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OSTEONECROSE DE MANDÍBULA ASSOCIADA AO USO DE BISFOSFONATOS INTRAVENOSOS NO TRATAMENTO DO CÂNCER DE PRÓSTATA: REVISÃO DA LITERATURA E RELATO DE CASO

OSTEONECROSIS OF THE JAW ASSOCIATED WITH USE OF INTRAVENOUS BISPHOSPHONATES IN THE TREATMENT OF PROSTATE CANCER: A LITERATURE REVIEW AND CASE REPORT

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Case study

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RESUMO

Os bisfosfonatos podem ser utilizados para combater a ação tumoral maligna e melhorar a qualidade de vida de um paciente. Apesar dos benefícios desse medicamento, seu uso pode estar associado ao desenvolvimento de osteonecrose dos maxilares. Este estudo relata o caso de osteonecrose mandibular em paciente que utilizou ácido zoledrônico como tratamento para câncer de próstata. Clinicamente, observou-se drenagem submandibular extraoral e exposição óssea mandibular intraoral compatível com sequestro ósseo. A tomografia computadorizada revelou alteração da trabeculação mandibular, sendo hipodensa, difusa e com limites indefinidos. Na cintilografia, observou-se hipercaptação anormal do radiofármaco no maxilar inferior. O manejo envolveu suspensão do ácido zoledrônico e tratamento com antibioticoterapia sistêmica e local, com evidente melhora do quadro clínico. Neste momento, o paciente está em acompanhamento para avaliar a evolução da comorbidade. A revisão da literatura mostrou maior incidência da doença em homens com mais de 65 anos; o tratamento de escolha foi a administração de 4 mg de ácido zoledrônico, cerca de 57,1% dos casos ocorreram apenas em uma mandíbula, enquanto 42,9% ocorreram simultaneamente em ambas as mandíbulas. Para tratamento, os casos foram resolvidos com diferentes técnicas cirúrgicas, com resultados inconclusivos ou não informados a longo prazo. Em conclusão, o tratamento oral deve ser realizado com cautela antes de iniciar a terapia com bisfosfonatos para prevenir a osteonecrose, adotando condutas conservadoras e realizando encaminhamentos, quando necessário, para reduzir sua incidência em pacientes com câncer.

Palavras-chave: Osteonecrose mandibular; Bisfosfonatos; Câncer de próstata; Ácido Zoledrônico.

ABSTRACT

Bisphosphonates can combat malignant tumoral action and improve the quality of life of a patient. Despite the benefits of this medication, its use may associate with the development of osteonecrosis of the jaws. This study reports mandibular osteonecrosis in a patient who used zoledronic acid to treat a prostate cancer. Extraoral submandibular drainage and intraoral mandibular bone exposure compatible with bone sequestration were clinically observed. Computed tomography revealed a change in mandibular trabeculation, being hypodense, diffuse, and with indefinite limits. For scintigraphy, abnormal hypercaptation of the radiopharmaceutical in the lower jaw was observed. Management involved the suspension of zoledronic acid and the treatment with systemic and local antibiotic therapy, with an evident improvement of the clinical picture. At this moment, the patient is being followed to evaluate the evolution of comorbidity. The literature review showed a higher incidence of the disease in men older than 65; the treatment of choice was the administration of 4 mg of zoledronic acid; about 57.1% of the cases occurred only in one mandible, while 42.9% co-occurred in both. For treatment, the cases were solved with different surgical techniques, with inconclusive or non-informed results in the long term. In conclusion, oral treatment should be carried out before initiating bisphosphonate therapy to prevent osteonecrosis. Conservative approaches shoujd be adopted, and conducting referrals, when necessary, to reduce its incidence in cancer patients.
Keywords: Mandibular osteonecrosis; Bisphosphonates; Prostate cancer; Zoledronic acid.

