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TITO LÚCIO FERNANDES

TRATAMENTO DA OSTEONECROSE MEDICAMENTOSA DOS MAXILARES: ESTUDO DE SÉRIE DE CASOS

PONTA GROSSA

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Tese apresentada para obtenção do título de Doutor em Odontologia pela Universidade Estadual de Ponta Grossa. Área de Concentração em Clínica Integrada. Linha de Pesquisa em Etiologia, Diagnóstico e Tratamento das Doenças Bucais.

Orientador: Prof. Dr. Gilson Cesar Nobre Franco

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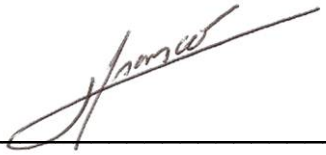

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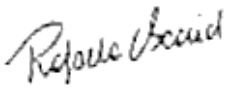

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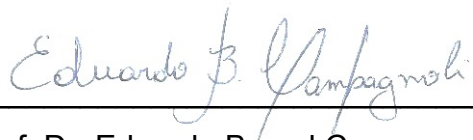

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DEDICATÓRIA

Dedico este trabalho aos meus pais **Rene e Therezinha**, exemplos vivos de otimismo, honestidade e dedicação ao trabalho, e que trilharam os meus primeiros passos nesta maravilhosa profissão.

À minha querida e amada esposa **Lucia**, pela carinhosa paciência e compreensão durante esta difícil jornada. Suas palavras de incentivo e esperança sempre me mantiveram em pé diante das adversidades.

Aos meus filhos **Bruno e Ana Carolina**, meus maiores incentivadores e exemplos de dedicação ao estudo. Vocês são meu orgulho e também são responsáveis por eu chegar ao final desta jornada**.**

Amo vocês todos!

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DADOS CURRICULARES

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RESUMO

Fernandes TL. **Tratamento da osteonecrose medicamentosa dos maxilares: estudo de série de casos.** [Tese de Doutorado em Odontologia – Área de Concentração em Clínica Integrada]. Ponta Grossa: Universidade Estadual de Ponta Grossa; 2023.

O objetivo deste estudo foi avaliar de forma retrospectiva o resultado do tratamento de uma série consecutiva de 11 pacientes diagnosticados com osteonecrose medicamentosa dos maxilares (ONMM). Todos pacientes eram do sexo feminino e com idade média de 74,8 anos. Nove pacientes foram medicadas com bifosfonatos orais para tratamento de osteoporose e duas pacientes foram medicadas com zoledronato para tratamento de câncer de mama metastático. O tempo médio de exposição às drogas antirreabsortivas ósseas antes de desenvolver a doença foi de 6,7 anos. A ONMM prevaleceu na mandíbula, com a ocorrência de fratura patológica em uma paciente. A maioria das pacientes foi classificada no estágio 2 da doença, e os fatores desencadeantes mais frequentes foram a extração dentária e o tratamento com implantes dentários. Todas pacientes foram submetidas a tratamentos conservadores e cirúrgicos, mas nenhuma delas necessitou de ressecção cirúrgica segmentar. O tratamento adjuvante da ONMM foi usado em cinco pacientes, com a administração de pentoxifilina com tocoferol e oxigenoterapia hiperbárica. Os períodos médios de tratamento e acompanhamento foram de 5 e 21,3 meses, respectivamente. Houve a resolução completa da doença em todas pacientes, sem recorrência nos locais operados. A ONMM pode levar a sequelas locais graves em seus estágios mais avançados, como fraturas mandibulares, e complicações à distância, embora raras, podem acontecer com a disseminação hematogênica do agente infeccioso. Uma das paciente da série de casos apresentou fratura mandibular patológica relacionada ao estágio 3 da doença, além de fratura atípica e osteomielite do fêmur. Concluiu-se que a ONMM deve ser diagnosticada precocemente e pode ser tratada com terapias conservadoras e cirurgias minimamente invasivas, evitando ressecções cirúrgicas segmentares e reconstruções ósseas extensas.

Palavras-chave*: Osteonecrose; Drogas Antirreabsortivas; Osteonecrose Associada a Bifosfonatos; Procedimentos Cirúrgicos Minimamente Invasivos; Procedimentos Maxilofaciais; Fraturas Mandibulares; Fraturas Femorais; Osteomielite.

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* Em acordo com os Descritores em Ciências da Saúde (DeCS) disponível no domínio http://decs.bvs.br

ABSTRACT

Fernandes TL. **Treatment of medication-related osteonecrosis of the jaw: case series study.** [Tese de Doutorado em Odontologia – Área de Concentração em Clínica Integrada]. Ponta Grossa: Universidade Estadual de Ponta Grossa; 2023.

The aim of this study was to retrospectively evaluate the treatment outcome of a consecutive series of 11 patients diagnosed with medication-related osteonecrosis of the jaws (MRONJ). All patients were female with a mean age of 74.8 years. Nine patients were medicated for osteoporosis with oral bisphosphonates and two patients were treated for metastatic breast cancer with zoledronate. The mean time of exposure to bone antiresorptive drugs before developing the disease was 6.7 years. MRONJ prevailed in the mandible, with the occurrence of a pathological fracture in one patient. Most patients were classified as MRONJ stage 2, and the most frequent triggering factors were tooth extraction and dental implant therapy. All patients underwent conservative therapies and surgical treatments, but none of them required segmental surgical resection. Adjunctive treatment of MRONJ was used in five patients, with the administration of pentoxifylline with tocopherol and hyperbaric oxygen therapy. Mean treatment and follow-up periods were 5 and 21.3 months respectively. There was complete resolution of the disease in all patients without recurrence in the operated sites. MRONJ can lead to serious local sequelae in its more advanced stages, such as mandibular fractures, and distant complications, although rare, can occur with hematogenous dissemination of the infectious agent. One of the patients in the case series had a pathological mandibular fracture related to stage 3 of the disease, in addition to an atypical fracture and osteomyelitis of the femur. It was concluded that MRONJ must be diagnosed early and can be treated with conservative therapies and minimally invasive surgeries even in advanced stages, avoiding segmental surgical resections and extensive bone reconstructions.

Key words*:

Osteonecrosis; Antiresorptive drugs; Bisphosphonate-Associated Osteonecrosis of the Jaw; Minimally Invasive Surgical Procedures; Maxillofacial Procedures; Mandibular Fractures; Femoral Fractures; Osteomyelitis.

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* In accordance with the Health Sciences Descriptors (DeCS) available at https://decs.bvsalud.org/I/homepagei.htm

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LISTA DE ABREVIATURAS E SIGLAS

3D	three-dimensional
AAOMS	American Association of Oral and Maxillofacial Surgery
Ant	Anterior teeth (incisors and canines)
ARD	Antiresorptive Drug
CT	Computed tomography
DAR	Droga Antirreabsortiva
FMP	Fratura Mandibular Patológica
HBOT	Hyperbaric Oxygen Therapy
IV	Intravenous
Md	Mandible
mg	milligrams
MRONJ	Medication-related Osteonecrosis of the Jaws
Mx	Maxilla
ONMM	Osteonecrose Medicamentosa dos Maxilares
OTHB	Oxigenoterapia Hiperbárica
PENTOCO	Pentoxifilina + Tocoferol (Pentoxifylline + Tocopherol)
PMF	Pathologic Mandibular Fracture
Post	Posterior teeth (premolars and molars)
PRF	Fibrina Rica em Plaquetas (Platelet-rich fibrin)
PRP	Plasma Rico em Plaquetas (Platelet-rich plasma)

LISTA DE SÍMBOLOS

%	percent
<	less than
≥	greater than or equal to

SUMÁRIO

1 INTRODUÇÃO

A osteonecrose medicamentosa dos maxilares (ONMM) é uma doença rara descrita pela primeira vez por Marx[1] em 2003, que consiste em uma reação adversa a drogas antirreabsortivas (DARs), usadas isoladamente ou em combinação com imunomoduladores ou drogas antiangiogênicas, em pacientes tratados anteriormente ou em tratamento para condições relacionadas ao câncer, osteoporose e osteopenia (Ruggiero et al.[2] 2014, Ruggiero et al.[3] 2022).

Existem milhões de pessoas em todo o mundo com diagnóstico de osteoporose e os medicamentos mais utilizados no seu tratamento são os bisfosfonatos, denosumabe, raloxifeno, teriparatida e, mais recentemente, o romosozumabe (Ayub et al.[4] 2021).

As principais hipóteses relacionadas à fisiopatologia da ONMM são inibição da remodelação óssea, inflamação ou infecção, inibição da angiogênese, disfunção imune inata ou adquirida e predisposição genética (Ruggiero et al.[3] 2022).

A Associação Americana de Cirurgia Oral e Maxilofacial (AAOMS) atualizou recentemente o sistema de estadiamento da ONMM para melhor caracterizar todos os aspectos de sua apresentação clínica e radiográfica (Ruggiero et al.[2] 2014, Ruggiero et al.[3] 2022).

O risco de desenvolver ONMM em pacientes expostos à terapia antirreabsortiva para o tratamento da osteoporose com bifosfonatos orais é de 0,02% a 0,05%, com denosumabe o risco é de 0,04% a 0,3% e com romosozumabe é de 0,03% a 0,05%. Por outro lado, em pacientes com câncer tratados com denosumabe, o risco de ONMM é de 6,9% e em pacientes expostos ao zoledronato pode chegar a 18% (Ruggiero et al.[3] 2022).

Devido ao crescente conhecimento da ONMM pelos profissionais de saúde, um grande número de pacientes foi diagnosticado no estágio 0 da doença, o que destaca a importância do diagnóstico precoce para obter melhores resultados do tratamento (Badr et al.[5] 2017).

