

UNIVERSIDADE PAULISTA – UNIP
PROGRAMA DE MESTRADO EM ODONTOLOGIA

**OSTEONECROSE DOS MAXILARES POR
BIFOSFONATOS: AVALIAÇÃO DE UMA SÉRIE DE
CASOS DE UMA FACULDADE DE ODONTOLOGIA**

LUIZ FERNANDO SCALLI MATHIAS DUARTE

Dissertação apresentada ao Programa de Pós-graduação em Odontologia da Universidade Paulista – UNIP para a obtenção do título de mestre em Odontologia

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APROVADO EM:

BANCA EXAMINADORA

_____/_____/_____
PROF. DR. MARCO ANTONIO TREVIZANI MARTINS
UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

_____/_____/_____
PROF. DR. MARCIO ZAFFALON CASATI
UNIVERSIDADE PAULISTA - UNIP

_____/_____/_____
PROF. DR. LUCIANO LAURIA DIB
UNIVERSIDADE PAULISTA - UNIP

DEDICATÓRIA

Dedico este trabalho aos meus pais, **Luiz Roberto** e **Maria Izilda**, que tornaram esta conquista possível e aos meus irmãos, **Andrea**, **Alexandre** e **Luciana** que sempre apoiaram minhas decisões e encararam comigo este desafio.

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RESUMO

Bifosfonatos são drogas que apresentam atividade osteoclástica e anti-angiogênica, utilizadas no tratamento de doenças que afetam o metabolismo ósseo como a osteoporose e metástases ósseas. Desde 2003, um efeito adverso chamado “Osteonecrose dos maxilares por bifosfonatos” (OMB) tem sido relatado e os mecanismos associados à sua ocorrência e evolução ainda não são completamente conhecidos.

O objetivo do presente estudo foi avaliar retrospectivamente prontuários de pacientes com lesões orais tratados na clínica de Estomatologia da Faculdade de Odontologia da Universidade Paulista (UNIP) da cidade de São Paulo, no período entre janeiro de 2004 a dezembro de 2011 em busca de pacientes portadores de OMB, com ênfase na identificação de fatores relacionados ao aparecimento e evolução da doença.

Dentre os 2342 prontuários avaliados, 13 casos corresponderam aos objetivos do estudo, sendo 12 do sexo feminino. Nove utilizavam a droga em decorrência de metástases de câncer de mama, 1 de câncer de próstata e 3 por osteoporose. Dez eram usuários de bifosfonatos intravenosos e 3 faziam uso oral da droga. Oito casos ocorreram em mandíbula, 4 em maxila, e 1 em mandíbula e maxila. Os 13 pacientes apresentavam estágio II da doença no diagnóstico. Sete casos ocorreram após extrações dentárias, 2 após fixação de implantes, 2 espontaneamente e 2 em pacientes que apresentavam doença periodontal. Seis pacientes realizaram a dosagem de CTX, observando-se em 3 deles alterações com a interrupção da medicação. O tratamento cirúrgico foi realizado em 10 pacientes, sendo em 6 deles associado ao PRP. Três pacientes tratados conservadoramente apresentaram boa evolução ao tratamento. A cura da OMB ocorreu em 4 casos, 6 regrediram para o estágio I e 3 se mantiveram em estágio II. Em 8 pacientes houve a interrupção temporária do uso da droga, não observando-se relação com a evolução do tratamento. Sete pacientes foram reabilitados pós-tratamento, sendo 5 deles por meio de próteses parciais removíveis, 1 através de prótese total e 1 com prótese sobre implante do tipo *overdenture*.

Diante das diversas controvérsias que ainda existem na literatura, torna-se necessária a realização de novos estudos multiinstitucionais sobre o assunto e fica patente a importância das faculdades de Odontologia na formação de cirurgiões-dentistas preparados para intervir em equipes multiprofissionais na área.

Palavras-chave: Osteonecrose. Maxilares. Bifosfonatos

LISTA DE ABREVIATURAS

OMB – Osteonecrose dos maxilares por bifosfonatos

UNIP – Universidade Paulista

CTX – Telopectídeo C-terminal de colágeno tipo 1

PRP – Plasma rico em plaquetas

FDA – Administração de medicamentos e alimentos

AAOMS – Associação Americana de Cirurgiões Orais e Maxilofaciais

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1. INTRODUÇÃO

Medicamentos da classe dos bifosfonatos atuam na remodelação óssea ao interferirem na atividade osteoclástica e angiogênese. Dessa forma, são considerados drogas importantes para pacientes acometidos por doenças ósseas metabólicas como a osteoporose, mielomas múltiplos e metástases ósseas, que ocasionam distúrbios osteopênicos causadores de susceptibilidade dos ossos à dor e fratura⁽¹⁻³⁾.

Os bifosfonatos são classificados em não nitrogenados (etidronato e clodronato) e nitrogenados (pamidronato, risedronato, alendronato e ácido zoledrônico). Embora seu mecanismo de ação ainda não seja totalmente esclarecido, já se conhece sua atuação no aumento da apoptose e inibição da diferenciação osteoclástica, na quebra da interação osteoblasto-osteoclasto, atuando como potentes inibidores da reabsorção óssea e interferindo na regeneração⁽⁴⁻⁶⁾.

Com a autorização, inicialmente pelo pamidronato, nos anos 90 pela *Food and Drug Administration (FDA)* e com a aprovação do ácido zoledrônico em 2002, milhares de pacientes mundialmente recebem esse tipo de tratamento com indicações principais de metástases ósseas e osteoporose⁽⁷⁾.

A Osteonecrose dos Maxilares por Bifosfonatos (OMB) foi primeiramente descrita como efeito adverso da droga em 2003 por Marx⁽⁵⁾, sendo definida pela presença de osso necrótico exposto em região maxilofacial por mais de oito semanas em pacientes usuários de bifosfonatos que não haviam realizado radioterapia de cabeça e pescoço^(5,7).

A incidência da doença é indefinida, podendo variar de 1 a 12% de casos em usuários de drogas intravenosas e, menos comum em usuários orais, com incidência menor que um caso por 100,000 pessoa - ano de exposição⁽⁸⁻⁹⁾.

Os bifosfonatos são utilizados na forma oral, mais comumente no tratamento da osteoporose e, na forma intravenosa, frequentemente em casos de metástases ósseas. A forma intravenosa é considerada mais potente e com maior risco de

causar a OMB ⁽¹⁰⁾. Esse risco pode ser potencializado pelas condições gerais fragilizadas de pacientes com câncer metastático e comorbidades como diabetes mellitus e imunossupressão, além do uso concomitante de medicações como quimioterápicos e corticoides. Usuários das formas orais são frequentemente mais saudáveis utilizando a medicação de forma preventiva para osteoporos, o que pode também contribuir para a menor incidência de OMB ⁽¹¹⁾.

Manifestações clínicas como dor intensa, áreas de parestesia, ulcerações na mucosa e exposição óssea subjacente foram observadas como características da OMB em estágios mais avançados. No entanto, em fases iniciais, frequentemente não existem sintomas e as manifestações radiográficas podem não ser detectadas ⁽¹¹⁻¹²⁾. Em 2006 foi criada uma classificação clínica conforme a severidade em que a doença se apresenta. O estágio I da OMB foi definido por exposição óssea necrótica assintomática, o estágio II pela necrose óssea com exposição associada à dor e infecção e o estágio III pela necrose óssea com exposição associada à dor, infecção, fraturas patológicas ou fístulas cutâneas ⁽¹⁾.

Os fatores de risco para desenvolvimento da necrose podem estar relacionados à natureza da droga, fatores locais e sistêmicos, assim como à potência e duração da medicação ⁽¹³⁾. Cirurgias dentárias são consideradas como principais causas da OMB, no entanto, a presença de uma mucosa fina e traumas protéticos também são considerados fatores de risco, assim como a ocorrência espontânea da doença ⁽¹⁴⁾. A mandíbula é relatada como local de maior prevalência, mas a ocorrência em maxila, ou em ambas as arcadas simultaneamente, também foi observada ⁽¹⁰⁾.

A dosagem do telopeptídeo C-terminal de colágeno tipo 1 (CTX) tem sido utilizada como indicador para se avaliar a supressão da remodelação óssea gerada pelos bifosfonatos, estabelecendo valores do exame abaixo de 100pg/ml como de alto risco para a ocorrência de OMB, entre 100 e 150 pg/ml de risco moderado e acima de 150 pg/ml de risco mínimo; todavia, exames radiográficos, clínico, uso concomitante de outras drogas e a história médica dos doentes devem ser considerados ao se determinar condições de risco de OMB ⁽¹⁵⁻¹⁶⁾. A AAOMS afirmou em 2007 que, pacientes usuários de bifosfonatos orais a menos de 3 anos que não apresentam fatores de risco, não necessitam de qualquer alteração ou atraso no

planejamento de um procedimento de cirurgia oral , mas sugeriu a confecção de um termo de consentimento informado sobre o risco de OMB ⁽⁷⁾.

Diante das incertezas que existem diante da doença, a prevenção é a principal conduta preconizada na literatura ^(7, 17). No entanto, diversos autores têm relatado diferentes possibilidades de tratamento para a OMB, desde o uso de antissépticos bucais, como clorexidina a 0,12%, antibioticoterapia sistêmica, a intervenções cirúrgicas, associadas ou não a moduladores biológicos, como o plasma rico em plaquetas (PRP), que ainda não são consenso, por não serem entendidos os mecanismos patológicos de ocorrência da OMB. Fatores que têm sido considerados importantes pelos autores são quanto à necessidade ou não da interrupção dos bifosfonatos, assim como a interação multidisciplinar referente à tomada de decisões e condutas terapêuticas ^(7, 13, 18-22).

Diante das controvérsias sobre os fatores relacionados a ocorrência, diagnóstico e tratamento da doença, a proposta do presente estudo é avaliar uma série de casos diagnosticados e tratados em uma Faculdade de Odontologia, visando avaliar as causas e evolução clínica da OMB.