INTRODUCTION

The first report of osteonecrosis associated with bisphosphonates occurred in 2003. Such an index has increased significantly since then (YAZAN et al., 2016). Mandibular osteonecrosis occur in patients with tumors with bone metastases. This condition is suspected to be related to intravenous bisphosphonate treatment (WUTZL *et al.,* 2006) and associated with head and neck radiotherapy, surgical procedures in the anatomical region, local factors, systemic defects, and vascularization defects (MERIGO *et al.,* 2006).

Bone is one of the sites most frequently affected by tumor metastases in patients with advanced cancer: approximately 65% to 75% of patients with prostate cancer develop bone metastases (CHEN *et al.,* 2016). Prostate cancer is the malignant tumor with the highest incidence in the male population and the second most common cause of death among all types of cancer (AMERICAN CANCER SOCIETY, 2019). The mandibular bone presents intense vascularization and bone remodeling by continuous mechanical stress, which can make it vulnerable to the adverse effects of anticancer drugs. Hypotheses suggest this condition is restricted to the jaws by altered bone remodeling. It inhibits angiogenesis, and consistent microtrauma, and suppresses innate or acquired immunity and the possible effects of inflammatory processes (ZIRK *et al.,* 2019). Thus, bisphosphonates can inhibit bone remodeling, interfere with recruitment, osteoclast activity, and survival, and limit inflammation (CORSI *et al.,* 2017). Zoledronic acid is a bisphosphonate used as therapy for cancer involving the skeletal system. It is widely proposed to patients because it makes it possible to combat malignant tumor action and improves patients' quality of life (CHEN *et al.,* 2016).

Despite the benefits of this medication, its use may be associated with the development of maxillary osteonecrosis, a pathological condition that presents clinically as foci of necrotic infection in exposed gnathic bones in the oral cavity, which may be surrounded by intra- or extraoral fistulas in the maxillofacial region, persisting for at least eight weeks in patients without previous radiotherapy in this area. Once such lesions are established, the course of the disease becomes complicated, especially in the more advanced cases (DINIZ-FREITAS *et al.,* 2016; YAZAN *et al.,* 2017). Therefore, this study aims to present a case report of a patient who used bisphosphonates continuously for prostate cancer and developed mandibular osteonecrosis. It also aims to carry out a literature review on this topic.

CLINICAL CASE

A 70-year-old white male had a total superior prosthesis and a partial lower prosthesis, four teeth in the anteroinferior region, severe periodontitis, and poor oral hygiene conditions. He was referred to the stomatology and oral pathology center at the Federal University of Pelotas to evaluate bone exposure in the mandibular alveolar ridge. He reported

having been diagnosed with prostate cancer and had completed a nine month-treatment with zoledronic acid. Besides, he complained of pain associated with the ulcer with bone exposure in the lower right hemarcade, indicating as main symptoms severe pain in the bone, as well as increased volume and erythema. The prosthesis presented a lack of adaptation which contributed to the worsening of the ulcer. The patient was treated with zoledronic acid in doses of 4 mg diluted in 100 mL of saline and infused over 15 minutes with cycles every 28 days during the nine months. At the same time, the patient was treated with Abiraterone acetate 250 mg and Leuprorelin acetate 7.5 mg.

Clinical examination revealed an extraoral submandibular drainage and an intraoral mandibular bone exposure, which was compatible with osteonecrosis at the crest of the alveolar ridge. Bone scintigraphy examinations were requested. The computed tomography showed a change in the mandibular bone trabeculation, a diffuse hypodense aspect with poorly defined limits, an infiltrative aspect, a rupture of the cortical bone, and an absence of bone expansion, with a presumptive diagnosis of a malignant metastatic lesion. In the bone scintigraphy, abnormal hypercaptation of the radiopharmaceutical located in the lower jaw was observed.