O tratamento padrão da ONMM consiste em descontinuar o uso da DAR, usar antissépticos bucais ou antibióticos sistêmicos e realizar cirurgias, como o debridamento do osso necrótico ou a ressecção segmentar com reconstrução óssea vascularizada em estágios mais avançados da doença (Ruggiero et al.2 2014, Hinson et al.[6] 2015, Caldroney et al.[7] 2017).

A AAOMS desenvolveu recentemente uma série de algoritmos de tratamento para simplificar as estratégias de gerenciamento para pacientes com ONMM. Essas estratégias consistem em terapias cirúrgicas e não cirúrgicas, que podem ser utilizadas em todos os estágios da doença (Ruggiero et al.[3] 2022).

A forma mais avançada da doença é o estágio 3, que é debilitante e pode estar associado a morbidade significativa quando uma fratura mandibular patológica (FMP) ocorre. Os problemas resultantes podem ser crônicos e incluir dor, inchaço, halitose, drenagem purulenta, deficiência neurossensorial, disfunção mastigatória, com consequente diminuição da qualidade de vida (Caldroney et al.[7] 2017).

A osteomielite é uma das infecções mais difíceis de curar e pode ser causada por disseminação hematogênica em 22,97% dos casos (García del Pozo et al.[17] 2018). Alguns casos de osteomielite actinomicótica podem ocorrer nas pernas de pacientes saudáveis como resultado de disseminação hematogênica (Ryu et al.[18] 2019). Em relação à ONMM, e infecções oportunistas podem ser um importante fator de risco para a FMP. Embora raramente relatadas, complicações à distância da ONMM são possíveis e devem ser consideradas na avaliação clínica de pacientes com osteomielite de outros ossos. (Topaloglu Yasan et al.[19] 2021).

As opções de tratamento das FMPs relacionadas à ONMM variam desde o tratamento conservador a abordagens cirúrgicas relativamente simples combinadas com fixação intermaxilar, até cirurgias extensas e mais agressivas, como ressecções e reconstruções mandibulares com retalho miocutâneo livre, com o uso de fixações internas e externas (Caldroney et al.[7] 2017, Yao et al.[20] 2016, Pichardo et al.[21] 2018, Otto et al.[22] 2013, Yamachika et al.[23] 2015).

O objetivo deste estudo foi avaliar retrospectivamente os resultados do tratamento de uma série consecutiva de pacientes diagnosticados com ONMM em uma clínica particular de cirurgia bucomaxilofacial no sul do Brasil, e relatar um caso de FMP relacionada à ONMM e fratura atípica do fêmur.

2 ARTIGO I - TREATMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW WITHOUT SEGMENTAL RESECTION - A CASE SERIES

2.1 INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare disease first described by Marx[1] in 2003, which consists of an adverse reaction to antiresorptive drugs (ARDs), used alone or in combination with immunomodulators or antiangiogenic drugs, in patients either currently or previously treated for conditions related to cancer, osteoporosis and osteopenia (Ruggiero et al.[2] 2014, Ruggiero et al.[3] 2022).

There are millions of people around the world diagnosed with osteoporosis and the medications mostly used in its treatment are bisphosphonates, denosumab, raloxifene, teriparatide and, more recently, romosozumab (Ayub et al.[4] 2021)

The main hypotheses related to the pathophysiology of MRONJ are inhibition of bone remodeling, inflammation or infection, inhibition of angiogenesis, innate or acquired immune dysfunction, and genetic predisposition (Ruggiero et al.[3] 2022).

The American Association of Oral and Maxillofacial Surgery (AAOMS) recently updated the MRONJ staging system to better characterize all aspects of its clinical and radiographic presentation (Ruggiero et al.[2] 2014, Ruggiero et al.[3] 2022).(Table 1)

The risk of developing MRONJ in patients exposed to antiresorptive therapy for the treatment of osteoporosis with oral bisphosphonates is 0.02% to 0.05%, with denosumab the risk is 0.04% to 0.3%, and with romosozumab it is 0.03% to 0.05%. On the other hand, in cancer patients treated with denosumab the risk of MRONJ is 6.9% and in patients exposed to zoledronate it can be as high as 18% (Ruggiero et al.[3] 2022).

Due to the increasing knowledge of MRONJ by healthcare professionals, a large number of patients have been diagnosed at disease stage 0, which highlights the importance of early diagnosis to achieve better treatment results (Badr et al.[5] 2017)

Standard treatment for MRONJ consists of discontinuing the ARD, using antimicrobial rinses or systemic antibiotics, and performing surgeries such as debridement of necrotic bone or segmental resection and vascularized bone reconstruction in advanced stages of the disease (Ruggiero et al.[2] 2014, Hinson et al.[6] 2015, Caldroney et al.[7] 2017).

The AAOMS has recently developed a series of treatment algorithms to streamline the management strategies for patients with MRONJ. These strategies consist of non-operative (Fig 1) and operative therapies (Fig 2), used in all stages of the disease (Ruggiero et al.[3] 2022).

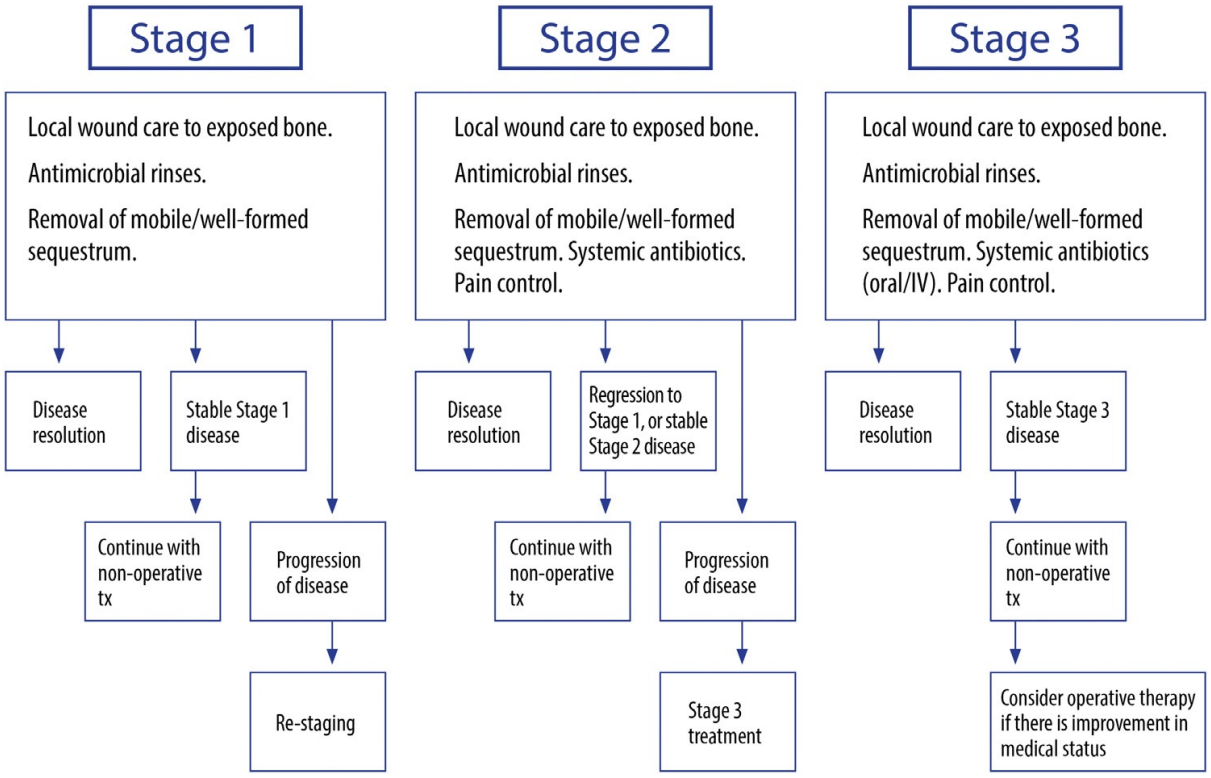


Figure 1 - Non-operative therapies for MRONJ

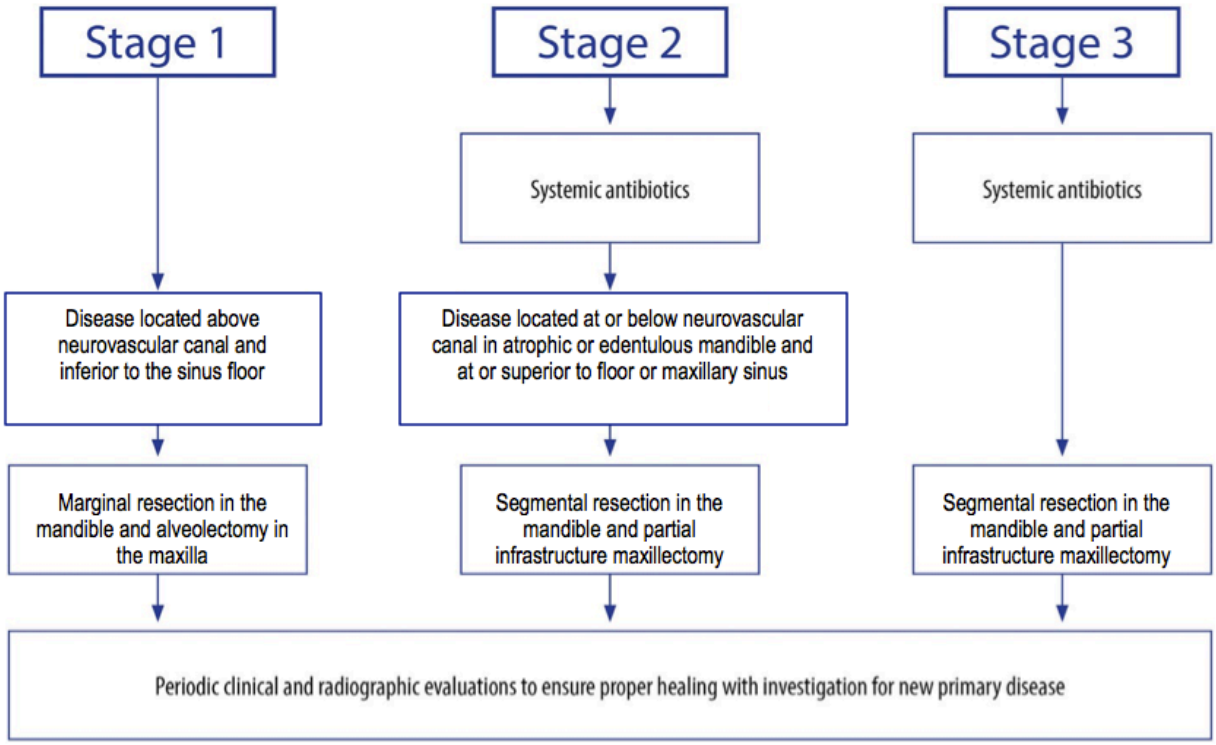
Source: Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update. *J Oral Maxillofac Surg* 2022;80(5):920–43.