2. PROPOSIÇÃO

A proposta do presente estudo foi avaliar retrospectivamente prontuários, exames de imagem, exames laboratoriais e fotografias de pacientes atendidos na Clínica de Estomatologia da Universidade Paulista (UNIP), no período entre janeiro de 2004 a dezembro de 2011, em busca de casos diagnosticados e tratados de Osteonecrose dos Maxilares por Bifosfonatos com ênfase na identificação de fatores relacionados ao aparecimento e evolução da doença.

3. ARTIGO

BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAWS: ANALYSIS OF A CASE SERIES AT A DENTAL SCHOOL.

ABSTRACT

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is an adverse effect of certain drugs that are used to treat bone metabolism diseases, such as osteoporosis and bone metastases.

The present study retrospectively evaluated the clinical characteristics and evolution of cases of BRONJ that were diagnosed and treated at a dental school from 2004 to 2011. During that period, 13 patients met the criteria of the study among a population of 2342 patients with oral lesions.

Of the 13 patients, 12 were females. Ten were intravenous bisphosphonate users, and nine had breast cancer as the primary disease. Eight mandibular cases were observed. Eight patients interrupted the use of the bisphosphonates temporarily during the treatment. Surgical treatment was conducted in 10 patients, which was associated with platelet-rich plasma (PRP) in six cases, which led to a regression to Stage I in 50% of the cases and cure in 33.3%. Of the total sample, four (30.8%) cases were cured, six (46.1%) regressed to Stage I, and three (23.1%) of the cases remained in Stage II after treatment. Dental rehabilitation was possible in seven patients.

The dissemination of knowledge among professionals is essential for the prevention and early diagnosis of BRONJ. Dental schools must act as reference centers and participate in the multidisciplinary care of bisphosphonate users.

INTRODUCTION

Bisphosphonate drugs act on bone remodeling by interfering with osteoclastic activity and angiogenesis. Consequently, bisphosphonates are indicated for patients with metabolic bone diseases, such as osteoporosis, multiple myeloma and bone metastases, which give rise to osteopenic disorders that cause susceptibility to bone pain and fractures ⁽¹⁻³⁾.

Bisphosphonates are classified as being non-nitrogenous (etidronate and clodronate) or nitrogen-containing (pamidronate, alendronate, risedronate and zoledronic acid). Although the mechanisms of these drugs are not yet fully understood, their action on increased apoptosis and osteoclastic inhibition is already known. These medications are also known to disrupt the osteoblast-osteoclast interaction, thereby interfering with the regeneration and inhibition of bone resorption ⁽⁴⁻⁶⁾.

Bisphosphonates were first used in the 1990s in the form of pamidronate. Their success in controlling osteoporosis and bone metastases led to a worldwide increase in the number of prescriptions ⁽⁷⁾.

These drugs can be administered orally, typically for the prophylactic or therapeutic treatment of osteoporosis, or intravenously as drugs of higher potency, which are often indicated in cases of bone metastases ⁽⁷⁻¹⁰⁾.

Since 2003, an adverse effect called bisphosphonate-related osteonecrosis of the jaws (BRONJ) began to be reported. BRONJ is characterized by exposed necrotic bone in the maxillofacial region for more than 8 weeks in bisphosphonate users with no history of head and neck radiotherapy ^(5, 7).

Considering the high volume of prescriptions, the incidence of BRONJ could be considered to be low. This incidence is also undefined, ranging from 1 to 12% in intravenous users and less among oral users, with an incidence of less than one case per 100,000 person-years of exposure ⁽¹⁰⁻¹¹⁾.

The tendency of osteonecrosis to affect the maxillary bones can be explained by the greater concentration of bisphosphonates in these structures, which are

subject to constant functional trauma from chewing and consequent constant bone remodeling ^(8, 12-14).

Clinical manifestations, such as intense pain, paresthesias, mucosal ulcerations and exposed underlying bone, are characteristics of advanced stages of BRONJ ⁽¹⁵⁾. However, in the early stages, there are often no symptoms, and radiographic manifestations may not be detected ⁽¹⁶⁻¹⁷⁾. In 2006, a classification based on the clinical presentation of the disease was created. This classification system defines Stage I of BRONJ as asymptomatic necrotic bone exposure, Stage II as bone necrosis with exposure combined with pain and infection and Stage III as bone necrosis with exposure combined with pain, infection, pathological fractures or cutaneous fistulas ⁽¹⁾.

The mandible has been reported as the site of the greatest prevalence of BRONJ, but the maxilla can also be involved, and both arches can be affected simultaneously ⁽⁸⁾. Several risk factors can be related to an outbreak of the disease, including the nature of the drugs, local and systemic factors, the drug's potency, the duration of use and the drug's absorption rate ^(9, 18). Necrosis can occur spontaneously; however, dental surgeries are considered to be the main triggering factors, followed by prosthetic trauma, periodontal disease and implant fixation ^(8, 13, 15). One of the exams used to assess BRONJ risk is the serum C-terminal telopeptide level of Type 1 collagen (CTX), which can provide an index of bone turnover suppression; however, x-ray examinations, clinical examinations, concomitant use of other drugs and the patient's medical history must always be considered ⁽¹⁸⁻¹⁹⁾.

Regarding the treatment of BRONJ, reported therapeutic options include the use of such antiseptics as 0.12% chlorhexidine, systemic antibiotics and surgical interventions, either alone or combined with biological modulators such as platelet-rich plasma (PRP). However, there is still no consensus because the exact pathological mechanisms of disease occurrence are not understood, leading to varied therapeutic responses. Possible important factors include whether bisphosphonate interruption is indicated in the presence of BRONJ and the need for multidisciplinary interaction regarding decision-making and therapeutics ^(7, 9, 20-24).

Prevention should be the primary strategy for bisphosphonate users ^(7, 25); however, many of these patients are regularly treated by different dentists, not all of

whom are knowledgeable about the subject. Therefore, the therapeutic and preventative issues related to bisphosphonate use should be emphasized in professional dentistry training, and the college's role in this training must be valued.

In view of the controversies over the factors related to the occurrence, diagnosis and treatment of BRONJ, this study proposes to evaluate the clinical features of a case series diagnosed and treated at a dental school.

MATERIALS AND METHODS

The files of the Stomatology Clinic of Paulista University (UNIP) Dental School from January 2004 to December 2011 were reviewed in search of cases with records of BRONJ. During that period, 2342 new patients with oral lesions were treated, and 13 matched the object of study and were analyzed retrospectively. The 13 cases were referred to the UNIP Stomatology Clinic by different clinics and professionals outside the College after the occurrence of jawbone exposure, which could not be properly diagnosed or treated at the referring centers.

The data collected were compared with respect to gender, age, type of bisphosphonate used, reason for drug use, presence of comorbidities, region of involvement, initial BRONJ stage ⁽¹⁾, triggering event, drug interruption, CTX dosage, treatment, adjuvant therapies, anatomopathological examination, final BRONJ stage and post-treatment dental rehabilitation.

This study was approved by the Committee of Ethics in Research of UNIP under Protocol Number 949/11 CEP/ICS/UNIP.

RESULTS

The demographic data and clinical characteristics of the patients in this study are shown in Table 1.

TABLE 1 (page 30)

The sample consisted of 12 (92.3%) women and one man (7.7%) with a mean age of 67.3 years (range: 48 to 84 years).

Three (23.1%) patients had osteoporosis. Ten (76.9%) had bone metastases, nine of which were due to breast cancer and one due to prostate cancer (Table 1).

Ten patients (76.9%) used bisphosphonates intravenously. Of these, seven used zoledronic acid, two used pamidronate and one used a combination of zoledronic acid and pamidronate. Three (23.1%) patients used oral alendronate (Table 1).

Comorbidities were found in two (15.4%) patients: one cardiac patient and one diabetic and hypertensive patient.

The site affected by BRONJ was the mandible in eight (61.5%) cases, the maxilla in four (30.8%) cases and both arches in one (7.7%) case (Table 1).

At diagnosis, all 13 patients presented with Stage II of BRONJ, which is characterized by exposed necrotic bone, pain and infection (Table 1).

A history of tooth extraction at the site of necrosis was reported by seven (53.8%) patients. Spontaneous lesions occurred in two (15.4%) cases. Two (15.4%) patients presented with severe periodontal disease (Figure 1) in the affected area, and in two (15.4) cases, BRONJ occurred after osseointegrated implants were affixed (Figure 2; Table 1).

CTX levels were assessed for six (46.1%) patients, three before and after drug discontinuation. The values are presented in Table 2.

TABLE 2 (page 31)

Surgical resection of bone necrosis was performed in ten (76.9%) patients, and PRP was used (Figure 1) on the remaining bone in six (46.1%) patients (Figure 1). In the three (23.1%) nonsurgical cases, only conservative therapies were performed, including clindamycin-based antibiotics (300 mg, every 6 hours) and irrigation with an antiseptic (chlorhexidine 0.12%) (Tables 1 and 3).

TABLE 3 (page 32)

The progression of each treatment was defined as follows: cured, regression to Stage I, persistence of Stage II or progression to Stage III.

Of the six (46.1) cases treated surgically with PRP, two (33.3%) were cured, and three (50%) regressed to Stage I (Figure 1 D). One patient (16.7%) who received this treatment remained in Stage II (Table 3).