Local irrigation was performed with 0.12% chlorhexidine to control the infection on the right side of the face, and the patient was instructed to perform homemade mouthwashes four times a day with the same solution for monitoring oral hygiene. The patient was also instructed not to use the partial inferior prosthesis to avoid the onset of traumatic ulcerations at the site of the lesion. In the following evaluation, the presence of an extraoral fistula in the mandibular body, without drainage and bone exposure, and the absence of local sensitivity persisted. The conduct was to interrupt the use of BF, instituting local and systemic antibiotic therapy with amoxicillin 500 mg. The patient remains in weekly follow-up for local irrigation with chlorhexidine and control of oral hygiene to avoid possible infections due to the accumulation of bacterial biofilms. Thus, the goal of treatment is to maintain adequate local hygiene to control the area of mandibular bone exposure.

METHODOLOGY

A literature review was carried out on the PubMed platform via MEDLINE of scientific articles published only in English in the last ten years. The descriptors were: (Diphosphonates) OR (Imidazoles) AND (Bisphosphonate Associated Osteonecrosis of the Jaw) OR (Bisphosphonate-Induced Osteonecrosis of the Jaw) OR (Osteonecrosis of the Jaws, Bisphosphonate-Associated) OR (Bisphosphonate-Associated Osteonecrosis) OR (Bisphosphonate Osteonecroses) OR (Osteonecroses, Bisphosphonate) OR (Osteonecrosis, Bisphosphonate) AND ((Prostate Neoplasms) OR (Prostatic Cancer) OR (Cancer, Prostatic) AND (“2008”(Date - Entrez): “3000”(Date - Entrez)). Articles that met the following

eligibility criteria were considered in this study: bone exposure reports compatible with osteonecrosis in the posterior region of the mandible, measurement of the use of zoledronic acid to control prostate cancer, and the presence of osteonecrosis affecting predominantly the lower jaw. The following information was collected: number of patients evaluated, age of the patient, country of origin, medication dose, duration of use, side effects of the disease, history of dental history, presence of case follow-up, and prognosis of reported clinical condition.

RESULTS

A total of 73 articles were selected; 38 were removed after reading the titles and 25 after reading the abstracts. Thus, ten articles were read in full, and three were excluded, totaling seven articles included in the review. The three articles selected were from three continents: America (1), Asia (1), and Europe (5). Data showed the mean age of patients affected by mandibular osteonecrosis associated with bisphosphonate use was 66.9 years. Concerning the anatomical site, 4 (57.1%) cases occurred in the mandible, while 3 (42.9%) occurred in the maxilla and mandible. None was recorded exclusively in the maxillary bone. Elective treatment based on the administration of 4 mg zoledronate (zoledronic acid) treated patients with comorbidities. The cases reported to date have been treated with different surgical techniques, with inconclusive or non-informed results in the long term. Table 1 summarizes the details of the review.

DISCUSSION

We present a case of osteonecrosis associated with bisphosphonates and a literature review of similar case reports. Osteonecrosis has been associated with the use of aminobisphosphonates and Denosumab. More than 90% of cases occur in cancer patients receiving high doses of intravenous bisphosphonates or subcutaneous Denosumab (KHAN *et al.,* 2015). The risk of developing osteonecrosis might be related to the dosage and duration of the treatment (MIGLIORATI *et al.,* 2011). The plasma half-life of bisphosphonates is approximately ten years, and their prolonged use may result in substantial accumulation of the drug in the skeleton (SEDGHIZADEH *et al.,* 2008). Also, patients with a metastatic bone disease or multiple myeloma, who underwent oncologic treatment with aminobisphosphonates or Denosumab, have a higher incidence of osteonecrosis (KHAN *et al.,* 2015).

Risk factors for osteonecrosis in the jaws include dentoalveolar surgery, periodontal disease, trauma, and misfit dentures (PAZIANAS *et al.,* 2007), which corroborates with the traumatic etiology of the present case. Besides, glucocorticoid therapy is associated with an increased risk of developing the disease, which could be due to multiple factors, such

as inhibition of osteoblastic function and increased apoptosis of osteoblasts and osteocytes, increased bone resorption, immunosuppression, and increased risk of local infection (SAAD *et al.,* 2012). Vitamin D deficiency has also been identified as a possible risk factor (HOKUGO *et al.,* 2010) in addition to age, obesity, and tobacco consumption (MIGLIORATI *et al.,* 2011).