Table 1. AAOMS clinical and radiographic staging system of MRONJ		
Stage	Symptoms and clinical findings	Radiographic findings
0	No clinical evidence of exposed and necrotic bone in patients with the presence of non-specific symptoms or clinical findings: • Odontalgia not explained by an odontogenic cause • Dull, aching bone pain in the jaw, which may radiate to the temporomandibular joint region • Sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall • Altered neurosensory function • Loosening of teeth not explained by chronic periodontal disease • Intraoral or extraoral swelling	• Alveolar bone loss or resorption not attributable to chronic periodontal disease • Changes to trabecular pattern sclerotic bone and no new bone in extraction sockets • Regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone • Thickening/obscuring of periodontal ligament
1	Exposed and necrotic bone in asymptomatic patients with no evidence of infection/inflammation	Stage 0 findings localized to the alveolar bone region
2	Exposed and necrotic bone in symptomatic patients with evidence of infection/inflammation	Stage 0 findings localized to the alveolar bone region
3	Stage 2 plus: • Exposed and necrotic bone extending beyond the region of alveolar bone • Pathologic fracture • Extraoral fistula • Oral antral/oral-nasal communication • Osteolysis extending to the inferior border of the mandible or sinus floor	Stage 0 findings localized beyond the alveolar bone region: • Inferior border and ramus in the mandible • Maxillary sinus and zygoma in the maxilla

Source: Adapted from Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update. *J Oral Maxillofac Surg* 2022;80(5):920–43.

The aim of this study was to retrospectively evaluate the treatment outcomes of a consecutive series of patients diagnosed with MRONJ at a private oral and maxillofacial surgery clinic in southern Brazil.

Figure 2- Operative therapies for mandibular and maxillary diseases



Source: Adapted from Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update. J Oral Maxillofac Surg 2022;80(5):920–43.

2.2 MATERIALS AND METHODS

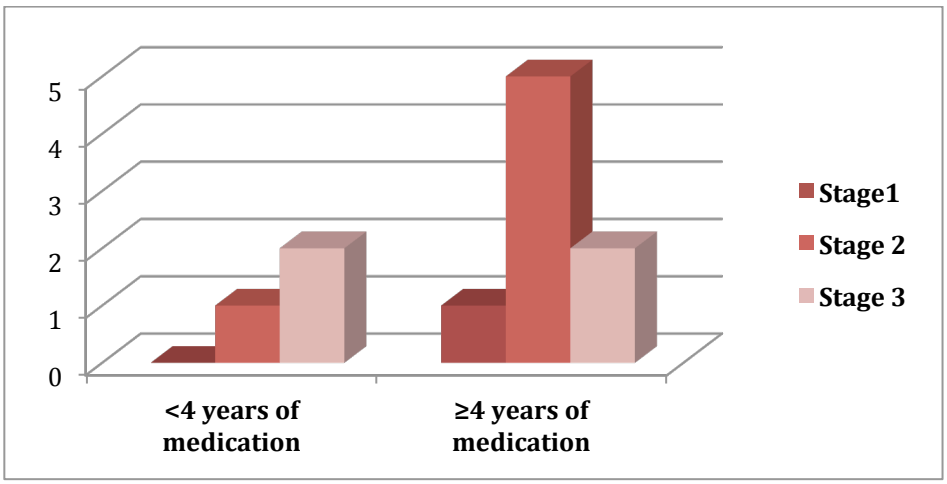
Institutional research ethics board approval was obtained for the study (Annex A), and a retrospective database review of a private oral and maxillofacial surgery clinic was performed. Adult patients with osteonecrosis of the jaws from September 2011 to August 2022 were included, and patients with malignant diseases of the jaws or those undergoing head and neck radiotherapy were excluded.

A review of the medical records of the selected individuals was carried out to obtain data such as age and sex, history of anti-resorptive therapy with indication of the pathology for which it was used, type, route and duration of administration, co-morbidities and predisposing factors for MRONJ. Clinical and imaging characteristics were also registered at the initial presentation, with location, triggering factors and stage of disease. Operative and non-operative treatments performed were registered, as well as adjuvant treatments used, duration and results of treatments, incidence of complications, recurrence of MRONJ, and follow-up time.

2.3 RESULTS

A total of 11 female patients were included in this study. The mean age at the start of treatment was 74.8 years (range, 67 to 85 years). Most patients (81.8%) were medicated to treat osteoporosis with oral bisphosphonates, two of which were initially treated with bisphosphonate and later received denosumab. Only two patients (18.2%) were exposed to IV zoledronate to treat metastatic breast cancer. The time of exposure to ARDs ranged from 22 months to 20 years (mean 6.7 years) and most patients who used medications for more than 4 years (7 out of 8) presented with a more advanced stage of the disease (Fig 3).

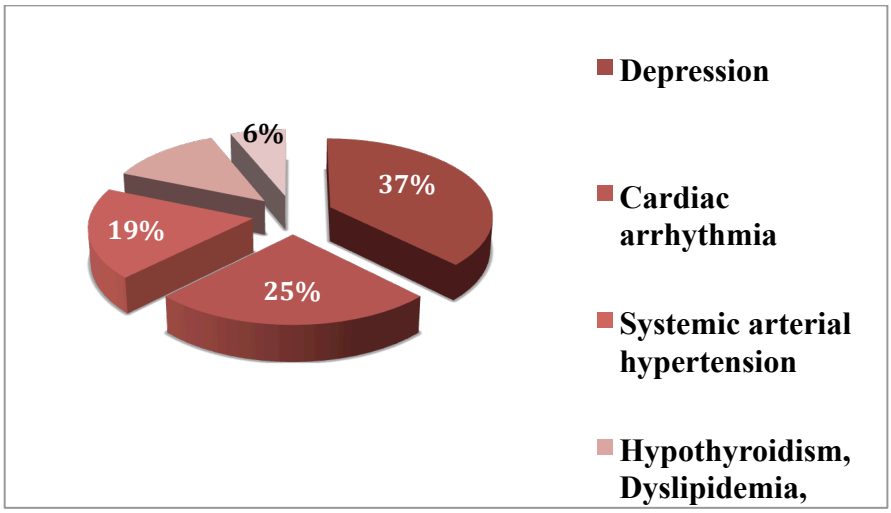
Figure 3 – Distribution of patients according to ARD exposure and MRONJ stage



Source: The author.

The most frequent comorbidities observed in patients were depression, cardiac arrhythmia, and systemic arterial hypertension, followed by hypothyroidism, dyslipidemia, smoking, femoral osteomyelitis, bronchial asthma, autoimmune myositis, hemorrhagic gastritis, sarcopenia, fibromyalgia, rheumatoid arthritis, osteoarthritis, diabetes mellitus and alcoholism (Fig 4). In addition, some patients had more than one comorbidity and had up to five of them.

Figure 4 – Frequency of comorbidities observed in patients with MRONJ



Source: The author.

MRONJ lesions were mostly diagnosed in the posterior region of the mandible (45.4%), followed by the anterior mandible (36.4%), anterior and posterior regions of the maxilla (9.1% each). At the initial clinical presentation, alveolar bone exposure was found in 45.4% of cases. In addition, the patients presented clinical signs such as suppuration, edema or gingival hyperemia, paresthesia, intra and extraoral fistulas, spontaneous sequestration, mandibular neuralgia and verrucous lesions on the floor of the mouth. It is important to note that one patient initially presented with pathological fracture of the mandible related to MRONJ.

The initial imaging evaluation consisted of panoramic radiographs and computed tomography (CT) scans, which revealed alveolar osteolysis in most cases (90.9%) and extending beyond the alveolar bone in four of them. Only one patient

presented with alveolar osteosclerosis on the posterior maxilla. Patients were classified according to initial clinical and radiographic presentation as stage 1 (9.1%), stage 2 (54.5%) and stage 3 (36.4%). One patient who was initially classified as stage 3 MRONJ recurred and was later reclassified as stage 2.

The most frequent triggers for MRONJ observed in this group were tooth extraction and dental implant therapy (36.4% each), followed by prosthetic trauma (27.2%). There was one patient whose initial trigger was the installation of mandibular dental implants and later recurred of MRONJ in another region of the mandible due to prosthetic trauma. Two patients had dual MRONJ triggers: one required endodontic treatment adjacent to a tooth extraction site, while the second had prosthetic trauma and also suffered mandibular trauma from a fall.

The mean evolution of MRONJ before diagnosis and treatment beginning was 5 months (range, 1 to 12 months). All patients started non-operative treatment with 0.12% chlorhexidine oral rinses, and those who presented suppuration or underwent operative treatment received antibiotics. Surgeries were performed on all patients and consisted of sequestrectomies, dental implant removals and debridements. Two patients required marginal resections of the mandible with piezosurgery, and another one underwent open reduction and internal fixation of a pathologic mandibular fracture. Some patients required additional surgeries, such as sequestrectomy for MRONJ recurrence, removal of remaining dental implants, and an apicoectomy in a tooth adjacent to the osteonecrosis site.