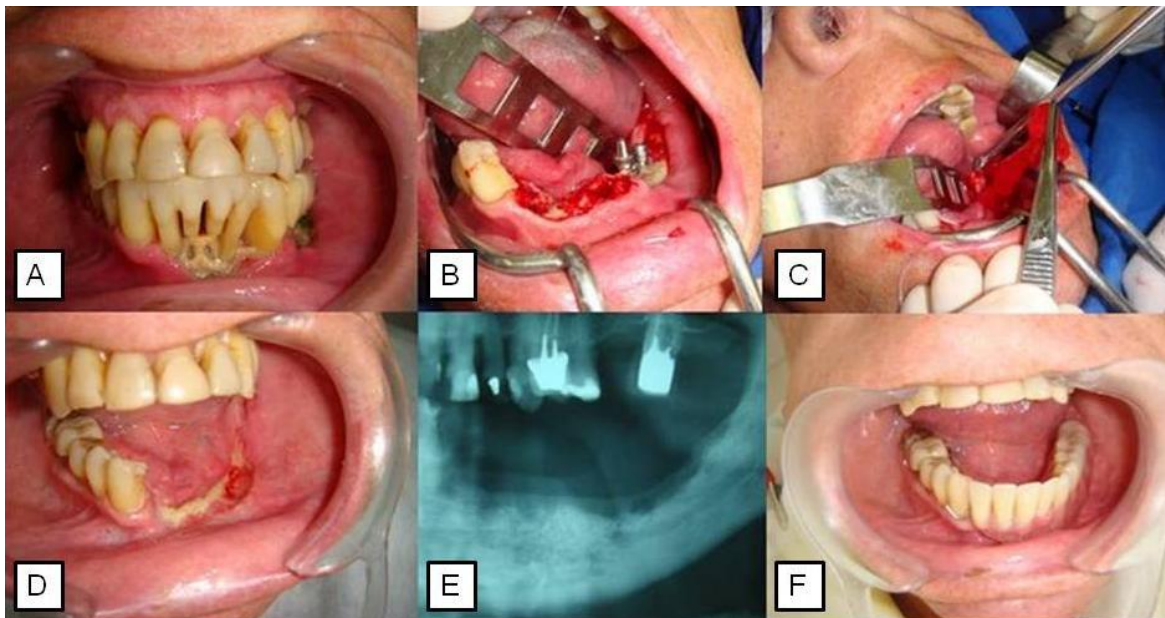


Fig. 1. A male patient, 71 years old, who was an intravenous user of zoledronic acid for metastatic prostate cancer. (A) Severe periodontal disease with bone exposure and necrotic alveoli. (B) Tooth extraction, implants and necrosis osteotomy. (C) Filling of the bone defect with PRP. (D) After three weeks, the disease has regressed to Stage I. (E) An image of the irregular crest after bone resection. (F) A partial removable denture with tissue conditioner in position.

Of the four (30.8%) cases subjected to resection without PRP, three (75%) regressed to Stage I, one (25%) remained in Stage II, and none were cured (table 3).

Among the three (23.1%) patients treated conservatively, two oral bisphosphonate users with osteoporosis were cured (Figure 2), and one intravenous user remained at Stage II.

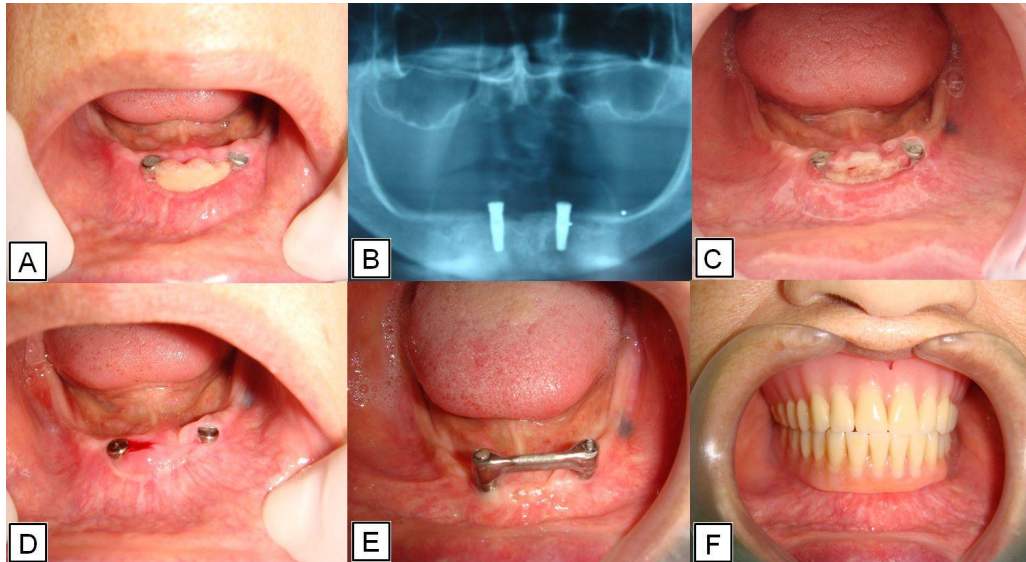


Fig. 2. A female patient, 82 years old, who was a user of oral alendronate for osteoporosis. (A) Bone exposure for three months after implant fixation. (B) The absence of signs of bone lysis. (C) Four months after drug suspension and irrigation with antiseptic and antibiotic therapy, initial healing is noted. (D) Full healing of the exposed area after six months of treatment. (E) Fixation of a bar between the implants ten months after the implants were installed. (F) Overdenture prosthesis in position.

Bisphosphonate use was interrupted during BRONJ treatment for a short period of time with the approval of the prescribing physician in eight (61.5%) patients who exhibited controlled primary disease. In this group, six (75%) patients showed good progress, with three of them (37.5%) being healed, three (37.5%) regressed to Stage I, and one (25%) remained at Stage II. In the group of five (38.5%) patients for whom the primary disease did not allow drug interruption, four (80%) showed good treatment progress of BRONJ, including one patient (20%) who was healed and three (60%) who regressed to Stage I. One patient (20%) who continued using the medicine remained at Stage II after BRONJ treatment (Table 1).

Anatomopathological examinations were requested in ten surgically treated cases. Necrotic bone tissue was found in all of the specimens, and *Actinomyces sp.* were also observed in two (15.4%) specimens with bone necrosis.

Seven (53.8%) cases underwent post-treatment dental rehabilitation (Table 1). Removable partial dentures (Figure 1.F) were affixed in five (38.5%) patients, one (7.7%) was rehabilitated with full dentures and one (7.7%) received an overdenture (Figure 2 F) over implants that had been installed prior to the onset of BRONJ. Six (46.1%) patients were not rehabilitated; of these, three (23.1%) remained at Stage II after treatment, two (15.4%) died as a result of metastases, and one (7.7%) could not be rehabilitated due to technical difficulties caused by the extent of bone loss.

DISCUSSION

This study describes the clinical progression of BRONJ cases diagnosed and treated in a specialized mouth disease clinic at a dental school in the city of São Paulo. Considering that 2342 patients were treated with oral lesions at the clinic between January 2004 and December 2011, the 13 BRONJ cases represent a small number but one that is comparable with many studies in the literature ^(20,29,33,26). The low number of diagnosed cases at the dental school can be explained both by the generally low incidence of the disease and by the limited relationship between hospitals and dental schools.

In Brazil, the concept of dentists being part of medical teams is not widespread, so it is common to refer patients to private dentists when dental problems occur. These private dentists are often disconnected from the therapeutic interactions. Preventive measures and the early diagnosis of BRONJ can be improved by cooperation between clinicians, dentists, maxillofacial surgeons and oncologists ⁽¹⁵⁾. Therefore, it is essential that knowledge about the subject be disseminated and that specialized clinics in dental schools become open reference centers for the preventive and therapeutic management of bisphosphonate users.

The higher prevalence among women in our study is consistent with the findings of other studies ^(12, 22-23, 26-29). This imbalance could be explained by the fact that the primary diseases that are most often treated with bisphosphonates (i.e., osteoporosis and breast cancer metastases) are more common among women, although other gender differences could also be related to this observation.

The age of primary disease occurrence explains the mean age (67.3 years) of the patients included in this study ^(12, 21-22, 29-30). As the population ages, more people tend to suffer from and be treated for osteoporosis, and the number of necrosis cases in oral bisphosphonate users may increase ⁽¹⁰⁾.

The sample of patients analyzed in this study showed greater BRONJ involvement among oncological patients ^(12, 27, 22-23, 29-30), especially women with metastatic breast cancer. It is likely that the use of more powerful intravenous drugs for a longer period of time to control metastases generates greater toxicity and explains the prevalence of osteonecrosis in cancer cases. In addition, chemotherapy

treatment that involves immunosuppressants may be related to a greater risk of infections and BRONJ in these patients ⁽¹⁰⁻¹¹⁾.

Comorbidities were not commonly found in our study; however, they are discussed in the literature without conclusive links between patients' systemic conditions and the occurrence of osteonecrosis ⁽²⁶⁻²⁷⁾.

Similar to other case studies ^(15, 17-19, 21, 23, 30), this study demonstrated that the mandible was most likely to be affected by BRONJ. It is possible that the anti-angiogenic properties of bisphosphonates in less vascularized bone structures are responsible for the greater number of mandibular cases ⁽³¹⁻³²⁾.

All of the cases in the present study had been diagnosed after symptoms developed, which supports the literature's findings that the diagnosis of BRONJ is difficult during asymptomatic phases ^(22-23, 26-27). Although certain authors report that imaging tests can identify bone changes caused by bisphosphonates ⁽³²⁾, this identification often does not occur because the disease does not show early radiographic signs ⁽¹⁵⁻¹⁷⁾. The difficulty in diagnosis reinforces the importance of prevention as the main approach to BRONJ, with an emphasis on dental evaluation ⁽³³⁾ to identify outbreaks of periodontal disease or chronic infection prior to initiating therapy with bisphosphonates.

Dental extractions were the most frequent triggering factors for the patients in the present study, which is similar to the findings of other reports ^(8, 12, 15, 20, 22-23, 27, 29-30). This observation can be explained by the changes that bisphosphonates can cause in the osteoclastic function, which delay the beginning of alveolar healing and favor the development of BRONJ after tooth extractions ⁽²⁶⁾. Patients at risk for the disease should have good oral health when bisphosphonate therapy begins to avoid the need for tooth extractions during treatment with the drug ⁽³⁰⁾. In this study, two cases occurred after implant fixation (Figure 2.A) in patients who had used oral bisphosphonates for more than three years. This finding reinforces the view that surgical manipulation presents risks and requires caution. In addition, careful anamnesis is necessary to identify possible users of bisphosphonates and the dosage and duration of treatment prior to surgery ⁽³⁴⁾.