Bisphosphonates have direct biological effects on calcium metabolism, inhibiting calcification and bone resorption (BRUNELLO *et al.,* 2009). This drug can act through two mechanisms of action related to the anti-osteoclastic and antiangiogenic activity (RUGGIERO *et al.,* 2004). As bone metabolism is based on the processes of resorption and deposition, bone remodeling is compromised; however, bone tissue continues to mineralize and may become fragile, brittle, and less elastic (SEDGHIZADEH *et al.,* 2008).

Clinically, osteonecrosis can occur by the exposure of necrotic bone in exposed osteonecrosis. It is possible to show the presence of necrotic bone exposed through oral mucosa or facial skin, tending to affect the mandible more frequently than the maxilla. Manifestations such as swelling and erythema of soft tissues, pus secretion, fistula tracts, tooth loss, jaw deformity, pain, and sensory disturbances can be commonly presented (FILLEUL *et al.,* 2010). The exposed bone can range from a few millimeters to several inches, as in our case (BEDOGNI *et al.,* 2008).

According to research that shows the incidence of osteonecrosis, the case presented shares similar characteristics regarding the age of presentation, exposure factors, and location. According to cases reported in the literature in a study of 43 patients with a history of previous dental extraction or use of misfit prosthesis, the mean age of these patients who developed the disease was 70.3 years (WALTER *et al.,* 2008). Another case that evaluated 253 patients exposed before periodontal treatment, extraction, or endodontic treatment also obtained an average of approximately 70 years of mean age (MÜCKE *et al.,* 2016), corroborating the characteristics of the patient of the present clinical case report. In the literature, a study of 1621 cancer patients demonstrated that misfit dentures and dental extractions in patients receiving zoledronic acid were associated with an increased risk of osteonecrosis (YAMAZAKI *et al.,* 2012). According to a study, the mean time between exposure to these triggering agents and the diagnosis of osteonecrosis was around 5.7 months (PELAZ *et al.,* 2015).

A pharmacology study showed that zoledronic acid was the drug associated with osteonecrosis in 68.5% of the cases. In addition, pamidronate was used with two patients, and, in the other two cases, pamidronate and zoledronic acid were administered at different treatment periods (PELAZ *et al.,* 2015). In this study, zoledronic acid is the agent with fewer milligrams that developed the disease. Other drugs identified as inductors of osteonecrosis are alendronate and ibandronate (MARTINS *et al.,* 2017). The indication for the use of the-

se drugs was postmenopausal osteoporosis, rheumatoid arthritis, sarcoidosis, pemphigus, Addison's disease, and Paget's disease (KATSARELIS *et al.,* 2015).

Zoledronic acid is classified as an intravenous drug most frequently associated with osteonecrosis when administered parenterally (LO *et al.,* 2010). However, alendronate is the primary inducer of osteoporosis, since it has been considered the bisphosphate of choice for the treatment of osteoporosis (RUGGIERO *et al.,* 2004). Although some cases are reported in the mandible and maxilla, individually or simultaneously, the mandible is more affected because it is composed of a compact bone type (MONTEFUSCO *et al.,* 2008). Therefore, osteonecrosis presents a higher incidence in the mandible than in the maxilla, at a proportion of 2:1, especially in areas with less thick mucosa (SAWATARI *et al.,* 2007). Although bone remodeling in the maxilla is greater, there is no evidence that bisphosphonates accumulate at higher concentrations in the mandible or that its remodeling is affected to a higher degree (OTTO *et al.,* 2010). A recent study confirmed the uptake of bisphosphonates is not increased in the mandible compared with the maxilla (SAWATARI *et al.,* 2007).