Most surgeries (72.7%) were performed on an outpatient basis with local anesthesia and oral sedation, and three patients were treated under general anesthesia in a hospital setting.

Adjuvant treatment for MRONJ was performed in five patients (45.4%), and the most frequently used was oral administration of pentoxifylline 800 mg/day with tocopherol 800 mg/day (PENTOCO) in three patients. Two other patients underwent 30 sessions of hyperbaric oxygen therapy (HBOT), and one of these patients subsequently received PENTOCO for the treatment of recurrent MRONJ.

The mean duration of treatments was 5 months (range, 1 to 19 months). Ten patients evolved with complications related to the surgical wound and the most frequent was suture dehiscence (90%) requiring local wound care. Only one patient

had a postoperative wound infection that required a return to the operating room and prolonged use of intravenous antibiotics. One of the patients with suture dehiscence had an oronasal fistula for one month postoperatively, which healed spontaneously. In spite of such events, all patients had a good evolution of MRONJ, with resolution of oral symptoms, complete bone healing at the operated sites, and were pain-free after treatment.

There were no recurrences of MRONJ observed at the surgical sites, although one patient developed MRONJ at another site of the mandible due to the trauma caused by the postoperative use of a removable prosthesis. The mean follow-up of patients in this study was 21.3 months (range, 3 to 52 months) (Table 2).

2.4 DISCUSSION

MRONJ diagnostic criteria and treatment protocols have changed over the years. When initially described, it was a disease characterized by bone exposure of the jaws and restricted to patients who used bisphosphonates. It is currently known that MRONJ can present without necrotic bone exposure and, due to the emergence of new forms of treatment for osteoporosis and metastatic bone disease, it may be related to antiresorptive and antiangiogenic drugs other than bisphosphonates (Marx[1] 2003, Ruggiero et al.[2] 2014, Fedele et al.[8] 2010). Only one patient in this series initially presented without bone exposure but had an intraoral fistula. After 18 months of non-operative treatment, this patient evolved to bone exposure and required surgery.

MRONJ is limited to the jaws due to its greater vascularization and bone turnover rate. It prevails in the mandible (75%) and the occurrence may be related to the type, dose and route of administration of the ARD, with greater risk from the parenteral route. In addition, patients with more than four years of anti-resorptive therapy have a potential risk of MRONJ as high as 0.21% (Ayub et al.[4] 2021, Hallmer et al.[9] 2018, Beth-Tasdogan et al.[10] 2022). In this series all patients were female, most of them used oral bisphosphonates to treat osteoporosis and developed MRONJ in the mandible (81.8%). The only two patients exposed to intravenous

Table 2 - Patients treated for medication-related osteonecrosis of the jaws

Patient	Age (years)	Sex	Medication, duration	Pathology	Site	Initial symptoms	Initial images	Stage	Triggering factor	Treatment	Adjuvant treatment	Outcome	Follow-up, (months)
1	85	F	Zoledronate, 4 years	Metastatic breast cancer	Ant Mx	Alveolar bone exposition, suppuration	Osteolysis extending to the nasal floor	3	Prosthetic trauma	Chlorhexidine, antibiotics, sequestrectomy	No	Suture dehiscence, oronasal fistula	20
2	82	F	Alendronate, 4 years	Osteoporosis	Post Md	Spontaneous sequestration, suppuration	Alveolar osteolysis	2	Prosthetic trauma	Chlorhexidine, antibiotics, debridement	No	Suture dehiscence	12
3	81	F	Alendronate, 4 years	Osteoporosis	Post Md	Suppuration	Alveolar osteolysis	2	Tooth extraction	Chlorhexidine, antibiotics, sequestrectomy	No	Suture dehiscence	52
4	76	F	Alendronate, ibandronate 20 years	Osteoporosis	Ant Md	Alveolar bone exposition, extraoral fistula	Osteolysis extending to the base of the mandible	3 2*	Dental implant, prosthetic trauma*	Chlorhexidine, antibiotics, marginal resection, sequestrectomy*	HBOT, PENTOCO*	Recurrence*	46
5	63	F	Alendronate, 2 years	Osteoporosis	Ant Md	Alveolar bone exposition, suppuration	Mandibular osteolysis and fracture	3	Dental implant	Chlorhexidine, antibiotics, sequestrectomy, internal fixation	HBOT	Postoperative infection, reoperation	36
6	84	F	Ibandronate, 3 years	Osteoporosis	Post Md	Gingival swelling, paresthesia	Alveolar osteolysis	2	Dental implant	Chlorhexidine, antibiotics, implant removal	No	Suture dehiscence	11
7	70	F	Alendronate, denosumab, 13 years	Osteoporosis	Post Md	Mandibular neuralgia, gingival hyperemia	Alveolar osteolysis	2	Tooth extraction, endodontic treatment	Chlorhexidine, antibiotics, implant removal, apicoectomy	No	Suture dehiscence	20
8	85	F	Alendronate, denosumab, 10 years	Osteoporosis	Ant Md	Gingival swelling	Alveolar osteolysis	2	Tooth extraction	Chlorhexidine, antibiotics, sequestrectomy	PENTOCO	Suture dehiscence	6
9	67	F	Alendronate, ibandronate, 2 years	Osteoporosis	Ant Md	Warty lesions on the floor of the mouth, bone exposition*	Mandibular osteolysis	3	Prosthetic trauma, fall	Chlorhexidine, antibiotics, marginal resection, sequestrectomy	PENTOCO	Suture dehiscence	20
10	58	F	Alendronate, 20 years	Osteoporosis	Post Md	Gingival swelling, alveolar bone exposition, paresthesia	Alveolar osteolysis	2	Dental implant	Chlorhexidine, antibiotics, sequestrectomy	PENTOCO	Suture dehiscence	8
11	72	F	Zoledronate, 10 years	Metastatic breast cancer	Post Mx	Alveolar bone exposition	Alveolar osteosclerosis	1	Tooth extraction	Chlorhexidine, antibiotics, sequestrectomy	No	Suture dehiscence	3

medication to treat bone metastases developed the disease in the maxilla.

Diabetes mellitus, smoking, and immunosuppressive medications are risk factors for MRONJ, and patients with osteoporosis and immunodeficiency are at increased risk (Heifetz-Li et al.[11] 2019, Mirelli et al.[12] 2022) One patient in this series had diabetes mellitus, two patients were smokers and one of them was also an alcoholic. In addition, two other patients had autoimmune diseases (rheumatoid arthritis and autoimmune myositis), one of which used immunomodulators during the anti-resorptive therapy.

Therefore, MRONJ is a multifactorial disease with a synergistic effect of trauma, infection and decreased bone turnover. Tooth extractions and dental implants can also trigger the onset of MRONJ. Patients undergoing tooth extractions have a risk of developing MRONJ from 0.5% to 1%, reaching up to 5% in high-risk patients, which is similar to the risk of developing osteoradionecrosis in irradiated patients. Furthermore, patients with dental implants exposed to denosumab have a 0.5% risk of developing the disease (Heifetz-Li et al.[11] 2019, Dodson[13] 2015, Watts et al.[14] 2019). Hence, tooth extraction and dental implant were the most frequent triggering factors among patients in this series.

Current MRONJ treatment strategies emphasize that both non-operative and operative management are acceptable for all stages of the disease based on clinical judgment and individual patient factors. Patients who are refractory to non-operative treatment or who are unable to maintain adequate oral hygiene are candidates for operative therapy. Thus, the risk-benefit ratio should take into account the individual's ability for wound caring in order to prevent infection and spread of disease, the morbidity of an invasive surgical procedure, as well as oral rehabilitation concerns after marginal or segmental resection surgery (Ruggiero et al.[3] 2022). All patients in this series were initially treated non-operatively. Operative treatment was performed with minimally invasive surgeries in cases with bone sequestration and in those whose initial conservative treatment did not evolve satisfactorily. In addition, only two MRONJ stage 3 patients underwent mandibular marginal resection and no patient required segmental resection of the mandible.

Regardless of treatment modality and stage of MRONJ, discontinuation of the anti-resorptive therapy before or early in treatment is associated with faster disease

resolution, whereas continuation of this therapy can delay symptom resolution by approximately 4-6 months (Hinson et al.[6] 2015). All patients in this series had the anti-resorptive therapy discontinued at the beginning of treatment with the agreement of the prescribing physician, and were instructed to restart the medication from 3 to 6 months after the resolution of MRONJ.

Adjuvant therapies in the treatment of MRONJ may include the application of low-level laser, HBOT, ozone and photodynamic therapies, platelet-rich plasma (PRP) and Platelet-rich fibrin (PRF) in the surgical sites and the use of medication such as teriparatide and PENTOCO (Ruggiero et al.[3] 2022, Heifetz-Li et al.[11] 2019, Epstein et al.[15] 2010, Pardo-Zamora et al.[16] 2021, Almeida et al[17] 2021). In the early cases of this series, adjuvant therapies were not used for the treatment of MRONJ due to the lack of scientific evidence at the time. Over time, new treatment protocols emerged and in 2019 HBOT was used as an adjuvant therapy in two MRONJ stage 3 patients with good results, but this treatment became difficult because patients had to travel for daily sessions. Therefore, in the last years PENTOCO has been used as an adjuvant therapy for MRONJ in four patients with satisfactory clinical results.

Limitations of this study include its retrospective nature and small patient sample. Therefore, prospective studies and randomized clinical trials with larger patient samples are recommended. Current findings suggest that MRONJ can be responsibly prevented in patients using ARDs, and treated predictably in those patients who develop the disease. It is essential to emphasize the need for professional and scientific interaction between healthcare professionals, particularly between physicians who treat metabolic and metastatic bone diseases, and oral and maxillofacial surgeons who are responsible for the prevention, diagnosis and treatment of MRONJ.