In the present study, three patients who underwent the CTX examination were at risk for BRONJ, according to the values established by Marx *et al.* in 2005⁽⁸⁾ (Table 2). Patients with a high rate of bone remodeling demonstrate high serum indices, whereas those with reduced bone remodeling rates present low serum indices⁽³⁵⁾. The treatment for these three patients was defined by the CTX results, clinical dental examination and radiographic analyses^(19, 35), which resulted in curing two oral bisphosphonate users who were treated conservatively and in regression to Stage I for one intravenous bisphosphonate user who was surgically treated with PRP. The increase in CTX values after medication use was suspended and the subsequent good progress of the cases reinforce the significance of these values as an indicator of the bone remodeling rate, which can inform therapeutic decision-making. However, there are still doubts about the reliability of the exam because of possible interference in the results from the use of other medicines and from bone tissue metastases⁽¹⁹⁾.

The pathological and repair mechanisms of BRONJ are not fully understood, which raises doubts and controversies when choosing a therapy⁽²⁰⁾. This study showed better results with PRP use (Figures 1.B and 1.C) than with exclusively surgical treatments. PRP's high autologous platelet concentration provides a source of protein growth factors that improves wound healing and bone regeneration^(20, 22, 36). This feature may be responsible for improvements in the treatment progression.

The good progression of conservative treatment^(33, 37) in oral users is most likely related to the lesser extent of necrosis in patients who were users of less powerful medicines, with better general health conditions and with a greater possibility of interrupting the drug without affecting the primary disease (Figures 2.C and 2.D). This combination of factors may explain the healing of two patients in the present study who were oral users compared with the permanent Stage II status of one intravenous user who was treated conservatively.

Discontinuing the drug after BRONJ diagnosis is controversial. It is natural to imagine that the use of a drug that causes a serious side effect should be interrupted when that side effect appears. However, as these medications are used to control bone metastases of aggressive tumors, their benefits almost always outweigh their risks⁽²⁸⁾. In eight cases in this study in which the primary diseases were controlled,

the use of bisphosphonates was temporarily interrupted, in accordance with the prescribing physician's recommendations ^(24, 30). The comparison of the group of patients who discontinued the use of bisphosphonates with those who continued to use them showed no significant difference in the evolution of BRONJ. This result suggests that the decision about drug interruption should be discussed by the multidisciplinary team, assessing the characteristics of each case individually and considering the pros and cons, once other studies report that a temporary break in medication use can possibly reduce symptoms and help improve the clinical condition of BRONJ ⁽¹¹⁻¹²⁾.

The presence of *Actinomyces sp*, as was observed in two necrotic bone specimens in the present study, has been described in the literature ⁽¹⁴⁾; however, no reports have indicated whether the bacterium is pathogenic or whether it results from a secondary contamination.

Dental rehabilitation for BRONJ has been minimally discussed, most likely because there are still many aspects related to the etiology and treatment of the disease that remain to be discussed. However, the loss of support structures and teeth impacts the patients' quality of life. In this study, most of the rehabilitation cases involved removable partial dentures (Figure 1.F) using silicone tissue conditioners to minimize mucosal trauma ⁽¹³⁾. In one case, two osseointegrated implants served to support an overdenture after necrosis was cured, even though the implants were the triggering factor of BRONJ, (Figures 2.E and 2.F). Although it appears paradoxical, this outcome is consistent with studies showing that bisphosphonates promote osseointegration ⁽³⁸⁾.

The risk of retriggering local necrosis via prosthetic trauma must be weighed against the aesthetic benefits, masticatory functionality and emotional gains. Frequent follow-up visits for evaluations, prosthetic adjustments and replacement of the tissue conditioner are necessary to maintain the dentures in an appropriate condition that minimizes the patient's risk. Whereas a patient with BRONJ can present emotional and self-esteem problems related to the primary disease, early rehabilitation dentistry can be an important resource for improving their quality of life and can provide a stimulus to face the difficulties that the disease can present.

Within the limits of the study, we can observe that BRONJ, despite its relative rarity, presents serious manifestations and consequences. The impact of the disease appears to be increasing, based on the possible increase in the cases noted in the literature. It is known that patients are often not well referred, and few reference centers can diagnose and treat the disease. Dental schools should provide updated education to give undergraduate students and professionals the necessary knowledge to diagnose and, when necessary, refer patients to reference centers.

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Table 1: CLINICAL CHARACTERISTICS OF PATIENTS WITH BRONJ

Patients	Age	Gender	Primary disease	Bisphosphonate	Local	Stage at diagnosis	Trigger factor	Drug holiday	Treatment	Final stage	Rehab.
1	55	Fem	Osteoporosis	Alendronate	Mandible	II	Impl.	+	Cons.	Healed	RPD
2	82	Fem	Osteoporosis	Alendronate	Mandible	II	Impl.	+	Cons.	Healed	Overdenture
3	80	Fem	Osteoporosis	Alendronate	Mandible	II	Extrac.	+	Surg. + PRP	I	-
4	71	Fem	Breast cancer	Zoledronic acid	Maxilla	II	Extrac.	-	Surg.	I	RTD
5	64	Fem	Breast cancer	Zoledronic acid	Mandible	II	Extrac.	+	Cons.	II	-
6	54	Fem	Breast cancer	Zoledronic acid	Maxilla and mandible	II	Period.	-	Surg. + PRP	Healed	RPD
7	58	Fem	Breast cancer	Zoledronic acid	Maxilla	II	Extrac.	+	Surg. + PRP	Healed	RPD
8	63	Fem	Breast cancer	Zoledronic acid	Mandible	II	Spont.	-	Surg. + PRP	II	-
9	84	Fem	Breast cancer	Zoledronic acid	Mandible	II	Extrac.	-	Surg. + PRP	I	-
10	71	Fem	Breast cancer	Pamidronate	Mandible	II	Extrac.	+	Surg.	II	-
11	48	Fem	Breast cancer	Zoledronic acid + Pamidronate	Maxilla	II	Spont.	+	Surg.	I	-
12	74	Fem	Breast cancer	Pamidronate	Maxilla	II	Extrac.	-	Surg.	I	RPD
13	71	Male	Prostate cancer	Zoledronic acid	Mandible	II	Period.	+	Surg. + PRP	I	RPD

Abbreviations: BRONJ, Bisphosphonates related osteonecrosis of the jaws; Fem., female; Impl., dental implants; Extrac., dental extraction; Period., periodontal disease; Spont., spontaneous; Cons., Conservative; Surg., Surgery; PRP, Platelet Rich Plasma; Rehab., Dental Rehabilitation; RPD, Removable Partial Denture; RTD, Removable Total Denture

Table 2: CTX EVALUATION

PATIENT	BPS	TREATMENT	DRUG HOLIDAY	INITIAL CTX	FINAL CTX	FINAL STAGE
1	ORAL	CONS	YES	10 pg/ml	71 pg/ml after 3 months 113 pg/ml after 7 months 250 pg/ml after 14 months	HEALED
2	ORAL	CONS	YES	17 pg/ml	75 pg/ml after 4 months	HEALED
3	ORAL	SURG+PRP	YES	X	201 pg/ml	I
7	INTRAV	SURG+PRP	YES	X	331 pg/ml	HEALED
8	INTRAV	SURG+PRP	NO	223 pg/ml	X	II
13	INTRAV	SURG+PRP	YES	135 pg/ml	364 pg/ml after 9 months	I

Abbreviations: CTX, C- terminal telopeptide test; BPS, bisphosphonate; INTRAV, intravenous; CONS, conservative; SURG, surgery; PRP, platelet rich plasma.

Table 3: EVALUATION OF DISEASE PROGRESSION TO THE TYPE OF TREATMENT ACCORDING TO THE PRIMARY DISEASE

Primary disease	Clinical Stage	TREATMENT		
		CONSERVATIVE N (3)	SURGICAL N (4)	SURGICAL +PRP N (6)
OSTEOPOROSIS	Healed	2	-	-
	Regression from stage II to stage I	-	-	1
	Remained at stage II	-	-	-
CANCER	Healed	-	-	2
	Regression from stage II to stage I	-	3	2
	Remained at stage II	1	1	1

Abreviation: PRP, platelet rich plasma.

4. CONCLUSÕES

Após a extensa revisão da literatura e os resultados obtidos na análise retrospectiva dos casos tratados na Universidade Paulista, podemos apresentar os seguintes aspectos à guisa de conclusões:

1. A Osteonecrose dos Maxilares por Bifosfonatos é uma condição clínica que à despeito de sua baixa incidência, apresenta um importante significado clínico, podendo gerar graves conseqüências aos pacientes afetados;
2. Os mecanismos associados à sua ocorrência e evolução ainda não estão completamente conhecidos, entretanto os usuários de drogas injetáveis parecem apresentar um maior risco;
3. Diante do alto número de prescrições que ocorrem mundialmente, a expectativa de aumento da incidência é citada na literatura, tornando a participação do cirurgião-dentista fundamental, tanto na prevenção como na detecção precoce da condição;
4. O tratamento ideal ainda não está estabelecido, havendo controvérsias sobre condutas conservadoras e mais agressivas, com extensas ressecções das áreas afetadas. De modo geral, pode-se concluir que a doença tem curso crônico e que medidas sintomáticas e de melhoria de qualidade de vida são mais indicadas;
5. Quando indicado o tratamento cirúrgico, a associação com fatores de estimulação da cicatrização, como o plasma rico em plaquetas, parece apresentar efeitos benéficos;
6. A casuística apresentada nesse estudo retrospectivo da Faculdade de Odontologia da UNIP, embora seja pequena, apresenta um número de casos semelhantes à de diversas séries de casos descritas na literatura, o que mostra que ainda será necessário um maior agrupamento de casos para uma compreensão adequada dos aspectos relacionados à ocorrência e evolução da doença;

7. Quanto à distribuição epidemiológica e manifestação clínica, os resultados obtidos na presente análise estão semelhantes aos apresentados na literatura, destacando-se o fato de que a atuação terapêutica realizada na Faculdade de Odontologia da UNIP, também se preocupou com a reabilitação dentária durante e após o tratamento da osteonecrose, fato pouco discutido na literatura;
8. Diante das diversas controvérsias sobre a doença que ainda existem na literatura, torna-se necessária a realização de novos estudos multiinstitucionais sobre o assunto e fica patente a importância das faculdades de Odontologia na formação de cirurgiões-dentistas preparados para intervir em equipes multiprofissionais na área.