According to the literature review, osteonecrosis after chemotherapy treatment can be prevented by optimizing oral hygiene, antimicrobial mouthwashes, and systemic antibiotic therapy. To date, our case has responded satisfactorily after a six-month antibiotic therapy and reinforcing hygiene measures. Individuals who do not respond to conservative treatment or those in the advanced stages of osteonecrosis can be considered for surgery; data in recent years have demonstrated surgical success in this patient population (KHAN *et al.,* 2015). Osteotomy of the affected area may be recommended for patients at a more advanced stage of the disease. In the last few years, the number has increased reports of success following this surgical protocol in osteonecrosis lesions. The surgery is recommended to occur by leaving the total thickness of the mucoperiosteal flap high and extending it to reveal the entire area of the exposed bone. This affected bone can then be resected until it reaches the bleeding aspect with healthy characteristics. Besides, sharp edges should be smoothed, and the primary soft tissue closure is tension-free (DINIZ-FREITAS *et al.,* 2012). Other therapies are currently being evaluated and used in association with each other, including low-intensity laser therapy, platelet-rich plasma use, wound debridement, sequestrectomy, surgical resections, low parathormone doses, and hyperbaric oxygen in combination with surgery (MATINS *et al.,* 2012).

Also, for the treatment of mandibular osteonecrosis, experimental therapies such as the use of intra-*lesional* bone marrow stem cell transplantation and tissue grafting may be used. However, conservative measures focused on hygiene should always be considered the gold standard as the first measure in osteonecrosis therapies resulting from systemic use of chemotherapy (NGAMPHAIBOON *et al.,* 2011). In reducing the risk of osteonecrosis, dental surgeons are essential in applying the correct primary prevention protocol for the pre-treatment and treatment of patients (ROSELLA *et al.,* 2011). A standardized multidisciplinary

approach with a sustained dialog among the specialists involved should be taken to ensure the effectiveness of preventive strategies and to improve the patient's quality of life (VAN POZNAK *et al.,* 2017). It is the responsibility of the dental surgeon to accurately assess the risk factors that lead to the development of the disease since the synergy of the professionals and the patient's awareness allows the accomplishment of treatment with a common goal (DI FEDE *et al.,* 2018). Therefore, once the oncologist prescribes bisphosphonate therapy, the patient should be referred to a dental surgeon for tests, and the relationship between these professionals must be continuous (MARX *et al.,* 2005). Mandatory preventive measures for patients using bisphosphonates are correct oral cavity tracking and dental care since the main risk factors for osteonecrosis include a type of bisphosphonate, prolonged exposure to it, the patient's advanced age, and dental procedures performed during treatment (DE IULIIS *et al.,* 2014).

In cases where the patient requires invasive dental procedures, such as dental extraction, implant surgery, periodontal surgery, or endodontic therapy, delaying the start of treatment with these drugs for one month is recommended to allow sufficient time for recovery and bone healing. After initiating therapy with bisphosphonates, a surveillance scheme is necessary once every four months (MARX *et al.,* 2005). Several perioperative measures have been proposed to prevent this complication, including antiseptics before extraction and cure, antibiotic prophylaxis, alveoloplasty with primary closure, autologous platelet-rich fibrin, or plasma, atraumatic extraction with orthodontic traction, ozone therapy, and the limitation of the number of extractions performed in each session (DINIZ-FREITAS *et al.,* 2016). Dental surgeons should inform patients of the importance of maintaining oral hygiene in good condition without soft tissue injuries, and periodically perform dental care surveillance. Also, prophylactic antibiotic therapy should be recommended only when invasive dental procedures are preceded; however, a dental cleaning with a professional twice a year is recommended in addition to an evaluation by the oncologist at all follow-up visits; the tests should be done every three to four months, depending on the concomitant risk factors (BARALDI *et al.,* 2014).