2.5 CONCLUSION

This study highlighted the importance of early diagnosis of MRONJ and the use of more conservative treatments even in the advanced stages of the disease, applying minimally invasive surgical techniques and avoiding segmental surgical

resections that require extensive bone reconstruction for oral rehabilitation of patients.

3 ARTIGO II - PATHOLOGICAL MANDIBULAR FRACTURE AND ATYPICAL FEMORAL FRACTURE IN THE SAME PATIENT WITH MEDICATION-RELATED OSTEONECROSIS OF THE JAW – CASE REPORT

3.1 INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse effect of antiresorptive and antiangiogenic drugs that is characterized by exposed bone in the maxillofacial region that has persisted for longer than 8 weeks, with no history of radiation therapy or obvious metastatic disease to the jaws (Ruggiero et al.[2] 2014). The most advanced form of the disease is stage 3, which is debilitating and associated with significant morbidity when a pathologic mandibular fracture (PMF) is present. The problems experienced may be chronic and include pain, swelling, halitosis, purulent drainage, neurosensory deficit, masticatory dysfunction, and decreased quality of life (Caldroney et al.[7] 2017).

Osteomyelitis is one of the most difficult infections to cure and may be caused by hematogenous spread in 22,97% of the cases (García del Pozo et al.[18] 2018). A small number of cases of Actinomycotic osteomyelitis in the lower legs of healthy patients resulting from hematogenous spread have been reported (Ryu et al.[19] 2019). Regarding MRONJ, furthermore Actinomyces sp. is believed to be the most commonly bacteria involved in its pathogenesis, and opportunistic infections can be an important risk factor for PMF (Topaloglu Yasan et al.[20] 2021).

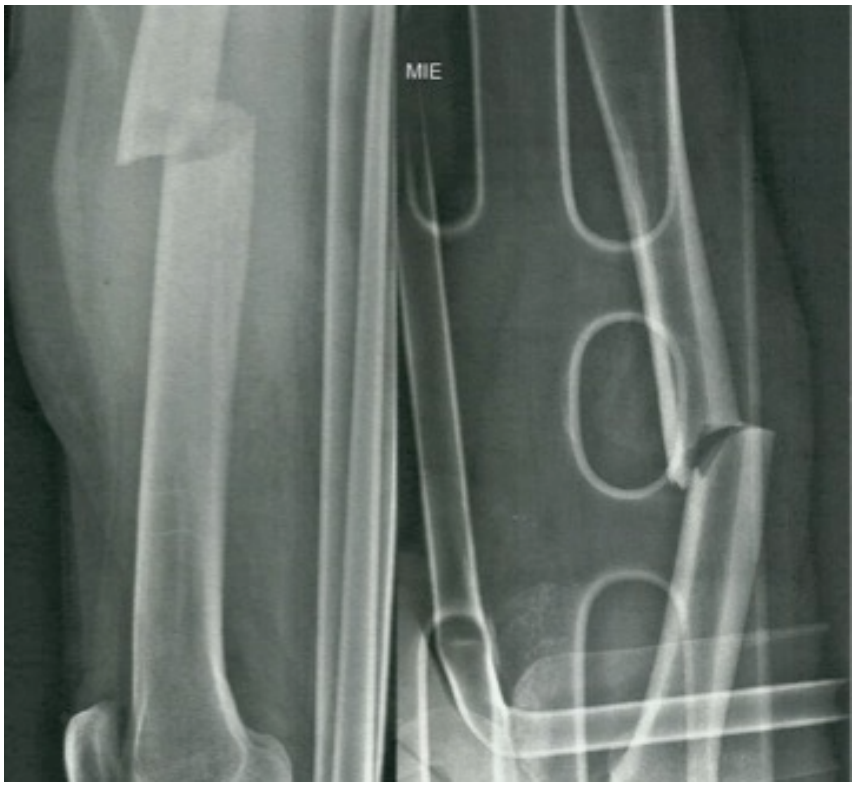
The MRONJ-related PMF treatment options range from conservative treatment (with the use of mouth rinses, oral antibiotics and teriparatide) or relatively simple surgical approaches combined with intermaxillary fixation, to extensive and more aggressive surgeries such as resection and musculocutaneous free flap mandibular reconstructions with the use of both internal and external fixations (Caldroney et al.[7] 2017, Yao et al.[21] 2016, Pichardo et al.[22] 2018, Otto et al.[23] 2013, Yamachika et al.[24] 2015).

Although rarely reported, distant complications of MRONJ are possible and must be considered in the clinical evaluation of patients presenting osteomyelitis of other bones. A case of MRONJ-related PMF associated to osteomyelitis of the femur that was incidentally diagnosed and successfully treated with surgical debridement and internal fixation is reported herein.

3.2 CASE REPORT

A 63-year-old woman presented with an atypical fracture of the left femur (Figure 5) caused by a fall that was treated with internal fixation by the orthopedic surgeon (Figure 6) and progressed to postoperative infection and osteomyelitis. Upon hospital readmission, the patient was medicated with ceftriaxone and a maxillofacial evaluation was requested to investigate an intraoral infection as a

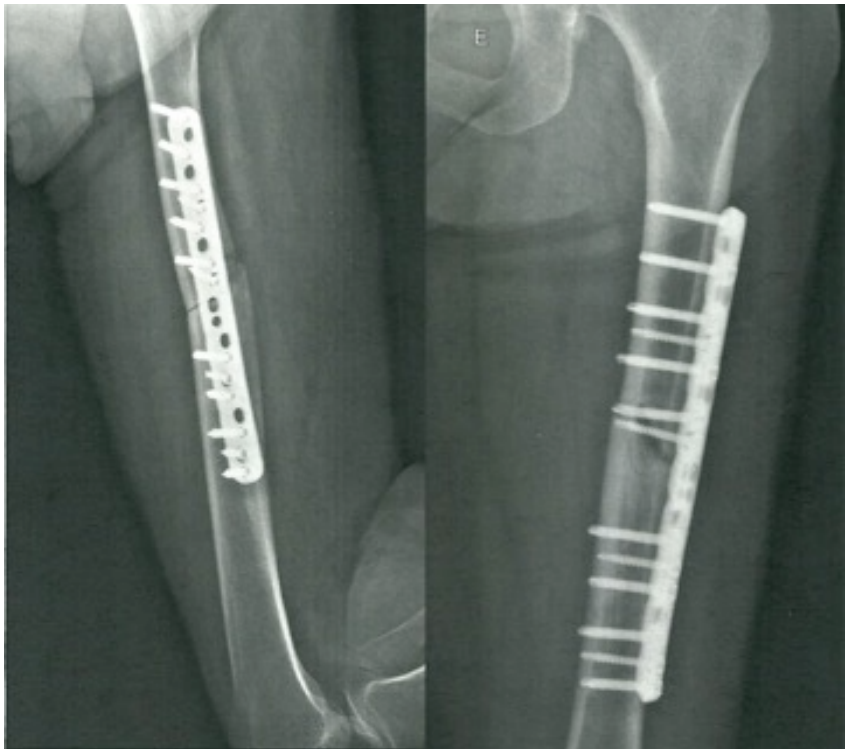
Figure 5 – Frontal and lateral views of the atypical femoral fracture



Source: Diagnostic Center - Unimed General Hospital - Ponta Grossa, Brazil.

possible cause of osteomyelitis of the femur. Clinical examination revealed hyperemia in the chin and intraoral suppuration with alveolar bone exposure in the anterior mandible. The CT scan showed a left parasymphyseal fracture (Figure 7) and mandibular osteolysis extending from the anterior alveolar crest to the mandibular base (Figures 8 and 9). The patient had previously undergone dental treatment for oral rehabilitation with four mandibular implants. One year after finishing treatment two implants failed and there was bone exposure with mandibular infection. The patient used alendronate to treat osteoporosis for two years and this medication

Figure 6 – Internal fixation of the femoral fracture



Source: Diagnostic Center - Unimed General Hospital - Ponta Grossa, Brazil.

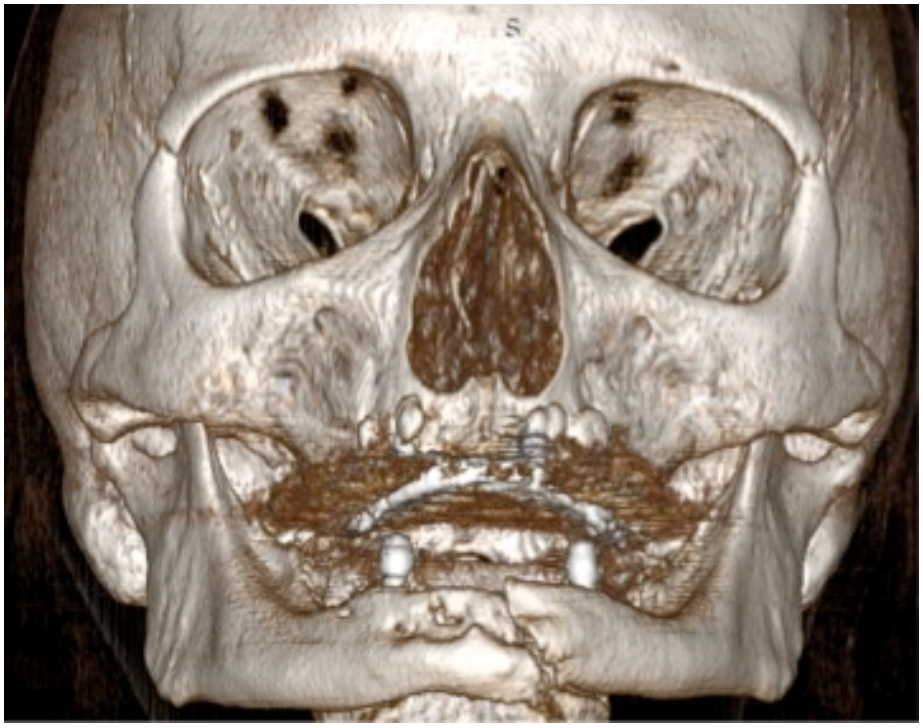
was not discontinued during the dental treatment. The diagnosis of PMF resulting from stage 3 MRONJ was then established.

