental procedure is cited as the main local risk factor for BRONJ, followed by trauma and behaviors that lead to bone damage [12]. In this case, the patient underwent endodontic procedure prior to BRONJ, suggesting that local trauma by the instrumentation or even the clamp pressure in the mucosa during the complete isolation procedure, which may have been the cause for the development of osteonecrosis. In this context, it becomes eminent responsibility of health professionals, especially the dentist in the search for knowledge about the current theme, in planning their activities in choosing elective procedures, as well as the minimization of any factor that may induce the osteonecrosis.

About the osteonecrosis clinical features, the jaw presents how most common site, mainly the lingual surfaces of the posterior region and thin mucosa areas over bony prominences [13]. The average age for its manifestation occurs around 66 years and mainly affects females [7]. The present study shows similar data for predominant location and age, but occurs in a male patient. A plausible explanation for the increased number of diagnoses occur in women, due the increase in annual incidence of osteoporosis [14] and hence the large BP prescription for its treatment [3]. The higher

frequency of multiple myeloma and breast cancer in women may also explain the higher incidence of osteonecrosis in this sex [15].

The BP intravenous administration appears to confer a greater risk than oral administration, since that intravenous BP are more potent and have greater bioavailability compared to oral use. About 50 % of intravenous BP is bioavailable for incorporation into the bone matrix, while that in via oral BP 1 % on average is embedded in the bone [16]. Additionally, treatment time with BP also has influence in the BRONJ appearance, so, as longer the treatment time, the risk of osteonecrosis increases [17]. Marx et al [5] showed that the average time from onset of lesions ranged from 9 to 14 months for patients who were intravenous therapy with pamidronate or zoledronic acid, and three years in patients taking alendronate for osteoporosis treatment. In our study, the patient used the zoledronic acid intravenously for approximately one year, which was enough time to onset of osteonecrosis, corroborating with literature findings.

Since 2003, BRONJ treatment is a source of concern for the dental area [18], provided that there is no definitive treatment protocols and the various treatments described in the literature have indexes success variables [7,8]. Accordingly, the classification stages of the disease can guide therapeutic choices [6,9], but the general health of the patient and the degree of biological response should be carefully evaluated by defining the choice of treatment, regardless of the clinical stage diagnosed.

In general, there is a strong tendency for more conservative treatments, which have a lower risk of bone exposure, edema, pain and bleeding [7, 19, 20], with the disadvantage of being a continuous therapy, may further weaken the patient systemic condition, and sometimes not get the stagnation, regression or the resolution of the lesion. However, the literature have demonstrated excellent results for more invasive approaches [21–23], with data rates

of 90 % success [24]. The surgical management has been proposed for cases where conservative treatment is unsuccessful or even as a top choice therapy [10, 25]. Our study presents a BRONJ at stage 1, for which initially applied a conservative therapy (mouthwash associated with systemic antibiotics) and lasting, not getting response; we opted for surgical intervention, which led to the case resolution. Thus, we confirm the healing findings by a more invasive technique contributing to the current literature through another example for the BRONJ management. On the other hand, remains the question whether the election of surgical treatment as a first option could provide an even better prognosis for this patient, with more rapid remission of the lesion and reduced antibiotics prescription.

Based on the presented case report and literature, we can conclude that the osteonecrosis of the jaws associated with the BP use is a serious complication; it can be harmful to the patient, besides being management difficult in the dental clinic. The knowledge of dentist about this pathology is essential to prevent, diagnose and treat this disease the most appropriate way. Although the treatment of BRONJ remains challenging and complex, surgical therapy is a treatment option for lesions in early clinical stages and resistant to conservative treatment, providing a better prognosis and quality of life for the patient.

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