Our case so far shows a response to conservative therapies. Literature indicates the importance of this therapy. In patients treated with oral and intravenous bisphosphonates, without osteonecrosis associated with mandibular chemotherapy, antibiotic prophylaxis before oral surgery is an important tool to prevent osteonecrosis and promote healing of the affected area (MONTEFUSCO *et al.,* 2008). If the patient has already had osteonecrosis associated with chemotherapy after tooth extraction, antibiotic prophylaxis is indicated to prevent recurrent osteonecrosis and promote healing of the extraction site (KADAKIA *et al.,* 2017). If osteonecrosis associated with chemotherapy is already present, antibiotic therapy is a vital part of a conservative treatment to reduce the symptomatology of osteonecrosis and prevent it from worsening (LODI *et al.,* 2010). Finally, the lack of clinical data and

randomized clinical trials makes it difficult to choose the most appropriate protocol for the various clinical situations studied.

On the duration of prophylactic antibiotic treatment before and after tooth extraction, no uniform approach is applied in all patients receiving oral or intravenous bisphosphonate treatment. Some articles propose that antibiotics be prescribed three or in patients treated with oral bisphosphonates. Likewise, post-extraction recommendations vary, with articles suggesting antibiotic prophylaxis be administered anywhere from 7 to 17 postoperative days (LODI *et al.,* 2010; SAIA *et al.,* 2010). For patients receiving intravenous bisphosphonate treatment, the recommendations of the articles for prescribing pre-extraction of antibiotics begin to vary from one, two, or three days before to seven days before extraction (LODI *et al.,* 2010; SAIA *et al.,* 2010; SCOLETTA *et al.,* 2011). Post-extraction antibiotic treatment is recommended to be initiated 5, 7, 9, or 17 days after the procedure. However, most authors agree that post-extraction treatment regimens in patients receiving oral and intravenous bisphosphonates should be continued until the surgical site is fully cured (LODI *et al.,* 2010; SAIA *et al.,* 2010; SCOLETTA *et al.,* 2011; RUGGIERO *et al.,* 2012).

The use of penicillin as an antimicrobial is indicated because the microorganisms most frequently found in the exposed bones are of the species *Actinomyces, Veillonella, Eikenella, Moraxella, Fusobacterium, Bacillus, Staphylococcus, Streptococcus*, and *Selenomone*, all of which are penicillin sensitive (RUGGIERO *et al.,* 2009). The use of amoxicillin with or without clavulanic acid (500 mg), Clindamycin (300 mg), Azithromycin (500 mg), or Metronidazole with beta-lactam antibiotics is indicated (PÉREZ-SAYÁNS *et al.,* 2017). Also, ozone therapy may be an alternative to treatment. Ozone is a natural gas produced by the atmosphere that has antimicrobial and curative properties; it is believed to induce tissue repair and mucosal healing (BOCCI *et al.,* 2004). A lot of studies have used this therapy as an adjunct to successful antibiotic treatments, although more standardized studies are needed to accurately determine their efficacy (RIPAMONTI *et al.,* 2011). Hyperbaric oxygen therapy is also discussed in the literature. This therapy is believed to stimulate tissue healing, reduce edema and inflammation that stimulate cell proliferation, and moderate the suppression of bone remodeling produced by bisphosphonates (VESCOVI *et al.,* 2010). Another therapy is the soft laser, an innovative and effective medical method acting to reduce pain, improve blood circulation in the area of the injury, and help regenerate nerves. At the oral level, it improves reepithelialization after periodontal or third molar surgery. These therapies are highly recommended, although the association of these adjuvant methods with medical and surgical therapy, particularly with appropriate antibiotic therapy, is indicated, ensuring good clinical results (VESCOVI *et al.,* 2014).