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6. ANEXOS

6.1. Fotos de casos clínicos de pacientes do estudo

Paciente 1

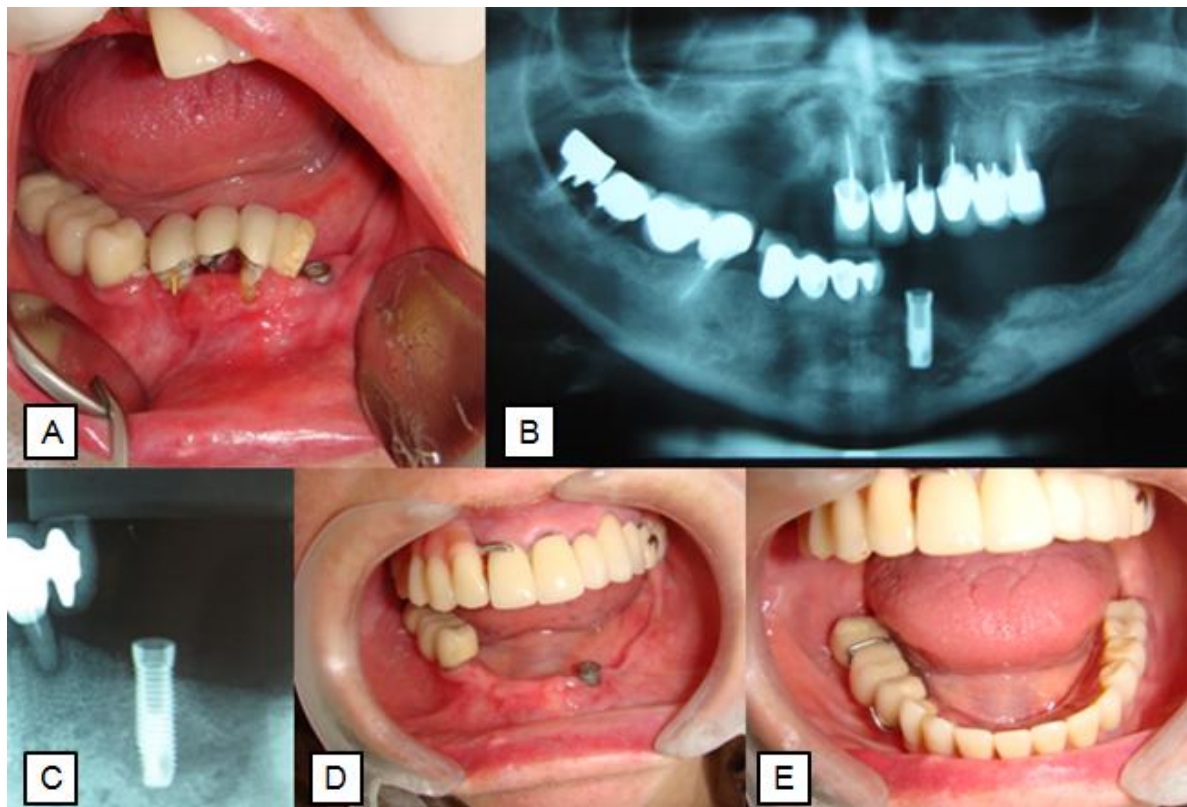


Fig. 1. Paciente do sexo feminino, 55 anos, usuária de alendronato por osteoporose.

(A) Exposição óssea por após a fixação de implante dentário.

(B) Radiograficamente observa-se imagem radiopaca difusa ao redor do implante e comprometimento periodontal dos dentes anteriores inferiores.

(C) Após 6 meses de suspensão da medicação e irrigações com antissépticos e antibioticoterapia, radiograficamente observa-se normalidade no trabeculado ósseo ao redor do implante.

(D) Mucosa saudável após extração de dentes comprometidos periodontalmente 8 meses após o início do tratamento.

(E) Prótese parcial removível com condicionador de tecido instalada 9 meses após o diagnóstico da OMB.

Paciente 2

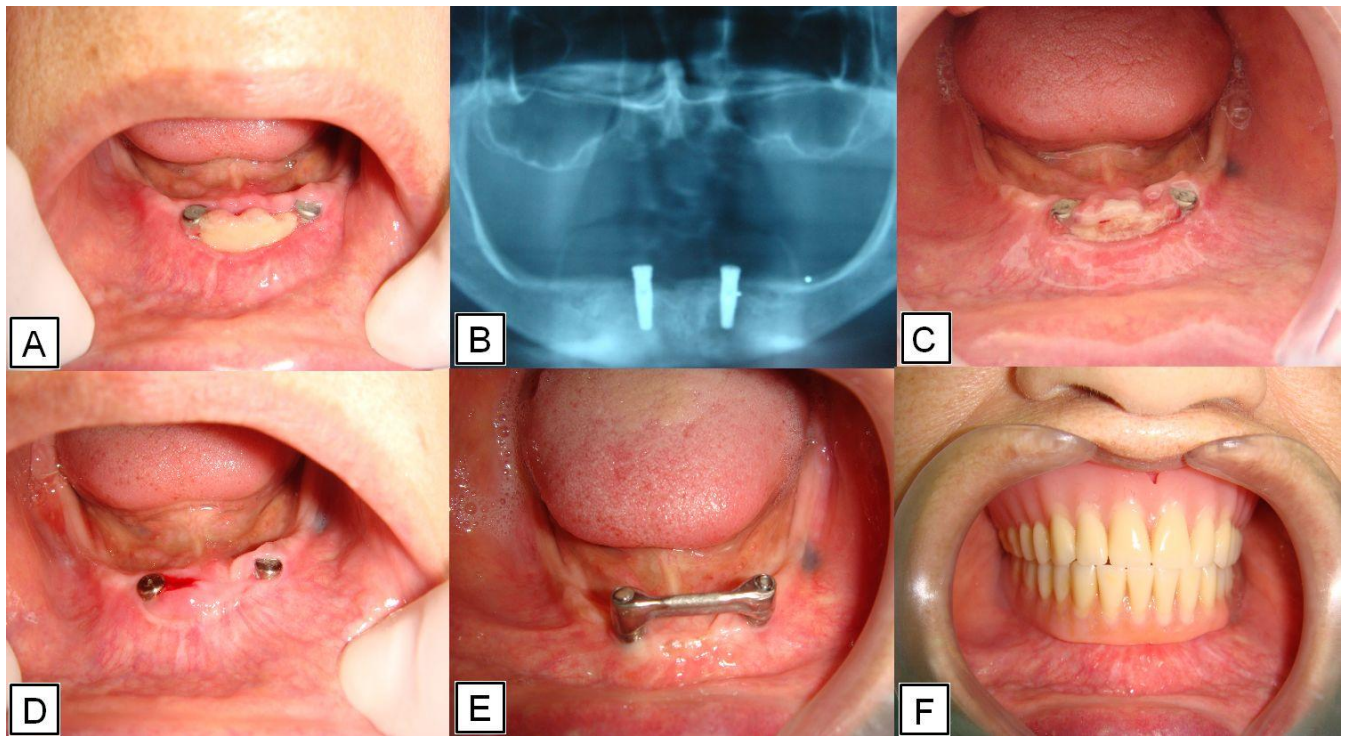


Fig. 2. Paciente do sexo feminino, 82 anos, usuária de alendronato por osteoporose.

(A) Exposição óssea por 3 meses após a fixação de implantes.

(B) Ausência de sinais de lise óssea.

(C) Após 4 meses de suspensão da medicação e com irrigações com antissépticos e antibioticoterapia, observa-se início de cicatrização.

(D) Após 6 meses de tratamento observa-se a cicatrização completa da área exposta.

(E) Fixação de barra entre os implantes após 10 meses de instalados os implantes.

(F) Prótese *overdenture* instalada.