The mandibular fracture was treated by stable internal fixation with a reconstruction plate extraorally (Figure 10) combined with debridement and removal of exposed necrotic bone intraorally. Clindamycin was added in the post-operative prescription, but after one week the patient had to be reoperated due to persistent mandibular suppuration. The two remaining mandibular implants were then removed and a new debridement with osteoplasty was performed intraorally. Postoperative recovery was uneventful, treatment with clindamycin was continued for another 5 days, and the mandibular infection was controlled after the second oral surgery.

Three weeks later, the patient was discharged from the hospital, instructed to discontinue the use of alendronate, and referred for thirty sessions of hyperbaric oxygen therapy as an adjuvant treatment for MRONJ.

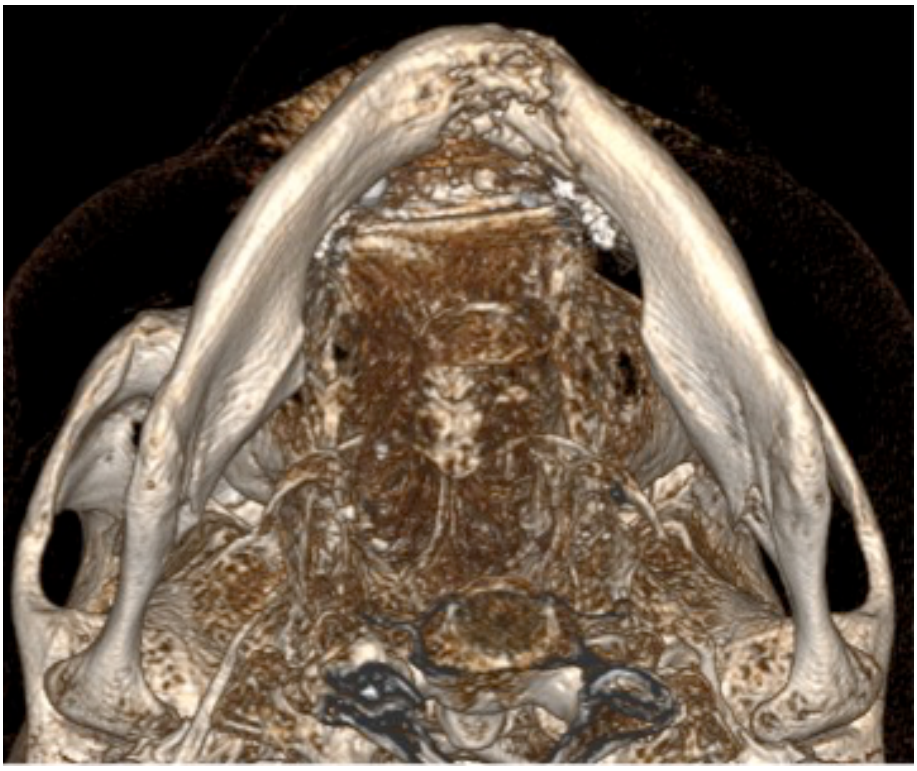
At the 2-month follow-up, the patient was asymptomatic and incisions healed satisfactorily (Figures 11 and 12). At 3 years of follow-up, the mandibular fracture was completely healed with no signs of bone exposure or intraoral infection. Currently, the patient is bedridden due to a spinal infection, which is being treated

Figure 7 – 3D CT scan frontal view of the MRONJ-related PMF



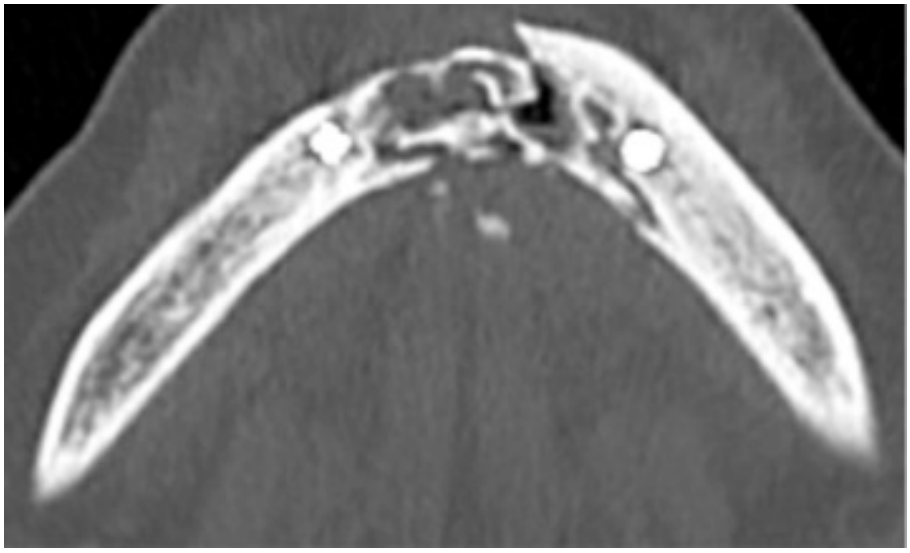
Source: Diagnostic Center - Unimed General Hospital - Ponta Grossa, Brazil.

Figure 8 – 3D CT scan axial view of the MRONJ-related PMF.



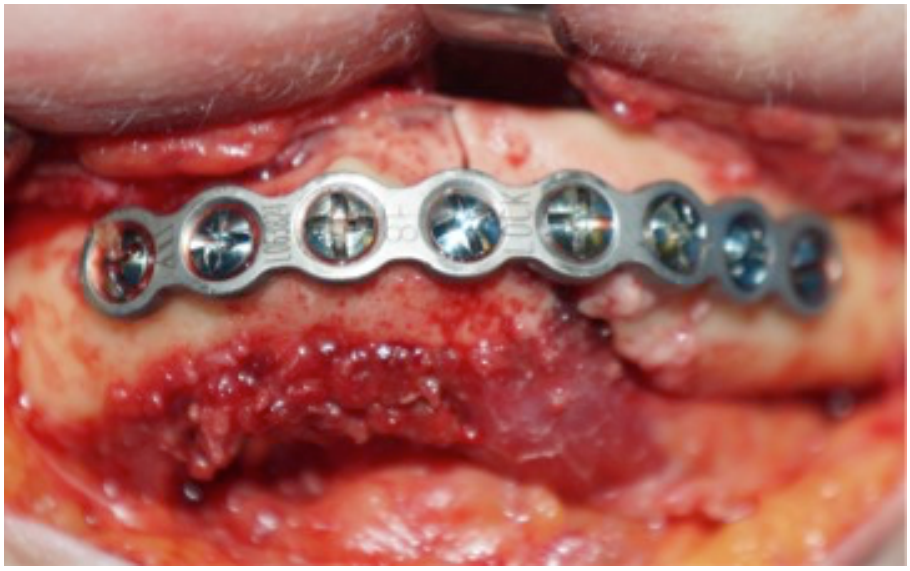
Source: Diagnostic Center - Unimed General Hospital - Ponta Grossa, Brazil.

Figure 9 – CT scan axial view of the osteonecrosis and PMF.



Source: Diagnostic Center - Unimed General Hospital - Ponta Grossa, Brazil.

Figure 10 – Intraoperative view of the internal fixation of the mandibular fracture.



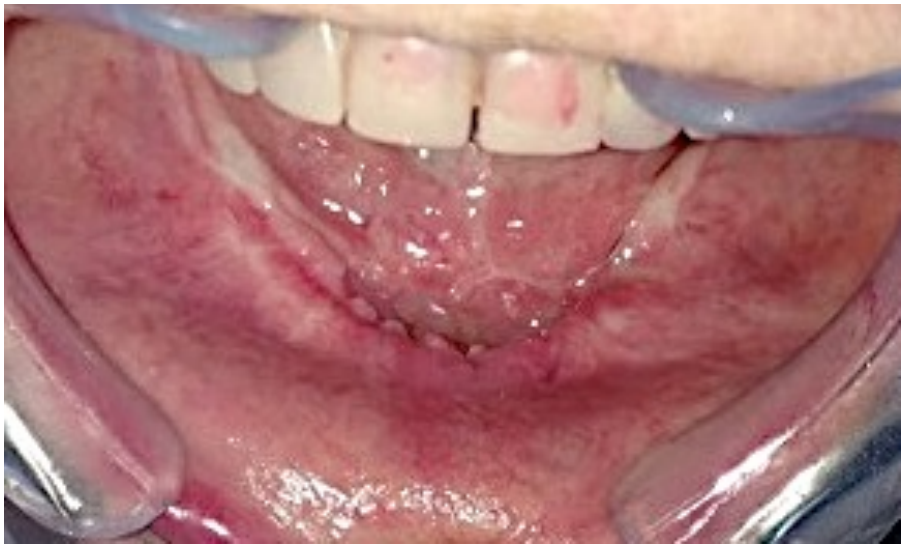
Source: File of Dr. Chigueyuki Jitumori.

with ciprofloxacin by an infectious disease specialist. In total, six surgical debridements without arthrodesis were performed on her spine, and several femur-lengthening surgeries with bone grafts were also performed.