CONCLUSION

Although rare, osteonecrosis of the jaw associated with intravenous bisphosphonates is a severe complication. To reduce its incidence in the male population with prostate cancer using bisphosphonates to improve quality of life, a full history and a face examination should be performed before initiating treatment with these drugs. A dental surgeon is the professional responsible for these procedures

This professional is also responsible for promoting a discussion with the patient on the relationship between these comorbidities and the responsible physician. Quarterly dental follow-ups are necessary as they significantly reduce the risk of osteonecrosis associated with bisphosphonates in cancer patients, especially those with prostate cancer.

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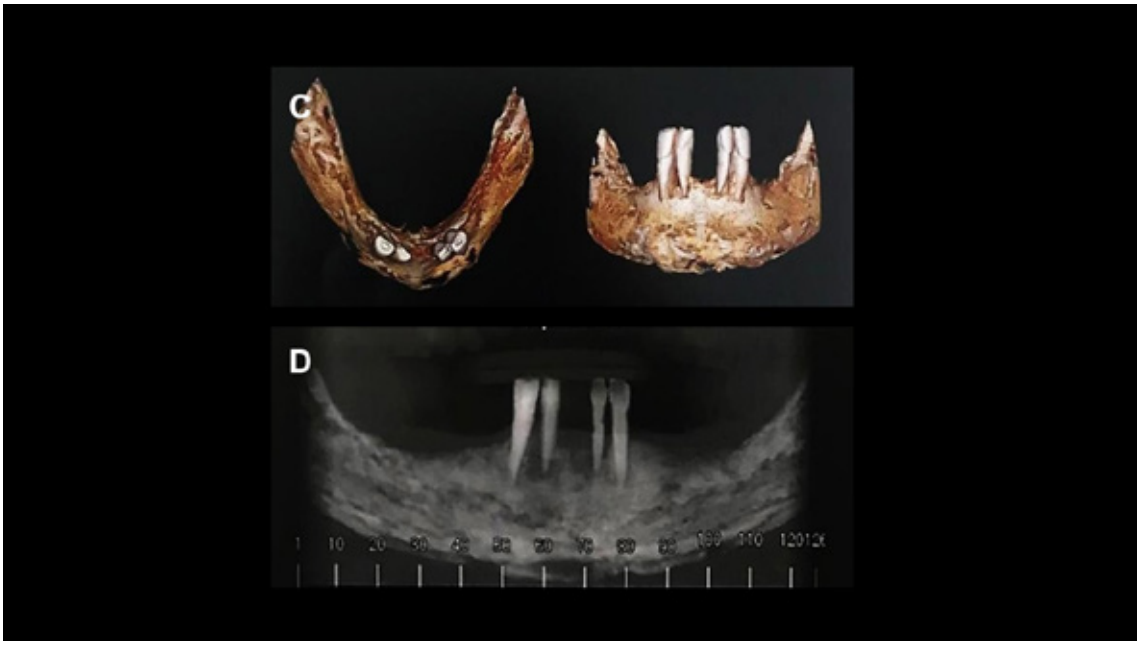
Figure 1. The aspect of the patient's oral lesion. In images [A and B], intraoral mandibular bone exposure compatible with osteonecrosis is observed.

Figure 2. A radiographic aspect of the lesion. These images [C and D] show a change in mandibular bone trabeculation, presenting a diffuse hypodense aspect, with poorly defined limits, infiltrative aspect, cortical bone rupture, and absence of bone expansion, diagnosed with the metastatic malignant lesion.