Paciente 3

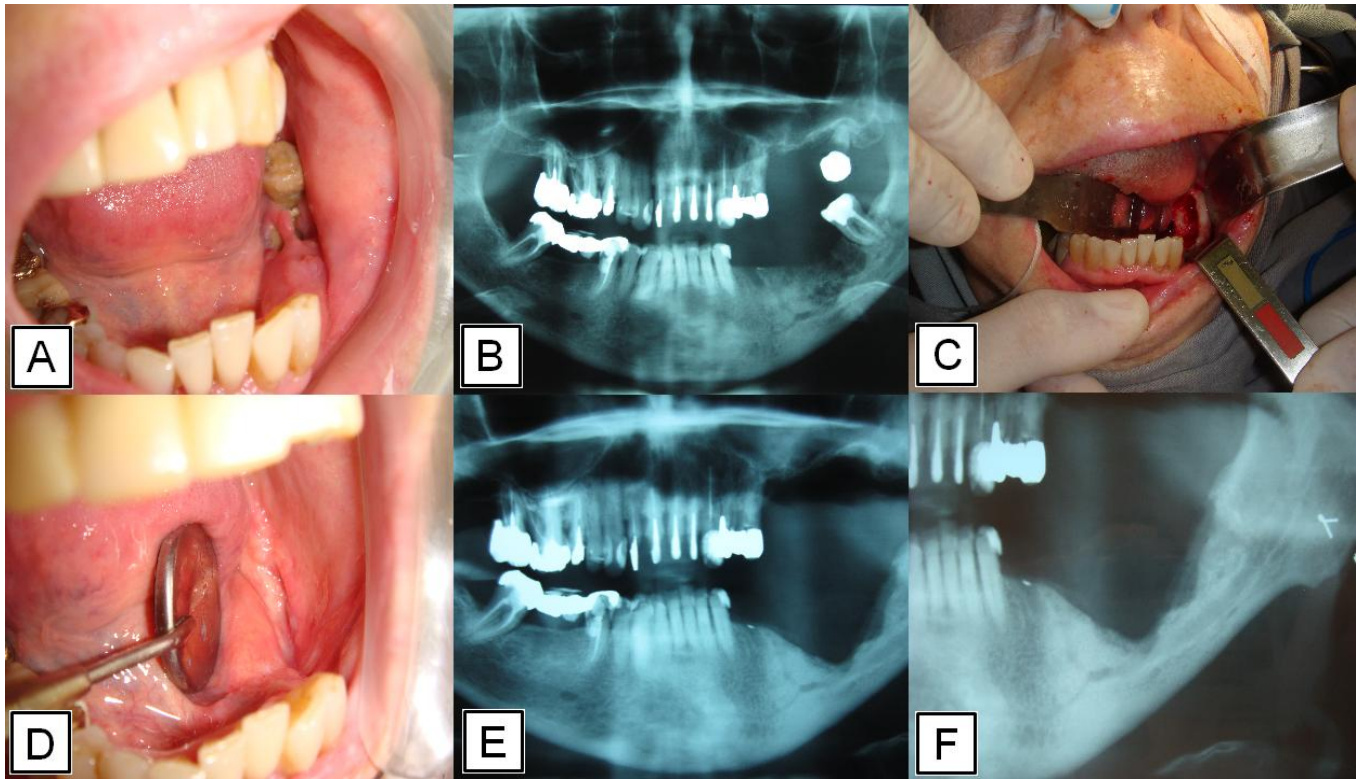


Fig. 3. Paciente do sexo feminino, 80 anos, usuária de alendronato por osteoporose.

(A) Exposição óssea pós extração dentária.

(B) Lise óssea em região necrótica.

(C) Abordagem cirúrgica com a utilização do plasma rico em plaquetas.

(D) 3 meses após o tratamento observa-se regressão para estágio I da OMB.

(E e F) Perda de estrutura óssea mandibular em decorrência da OMB impossibilitando reabilitação protética.

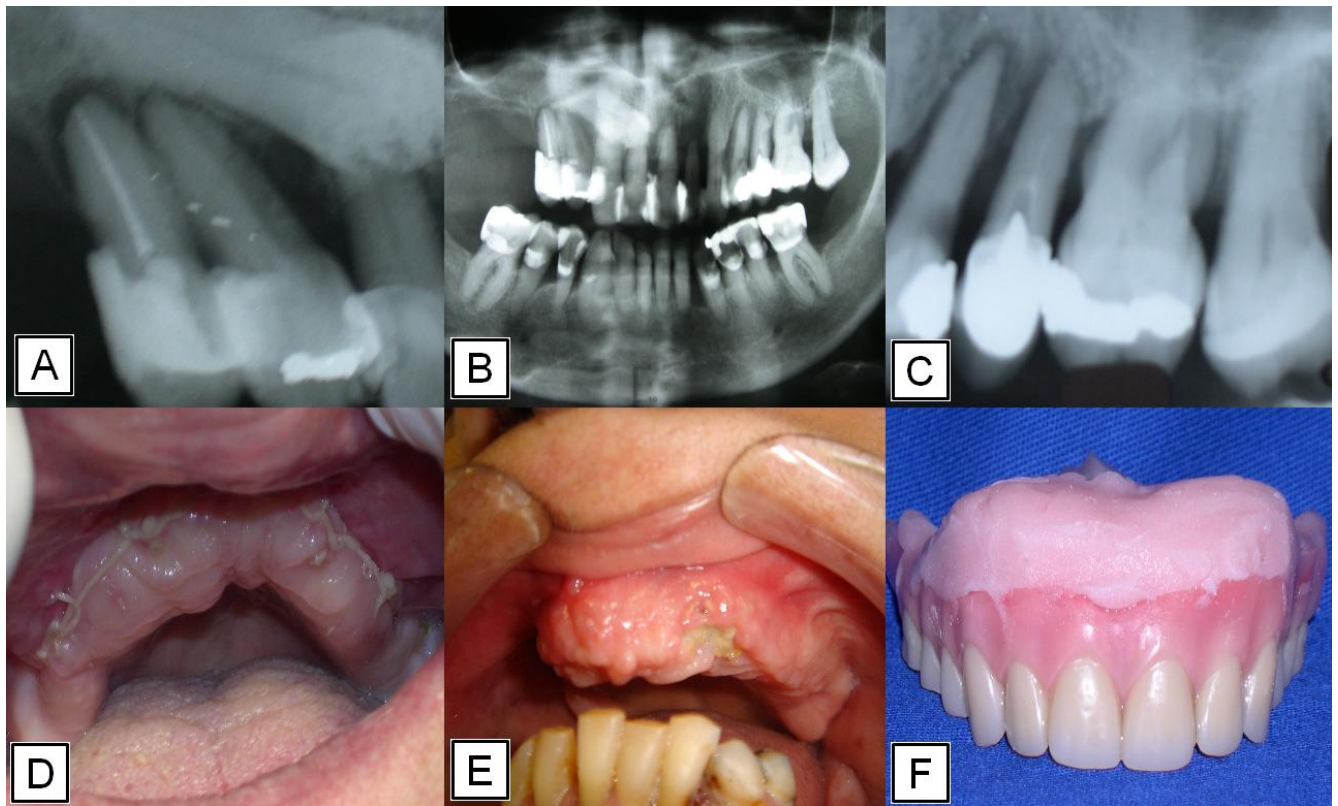
Paciente 4

Fig. 4. Paciente do sexo feminino, 71 anos, usuária de ácido zoledrônico por câncer de mama metastático.

(A - C) 40 Imagens radiográficas de arcada maxilar comprometida periodontalmente por perda de inserção óssea.

(D) Rebordo maxilar após extração dos dentes superiores.

(E) Exposição óssea maxilar tratada por ressecção de porção óssea necrótica.

(F) Prótese total reembasada com condicionador de tecido 3 meses após o tratamento.

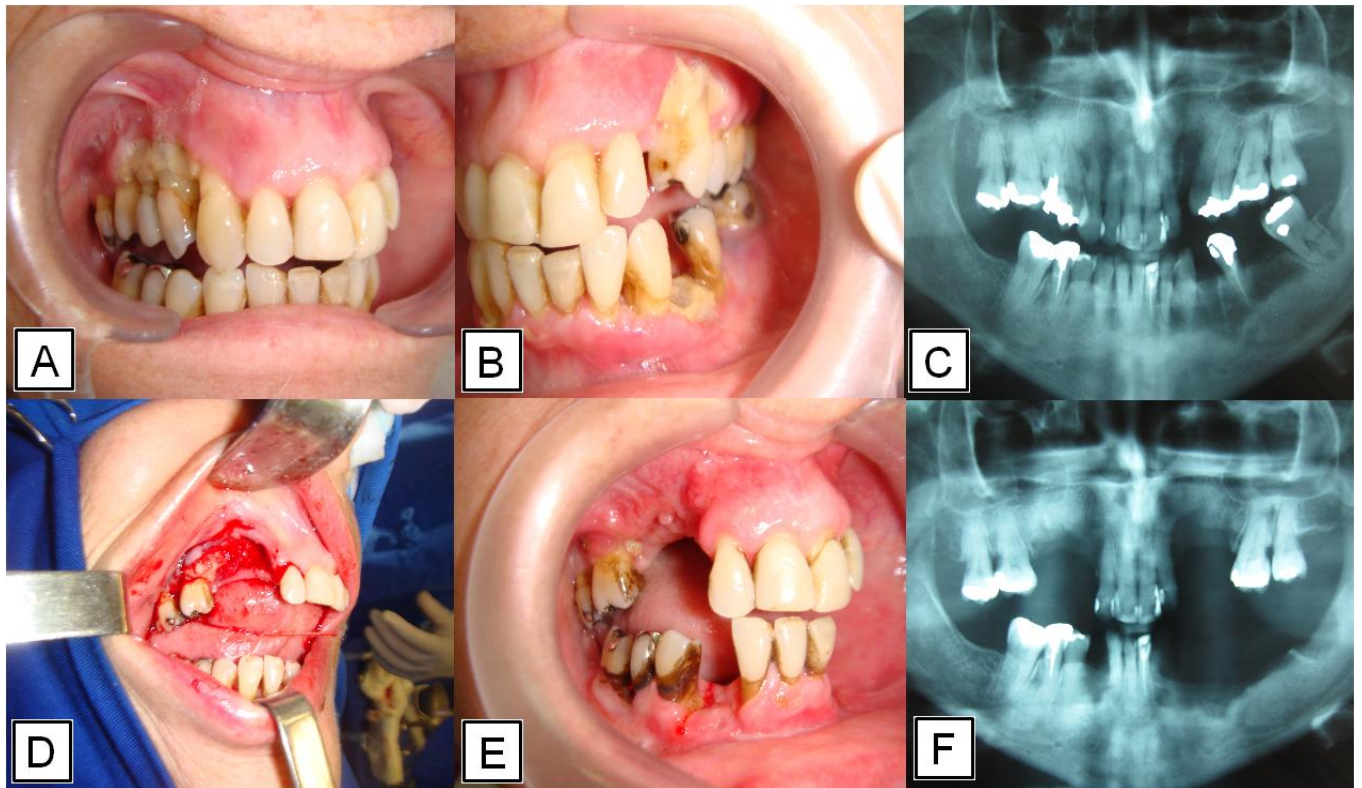
Paciente 6

Fig. 5. Paciente do sexo feminino, 54 anos, usuária de ácido zoledrônico por câncer de mama metastático.

- (A e B) Exposição óssea necrótica em arcadas periodontalmente patogênicas.
- (C) Radiografia panorâmica demonstrando áreas radiolúcidas difusas.
- (D) Extração de dentes e osteotomia da necrose.
- (E) Após 3 semanas observa-se a cura da paciente.
- (F) Radiografia panorâmica pós tratamento.