3.3 DISCUSSION

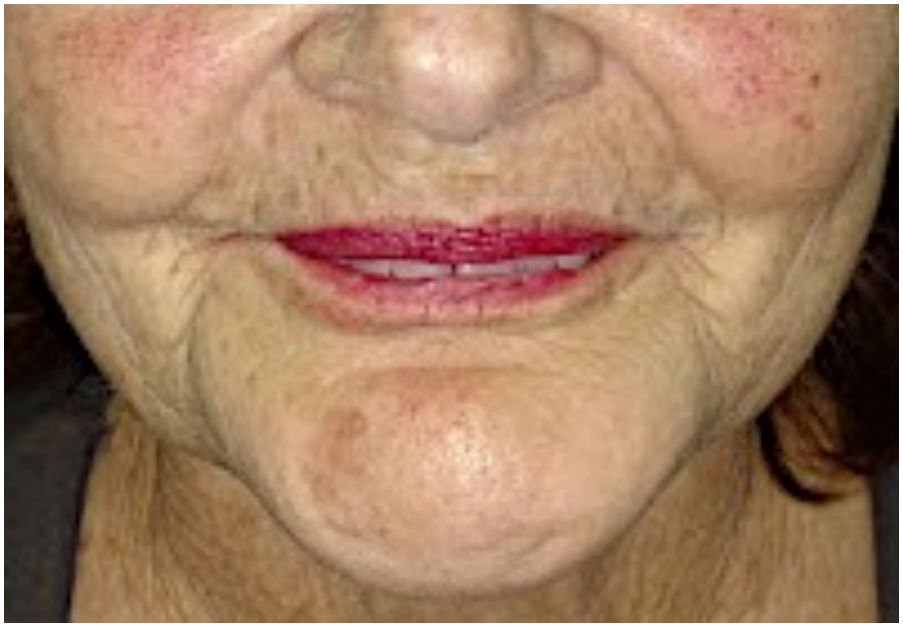
Pathologic fractures are more likely to appear in the mandible than in the

Figure 11 – 2-month postoperative view of intraoral healing.



Source: File of Dr. Chigueyuki Jitumori.

Figure 12 – 2-month postoperative extraoral view.



Source: File of Dr. Chigueyuki Jitumori.

maxilla because of its morphology (Ruggiero et al.[2] 2014, Otto et al.[23] 2013). When compared to the mandible, a pathologic fracture in the maxilla can rarely reach significant dimensions (Sukegawa et al.[25] 2016). There are limited data on the incidence of MRONJ-related PMF, with previous studies reporting from 2.9% to 4.31% of MRONJ cases (Topaloglu Yasan et al.[20] 2021, Otto et al.[23] 2013). The possible predisposing factors for MRONJ-related PMF may include medical

comorbidities, systemic factors, additive toxic effects of other medications (such as corticosteroids and chemotherapeutic agents), genetic factors, and specific pathogens (Ruggiero et al.[2] 2014).

In the present case, a medical comorbidity presented by the patient was osteomyelitis of the femur, which was possibly related to the hematogenous spread of infection from the mandible. Furthermore, a systematic review verified the prevalence of MRONJ in approximately 30% of patients treated with parenteral bisphosphonates who suffered an atypical femoral fracture (Graves et al.[26] 2016) Thus, it seems relevant to investigate the oral condition of patients requiring surgical treatment of atypical femoral fractures in order to anticipate further MRONJ-related complications.

It is important to know the causative factors and appropriate treatment protocol for MRONJ in order to prevent PMF. Traumatic extractions without the necessary preventive measures in susceptible patients should be avoided, as they present high risk for MRONJ-related PMF (Topaloglu Yasan et al.[20] 2021). Other precautions include informing patients about the severity of the disease and the importance of regular follow-up, as well as removing the necrotic bone and strengthening the weakened mandible with reconstruction plates as an early surgical intervention (Pedrazzoli et al.[27] 2016). In the reported case, the patient developed MRONJ after a two-year treatment for osteoporosis with alendronate. The medication was not discontinued prior to the placement of four mandibular implants, and the patient did not receive adequate treatment despite the previous failure of two implants.

There is no consensus regarding the treatment of advanced cases of stage 3 MRONJ in the elderly population, as well as there are no clear guidelines for the treatment of maxillofacial fractures in patients on active antiresorptive therapy (Yao et al.[21] 2016, Van Camp et al.[28] 2018). Removal of necrotic bone and internal fixation of fractures with load-bearing osteosynthesis plates provide better functional and esthetic results than resected-only cases. On the other hand, external fixation can also be used in cases with a high risk of infection and wound dehiscence, with consecutive exposure of osteosynthesis material or bone. Although surgical treatment of MRONJ-related PMF is the most frequently described (Otto et al.[23] 2013, Pedrazzoli et al.[27] 2016, Van Camp et al.[28] 2018), conservative management with administration of teriparatide as an adjuvant treatment has been reported with success (Yao et al.[21] 2016, Yamachika et al.[24] 2015). HBOT has also been

considered an effective adjuvant therapy for MRONJ cases, especially when combined with surgical treatment and antibiotics (de Souza Tolentino et al.[29] 2019). The present case of PMF was diagnosed due to the interaction between the surgical teams and was successfully treated with surgical debridement and open reduction with stable internal fixation, even though surgical re-approach was required to control the infection. In addition, the patient underwent thirty sessions of HBOT after hospital discharge as an adjuvant treatment for MRONJ.

3.4 CONCLUSION

Severe complications associated with antiresorptive and antiangiogenic drugs such as MRONJ-related PMF and atypical femoral fractures present a risk for potentially debilitated patients. It is important to emphasize the need for early diagnosis of MRONJ in order to prevent disease progression and the possible occurrence of PMF at later stages. Further studies concerning treatment strategies and guidelines for maxillofacial fractures in patients on active antiresorptive therapy are needed.

4 DISCUSSÃO

Os critérios de diagnóstico e os protocolos de tratamento da ONMM mudaram ao longo dos anos. Quando inicialmente descrita, era uma doença caracterizada pela exposição óssea dos maxilares e restrita a pacientes que faziam uso de bisfosfonatos. Atualmente, sabe-se que a ONMM pode ocorrer sem exposição óssea e, devido ao surgimento de novas formas de tratamento da osteoporose e da doença óssea metastática, pode estar relacionada a outras drogas antirreabsortivas e antiangiogênicas diferentes dos bisfosfonatos (Marx[1] 2003, Ruggiero et al.[2] 2014, Fedele et al.[8] 2010). Apenas uma paciente nesta série não apresentou exposição óssea inicialmente mas teve uma fístula intraoral. Após dezoito meses de tratamento coadjuvante, essa paciente evoluiu com exposição óssea e necessitou de cirurgia.

A ONMM é limitada aos maxilares devido à sua maior vascularização e taxa de remodelação óssea. Prevalece na mandíbula (75%) e a ocorrência pode estar relacionada ao tipo, dose e via de administração da DAR, com maior risco pela via parenteral. Além disso, pacientes com mais de quatro anos de terapia antirreabsortiva têm um risco potencial de até 0,21% de desenvolver a doença (Ayub et al.[4] 2021, Hallmer et al.[9] 2018, Beth-Tasdogan et al.[10] 2022). Nesta série todas as pacientes eram do sexo feminino, a maioria usava bisfosfonatos orais para tratar a osteoporose e desenvolveu a ONMM na mandíbula (81,8%). As duas únicas pacientes que desenvolveram a doença na maxila foram expostas à medicação intravenosa para tratamento de metástases ósseas.

Diabetes mellitus, tabagismo e medicamentos imunossupressores são fatores de risco para ONMM, e pacientes com osteoporose e imunodeficiência apresentam risco aumentado da doença (Heifetz-Li et al.[11] 2019, Mirelli et al.[12] 2022). Uma paciente nesta série tinha diabetes mellitus, duas eram tabagistas e uma delas também era etilista. Além disso, outras duas pacientes apresentavam doenças autoimunes (artrite reumatoide e miosite autoimune), sendo que uma delas fazia uso de imunomoduladores durante a terapia antirreabsortiva.

Portanto, a ONMM é uma doença multifatorial com efeito sinérgico de trauma, infecção e diminuição da remodelação óssea. Extrações dentárias e implantes dentários também podem desencadear o aparecimento da doença. Pacientes submetidos a extrações dentárias têm risco de 0,5% a 1% de desenvolver a doença, chegando a 5% em pacientes de alto risco, o que é semelhante ao risco de

desenvolver osteorradionecrose em pacientes irradiados. Além disso, pacientes com implantes dentários expostos ao denosumabe têm 0,5% de risco de desenvolver a doença (Heifetz-Li et al.[11] 2019, Dodson[13] 2015, Watts et al.[14] 2019). Assim, a extração dentária e o implante dentário foram os fatores desencadeantes mais frequentes entre as s desta série.

As estratégias atuais de tratamento da ONMM enfatizam que tanto o manejo não cirúrgico quanto o cirúrgico são aceitáveis para todos os estágios da doença com base no julgamento clínico e em fatores individuais do paciente. Pacientes refratários ao tratamento não cirúrgico ou incapazes de manter uma higiene oral adequada são candidatos à terapia cirúrgica. Portanto, a relação risco-benefício deve levar em consideração a capacidade do indivíduo de cuidar da ferida, a fim de prevenir a infecção e a disseminação da doença, a morbidade de um procedimento cirúrgico invasivo, bem como as preocupações com a reabilitação oral após a cirurgia de ressecção marginal ou segmentar (Ruggiero et al.[3] 2022). Todas as pacientes desta série foram tratadas inicialmente de forma conservadora. O tratamento cirúrgico foi realizado quando possível com cirurgias minimamente invasivas, nos casos com sequestro ósseo e naqueles cujo tratamento conservador inicial não evoluiu satisfatoriamente. Além disso, apenas duas pacientes com estágio 3 da doença foram submetidas à ressecção marginal e nenhuma paciente necessitou de ressecção segmentar da mandíbula.

Independente da forma de tratamento e do estágio da ONMM, a descontinuação da terapia antirreabsortiva antes ou no início do tratamento está associada a uma resolução mais rápida da doença, enquanto a continuação dessa terapia pode atrasar a resolução dos sintomas de 4 a 6 meses (Hinson et al.[6] 2015). Todas as pacientes desta série tiveram a terapia antirreabsortiva suspensa no início do tratamento com a concordância do médico prescritor, e foram instruídas a reiniciar a medicação de 3 a 6 meses após a resolução da doença.