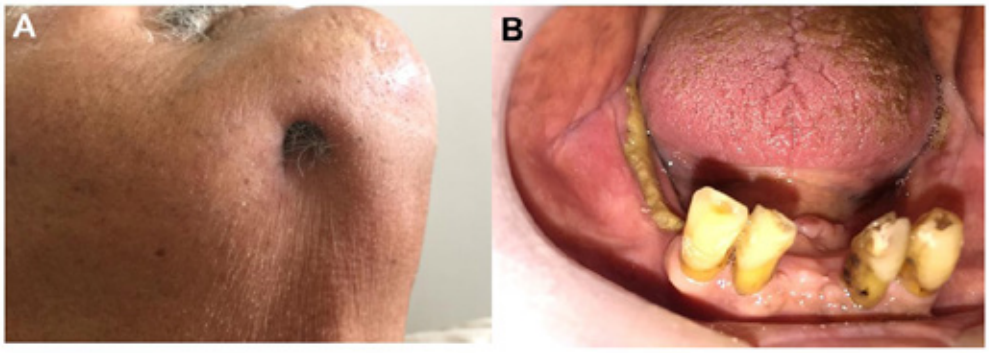


Table 1. Results of research in PubMed database

Author and year of publication	Number of patients evaluated	Middle ages (years)	Country	Dental history	Treatment time	Place of injury involvement	Bisphosphonate dose	Follow-up time (months)	Prognosis of treatment
(Walter et al., 2008)[9]	43	70,3	Germany	History of previous dental extraction or painful pressure resulting from use of a prosthesis	All patients received zoledronate at least 14 times	Mandible and maxilla	All patients received 4 mg of zoledronate intravenously (IV) 4 weeks (21.4 15.1 applications (min: 1, max: 59))	15	Eight patients developed osteonecrosis; six of these patients received antimicrobial treatment with amoxicillin and clavulanic acid; three patients underwent a sequestratomy; one underwent partial maxilectomy; and one received a partial thickness resection of the mandible followed by a recurrence and a second resection of more extensive partial thickness. One patient received partial thickness resection of the mandible.
(Frei, Bornstein, Schaller, & Reichart, 2010)[10]	1	60	Switzerland	History of dental extraction with unhealed wound	6 weeks.	Mandible. Second lower left molar area	Zoledronate received 4 mg / month intravenously for 4 years	12	Rinse with chlorhexidine solution twice a day for 1 minute, sequestractomy, patient received 1.2 g of IV antibiotics 3 times a day for 3 postoperative days and then 1 g orally 3 times a day for 2 weeks and 1 g twice daily for the next 6 weeks.
(Nakamura, et al., 2016)[11]	1	65	Japan	History of severe periodontal disease of teeth and tooth extraction was performed in November of the same year	22 meses.	Mandible. First left lower molar area .	The total dose of zoledronic acid was 88 mg .	6 months, recognized progression of cancer and death of the patient	Bisphosphonotherapy for osteonecrosis of the mandible, and all necrotic bones and teeth were removed. Subsequently, it was subjected to repeated cleaning and correction (immobilization) for an oral fistula and mandibular fracture.
(Haidar et al., 2009)[12]	53 patients evaluated, and 51 had metastatic prostate cancer	68	Denmark .	Two patients developed the disease. One developed symptoms spontaneously, while the other developed symptoms after tooth extraction	14 months	Mandible	All patients received 4 mg of zoledronate intravenously (IV) for 20 minutes every 4 weeks	14 months. Treatment was repeated every 4 weeks and patients were discharged after a brief observation	
(Ristow et al., 2014)[13]	21	70.48	Germany		24 months	Mandible and maxilla	All patients received 4 mg zoledronate every 4 weeks	24	

(Fiazzi et al., 2011)[14]	1901 patients, 951 of whom received zoledronic acid	About 77% of the patients were ≥65 years	The United States, where 342 centers were evaluated in 39 states	History of dental extraction, poor oral hygiene, or use of dental appliance	10 months for patients who received zoledronic acid	Mandibular osteonecrosis occurred infrequently in only 10 patients, 9 of these underwent chemotherapy	All patients received 4 mg of intravenous zoledronic acid every 4 weeks	11	Surgical treatment for osteonecrosis of the mandible was done in three patients in the zoledronic acid had limited surgery and one had bone resection, a mucosa was covered in one patient.
(Mücke at al., 2016)[15]	253	70	Germany	History of periodontal therapy, extraction, endodontics	28.76 months	Maxilla and mandible.	All patients received 4 mg of zoledronate intravenously (IV) every 4 weeks	72	90% of patients died.