Paciente 7

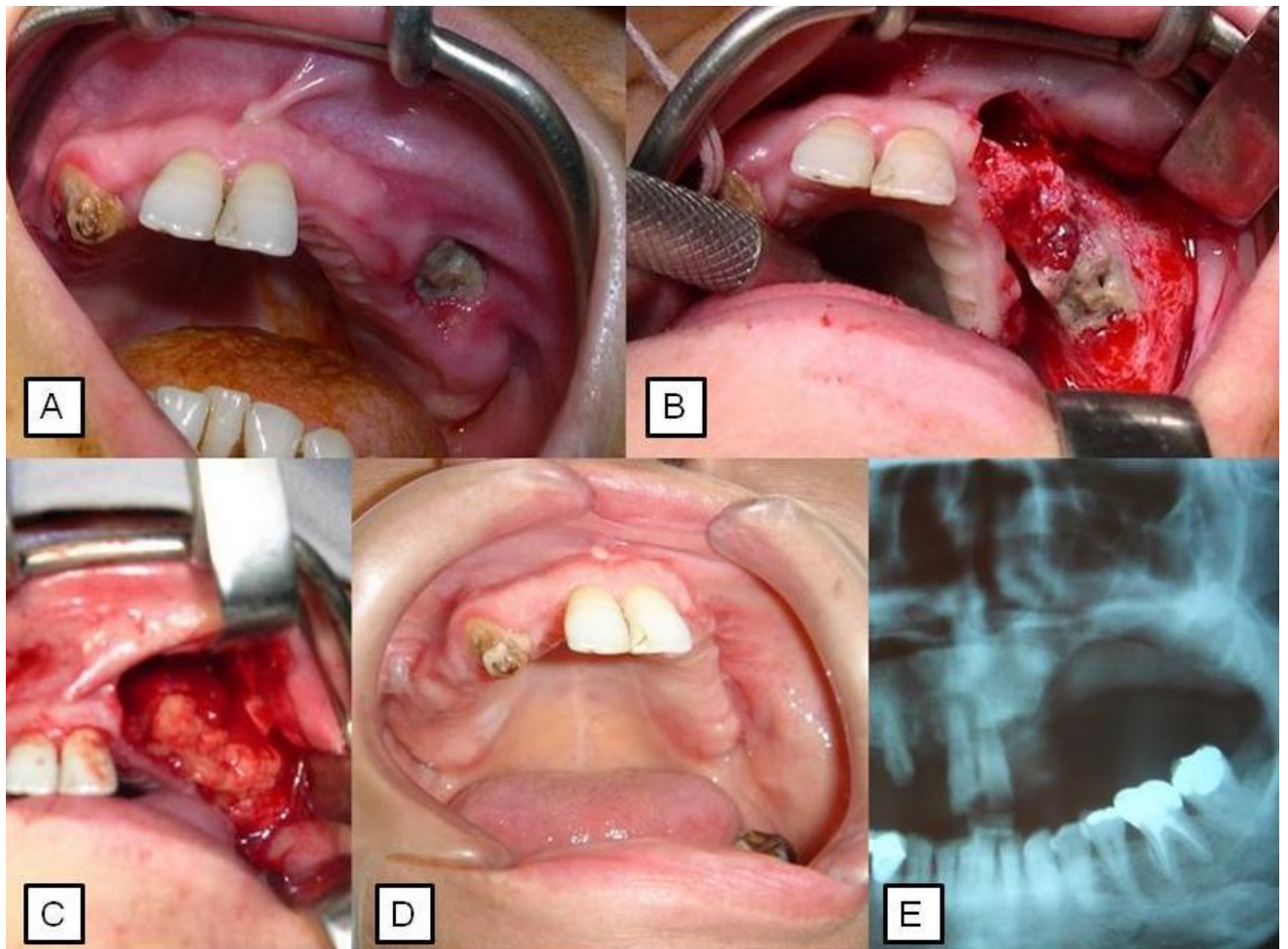


Fig. 6. Paciente do sexo feminino, 58 anos, usuária de ácido zoledrônico por câncer de mama metastático.

- (A) Exposição óssea necrótica em maxila após extração de molar superior esquerdo.
- (B) Exposição da região necrótica no momento da osteotomia.
- (C) Preenchimento do defeito maxilar com tecido adiposo bucal.
- (D) 2 meses após o tratamento observa-se ausência de exposição óssea.
- (E) Na radiografia final observa-se o defeito maxilar resultante da OMB.

Paciente 8

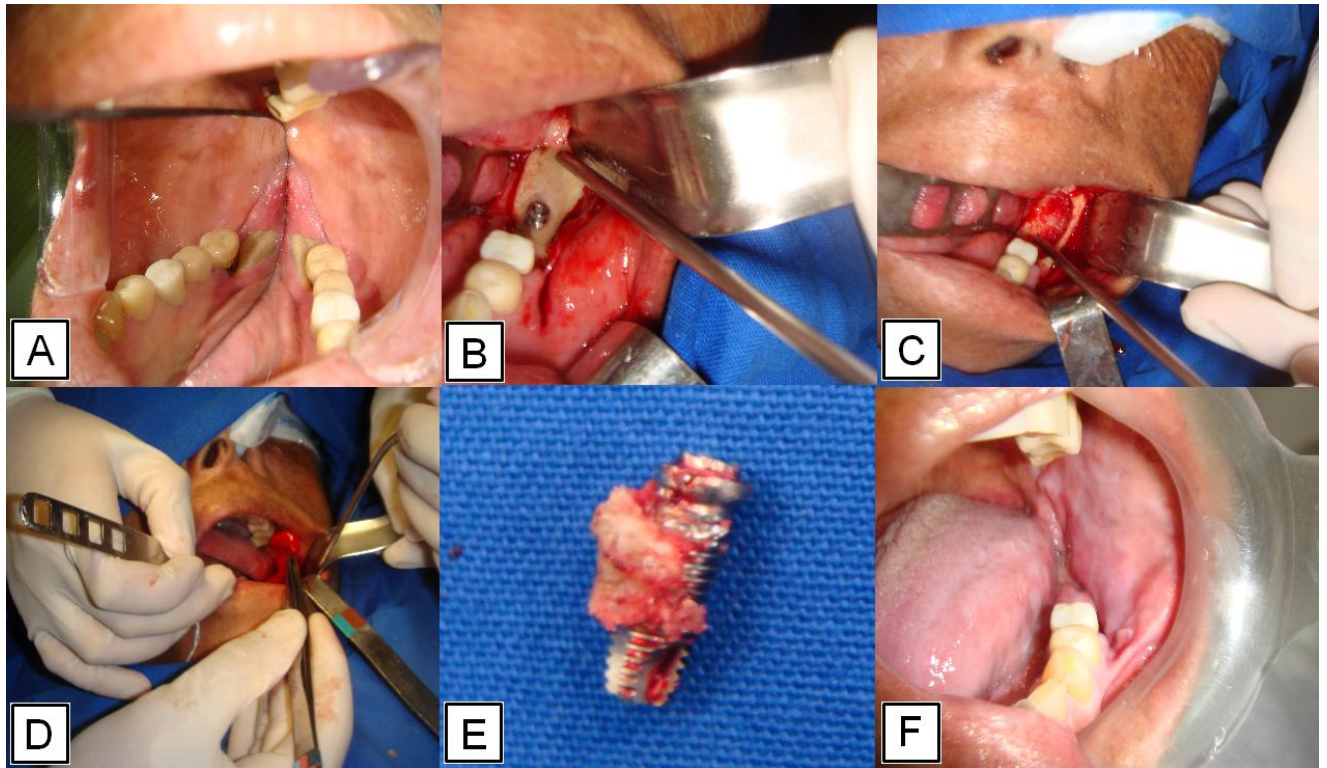


Fig. 7. Paciente do sexo feminino, 63 anos, usuária de ácido zoledrônico por câncer de mama metastático.

(A) Exposição óssea mandibular esquerda.

(B) Exposição de região necrótica envolvendo implante dentário instalado a mais de 3 anos.

(C) Osteotomia da necrose e remoção de implante.

(D) Preenchimento do defeito com plasma rico em plaquetas.

(E) Osseointegração osso/ implante.

(F) 8 meses após o início do tratamento observa-se exposição óssea e secreção na região.