As terapias coadjuvantes no tratamento da ONMM incluem a aplicação de laser de baixa intensidade, oxigenoterapia hiperbárica (OTHB), terapia com ozônio, aplicação de plasma rico em plaquetas (PRP) ou fibrina rica em plaquetas (PRF) nos locais cirúrgicos, e o uso de medicamentos como teriparatida e pentoxifilina com tocoferol (PENTOCO) (Ruggiero et al.[3] 2022, Heifetz-Li et al.[11] 2019, Epstein et al.[15] 2010, Pardo-Zamora et al.[16] 2021). Nos primeiros casos desta série, as terapias coadjuvantes não foram utilizadas no tratamento da ONMM devido à falta de

evidências científicas na época. Com o tempo surgiram novos protocolos de tratamento e em 2019 a OTHB foi utilizada em duas pacientes de estágio 3 da doença com bons resultados. Mas esse tratamento tornou-se difícil porque as pacientes precisavam se deslocar de cidade para sessões diárias. Portanto, nos últimos anos o PENTOCO foi usado como terapia coadjuvante em quatro pacientes com resultados clínicos satisfatórios.

Fraturas patológicas ocorrem mais na mandíbula do que na maxila devido à sua característica morfológica (Ruggiero et al.[2] 2014, Otto et al.[23] 2013), e quando comparada à mandíbula, uma fratura patológica na maxila raramente pode atingir grandes dimensões (Sukegawa et al.[25] 2016). Existem dados limitados sobre a ocorrência de FMP relacionada à ONMM, com a incidência estimada de 2,9% a 4,31% (Topaloglu Yasan et al.[20] 2021, Otto et al.[23] 2013). Os possíveis fatores predisponentes incluem as comorbidades médicas, fatores sistêmicos, efeitos tóxicos aditivos de outros medicamentos, como corticosteroides e agentes quimioterápicos, fatores genéticos e patógenos específicos (Ruggiero et al.[2] 2014).

No caso apresentado de FMP, a comorbidade médica apresentada pela paciente foi a osteomielite do fêmur, possivelmente relacionada à disseminação hematogênica da infecção da mandíbula. Além disso, uma revisão sistemática verificou a prevalência de ONMM em aproximadamente 30% dos pacientes tratados com bisfosfonatos parenterais que sofreram fratura femoral atípica (Graves et al.[26] 2016). Assim, parece relevante investigar a condição bucal de pacientes que necessitam de tratamento cirúrgico de fraturas femorais atípicas, a fim de antecipar novas complicações relacionadas à ONMM.

É importante conhecer os fatores causais e o protocolo de tratamento adequado da ONMM a fim de prevenir a ocorrência de FMP. Extrações traumáticas sem as medidas preventivas necessárias em pacientes suscetíveis devem ser evitadas, pois apresentam alto risco para FMP relacionada à ONMM (Topaloglu Yasan et al.[19] 2021). Outros cuidados incluem informar os pacientes sobre a gravidade da doença e a importância do acompanhamento regular, bem como remover o osso necrótico e fortalecer a mandíbula enfraquecida com placas de reconstrução como intervenção cirúrgica precoce (Pedrazzoli et al.[27] 2016). No caso relatado, a paciente desenvolveu a ONMM após dois anos de tratamento de osteoporose com alendronato. A medicação não foi descontinuada antes da

instalação de quatro implantes mandibulares, e a paciente não recebeu tratamento adequado, apesar da falha prévia de dois implantes.

Não há consenso sobre o tratamento de casos avançados de estágio 3 da ONMM na população idosa, assim como não há diretrizes claras para o tratamento de fraturas maxilofaciais nos pacientes sob terapia antirreabsortiva ativa (Yao et al.[21] 2016, Van Camp et al.[28] 2018). A remoção do osso necrótico e a fixação interna das fraturas com placas de reconstrução mandibular fornecem melhores resultados funcionais e estéticos do que os casos apenas ressecados. Por outro lado, a fixação mandibular externa também pode ser utilizada em casos de alto risco de infecção e deiscência da ferida, com consequente exposição óssea ou do material de osteossíntese. Embora o tratamento cirúrgico da FMP relacionada à ONMM seja o mais frequentemente descrito (Otto et al.[23] 2013, Pedrazzoli et al.[27] 2016, Van Camp et al.[28] 2018), o tratamento conservador da fratura com administração de teriparatida como tratamento coadjuvante foi relatado com sucesso (Yao et al.[21] 2016, Yamachika et al.[24] 2015). A utilização da OTHB também tem sido considerada eficaz no tratamento coadjuvante da FMP, especialmente quando combinada com o tratamento cirúrgico e a utilização de antibióticos (de Souza Tolentino et al.[29] 2019). O presente caso de FMP foi diagnosticado devido à interação entre as equipes médica e odontológica e foi tratado com sucesso, com debridamento cirúrgico e fixação interna estável da fratura, embora tenha sido necessária a reabordagem cirúrgica para controle da infecção. Além disso, a paciente foi submetida a trinta sessões de OTHB após a alta hospitalar como tratamento coadjuvante da ONMM.

5 CONCLUSÃO

Os achados atuais sugerem que a ONMM pode ser prevenida de forma responsável e tratada de forma previsível naqueles pacientes que desenvolvem a doença. É essencial enfatizar a necessidade da interação profissional e científica entre os profissionais da saúde, principalmente entre os médicos, que tratam as doenças ósseas metabólicas e metastáticas, e os cirurgiões bucomaxilofaciais, responsáveis pela prevenção, diagnóstico e tratamento de ONMM.

Este estudo destacou a importância do diagnóstico precoce da ONMM e do uso de tratamentos mais conservadores, mesmo nos estágios mais avançados da doença, aplicando técnicas cirúrgicas minimamente invasivas quando possível e evitando ressecções cirúrgicas segmentares, que requerem extensas reconstruções ósseas para a reabilitação oral dos pacientes.

Complicações graves associadas a medicamentos antirreabsortivos e antiangiogênicos, como as fraturas patológicas da mandíbula e fraturas femorais atípicas, representam um risco para pacientes potencialmente debilitados. As limitações deste estudo incluem a sua natureza retrospectiva e o tamanho amostral. Portanto, estudos sobre estratégias de tratamento e diretrizes para fraturas maxilofaciais em pacientes sob terapia antirreabsortiva, bem como estudos prospectivos e ensaios clínicos randomizados da ONMM com amostras maiores de pacientes são necessários.

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ANEXO A – Parecer consubstanciado do CEP.

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Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Tratamento da osteonecrose maxilar relacionada a medicamentos - estudo de série de casos

Pesquisador: TITO LUCIO FERNANDES

Área Temática:

Versão: 1

CAAE: 47185721.1.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.729.822

Apresentação do Projeto:

Projeto de Pesquisa:

Tratamento da osteonecrose maxilar relacionada a medicamentos – estudo de série de casos. Estudo observacional retrospectivo de série de casos

Objetivo da Pesquisa:

Objetivo Primário:

Revisar a literatura e apresentar uma série de casos diagnosticados com ONMRM e tratados conforme o padrão terapêutico atual

Avaliação dos Riscos e Benefícios:

Riscos:

Como é um estudo observacional retrospectivo, não há riscos envolvidos.

Benefícios:

Melhoria da qualidade de vida dos pacientes com a ONMRM.

Comentários e Considerações sobre a Pesquisa:

A osteonecrose dos maxilares relacionada a medicamentos (ONMRM) é uma doença rara que atinge pacientes usuários de medicação

antirreabsortiva óssea para o tratamento da osteoporose e de metástases ósseas. O estudo

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apresenta uma série de sete pacientes que foram
diagnosticados com ONMRM e tratados conforme o estágio evolutivo da doença. São detalhadas a terapêutica medicamentosa, as intervenções
cirúrgicas e as terapias adjuvantes utilizadas no tratamento.

Considerações sobre os Termos de apresentação obrigatória:
Em anexo e de acordo com as resoluções 466/2012 e 510/2016

Recomendações:
Enviar o relatório final ao término do projeto de pesquisa por Notificação via Plataforma Brasil para evitar pendências.

Conclusões ou Pendências e Lista de Inadequações:
Projeto foi aprovado sem restrições. O projeto se encontra dentro dos princípios éticos e metodológicos, de acordo com o Conselho Nacional de Saúde, Resolução 466/2012 e 510/2016.O termo de consentimento livre esclarecido deve ser elaborado em duas vias, sendo uma retida pelo participante da pesquisa, ou por seu representante legal, e uma arquivada pelo pesquisador.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1761059.pdf	24/05/2021 13:15:12		Aceito
Folha de Rosto	Folha_de_rosto.pdf	24/05/2021 13:03:19	TITO LUCIO FERNANDES	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Estudo_serie_casos.pdf	23/05/2021 22:52:46	TITO LUCIO FERNANDES	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Autorizacao_clinica_CEP.pdf	23/05/2021 22:26:35	TITO LUCIO FERNANDES	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PONTA GROSSA, 24 de Maio de 2021

Assinado por:
ULISSES COELHO
(Coordenador(a))

ANEXO B - Termo de consentimento livre e esclarecido.

TERMO DE CONSENTIMENTO DE PACIENTE

Eu, [illegible], RG 12.r.[illegible] 494 535 CPF [illegible], brasileiro(a), nascido(a) em 23/05/[illegible], autorizo o profissional CHIGUEYUKI JITUMORI, RG 6.899 330-2, CPF 596.335 061 15, a publicar minhas imagens em trabalhos acadêmicos, livros ou artigos científicos para fins de pesquisa.

Sendo isso verdade,

Cristiane Bueno dos Santos
Assinatura do(a) paciente
CPF: 025.967.939-97
RG: 7.398.572-2

Ponta Grossa, 13/10/2022