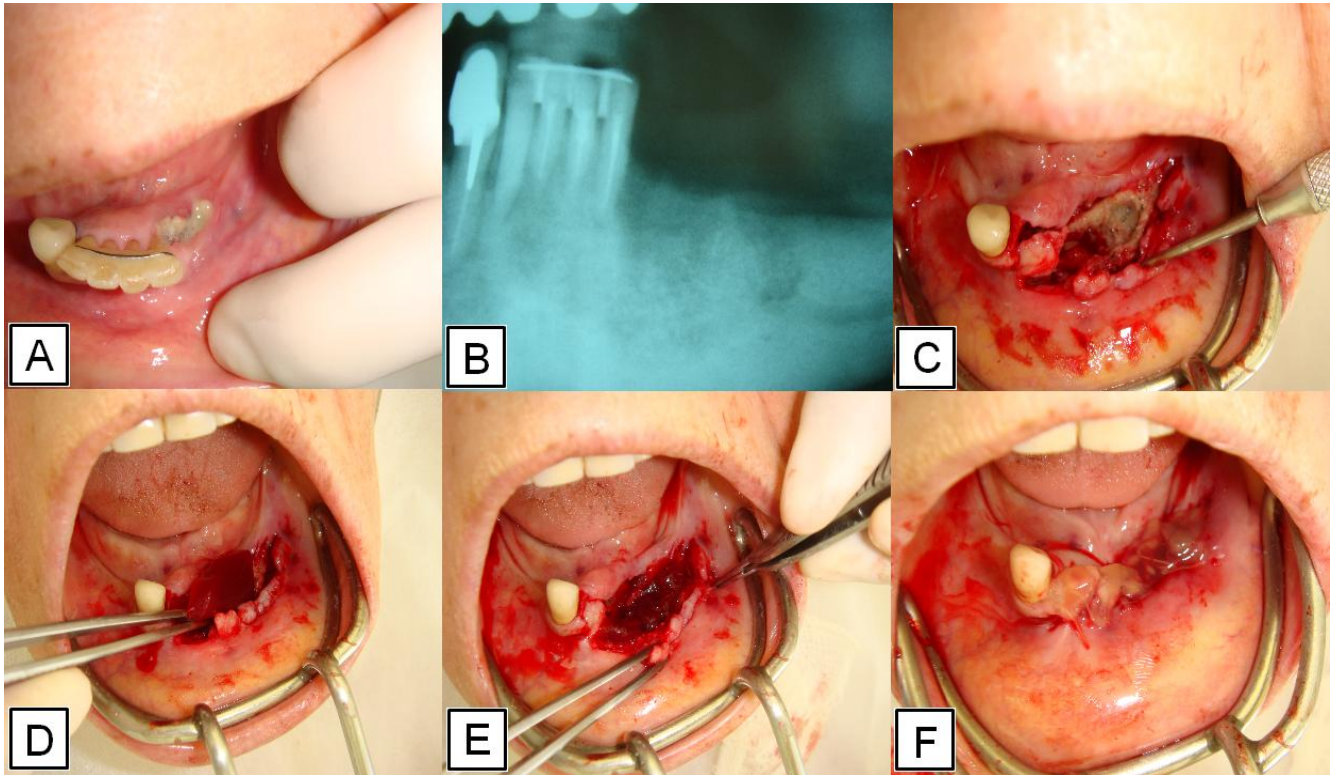
Paciente 9

Fig. 8. Paciente do sexo feminino, 84 anos, usuária de ácido zoledrônico por câncer de mama metastático.

- (A) Exposição óssea necrótica mandibular após extrações dentárias.
- (B) Radiograficamente observa-se alvéolos radiolúcidos sem sinais de neoformação óssea.
- (C) Extração de dentes e osteotomia da necrose.
- (D) Preenchimento do defeito mandibular com o plasma rico em plaquetas.
- (E) Sutura em 2 planos do retalho mucoperiostal.
- (F) Sutura final com recobrimento total do enxerto e tecido ósseo.

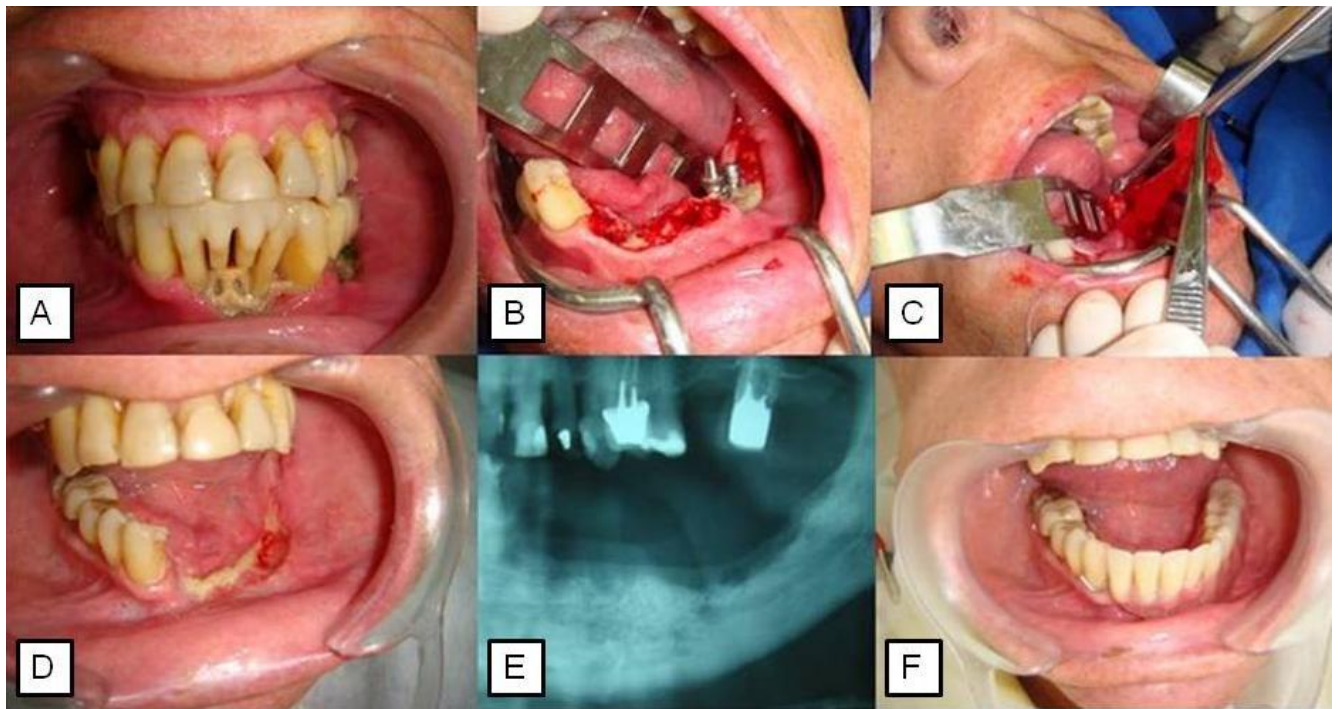
Paciente 13

Fig. 9. Paciente do sexo masculino, 71 anos, usuário de ácido zoledrônico por câncer de próstata metastático.

- (A) Doença periodontal severa com exposição óssea e alvéolos necróticos.
- (B) Extração de dentes, implantes e osteotomia da necrose.
- (C) Preenchimento do defeito ósseo com PRP.
- (D) Após 3 semanas observa-se regressão para o estágio I.
- (E) Imagem radiográfica da crista irregular após a ressecção óssea.
- (F) Prótese parcial removível com condicionador de tecido em posição.

6.2. Tabelas

Tabela 1: CARACTERÍSTICAS CLÍNICAS DOS PACIENTES COM OMB

Pacient e	Idade (anos)	Gênero	Doença Primária	Bifosfonato	Local da OMB	Estágio inicial	Evento	Interrup	Tratam	Estágio pós tratam	Reab
1	55	Fem	Osteoporose	Alendronato	Mandíbula	II	impl	+	Cons	Cura	P. PARCIAL
2	82	Fem	Osteoporose	Alendronato	Mandíbula	II	impl	+	Cons	Cura	OVERDENT URE
3	80	Fem	Osteoporose	Alendronato	Mandíbula	II	exo	+	Ciru + PRP	I	-
4	71	Fem	Câncer de mama	Ác. zoledrônico	Maxila	II	exo	-	Ciru	I	P. TOTAL
5	64	Fem	Câncer de mama	Ác. zoledrônico	Mandíbula	II	exo	+	Cons	II	-
6	54	Fem	Câncer de mama	Ác. zoledrônico	Maxila e mandíbula	II	perio	-	Ciru + PRP	Cura	P. PARCIAL
7	58	Fem	Câncer de mama	Ác. zoledrônico	Maxila	II	exo	+	Ciru + PRP	Cura	P. PARCIAL
8	63	Fem	Câncer de mama	Ác. zoledrônico	Mandíbula	II	espon	-	Ciru + PRP	II	-
9	84	Fem	Câncer de mama	Ác. zoledrônico	Mandíbula	II	exo	-	Ciru + PRP	I	-
10	71	Fem	Câncer de mama	Pamidronato	Mandíbula	II	exo	+	Ciru	II	-
11	48	Fem	Câncer de mama	Ác. zoledrônico e Pamidronato	Maxila	II	espon	+	Ciru	I	-
12	74	Fem	Câncer de mama	Pamidronato	Maxila	II	exo	-	Ciru	I	P. PARCIAL
13	71	Masc	Câncer de próstata	Ác. zoledrônico	Mandíbula	II	perio	+	Ciru + PRP	I	P. PARCIAL

Abreviação: OMB, osteonecrose dos maxilares por bifosfonatos; Fem, feminino; Masc, masculino; impl, implantes osseointegráveis; exo, exodontia; perio, doença periodontal; espon, espontâneo; Interrup, interrupção da medicação; Tratam, tratamento; Cons, conservador; Ciru, cirúrgico; PRP, plasma rico em plaquetas; Reab, reabilitação; P, prótese.

Tabela 2: Avaliação de CTX

PACIENTE	BFS	TRATAMENTO	INTERRUPÇÃO	CTX NO INICIAL	CTX FINAL	ESTÁGIO FINAL
1	ORAL	CONS	SIM	10 pg/ml	71 pg/ml após 3 meses 113 pg/ml após 7 meses 250 pg/ml após 14 meses	CURA
2	ORAL	CONS	SIM	17 pg/ml	75 pg/ml após 4 meses	CURA
3	ORAL	CIRU+PRP	SIM	X	201 pg/ml	I
7	INTRAV	CIRU+PRP	SIM	X	331 pg/ml	CURA
8	INTRAV	CIRU+PRP	NÃO	223 pg/ml	X	II
13	INTRAV	CIRU+PRP	SIM	135 pg/ml	364 pg/ml após 9 meses	I

Abreviação: CTX, carboxi telopeptideo de colágeno tipo 1; BFS, bifosfonato; DIAG, diagnóstico; INTRAV, intravenoso; CONS, conservador; CIRU, cirúrgico; PRP, plasma rico em plaquetas

Tabela 3: Avaliação entre a evolução da doença com o tipo de tratamento de acordo com a doença primária

Motivo do uso do BFS	Estágio	Tratamento		
		CONSERVADOR N (3)	CIRÚRGICO N (4)	CIRÚRGICO +PRP N (6)
OSTEOPOROSE	CURA	2	-	-
	Regressão de estágio II para estágio I	-	-	1
	Permanência no estágio II	-	-	-
NEOPLASIA	CURA	-	-	2
	Regressão de estágio II para estágio I	-	3	2
	Permanência no estágio II	1	1	1

Abreviação: BFS, bifosfonato; PRP, plasma rico em plaquetas.