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An Approach for the Prevention, Diagnosis, and Treatment of Jaw Osteonecrosis: Report of a Case Associated with Zoledronic Acid

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Manuscript Preparation E
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Patient: Female, 52-year-old
Final Diagnosis: Osteonecrosis of the jaw
Symptoms: Necrotic bone • pain
Medication: —
Clinical Procedure: Lesion removal
Specialty: Dentistry • Pathology • Rheumatology

Objective: Unknown etiology

Background: Osteonecrosis of the jaw is a condition manifesting as necrotic bone for 8 weeks or more, with no history of radiotherapy. It is linked to the use of antiresorptive drugs, such as bisphosphonates and denosumab. We discuss in this case report the importance of infection control during clinical procedures in patients taking antiresorptives.

Case Report: Our case report describes a 52-year-old woman who had received zoledronic acid injections for 7 years, who presented with osteonecrosis of the jaw in the region of teeth 24, 25, and 26, with no local trauma. The report proceeds to describe the extraction of these teeth. After the dental extractions, she did not have any recurrence of the lesion, and she is currently in follow-up care.

Conclusions: Osteonecrosis of the jaw can be prevented through infection control and local trauma prevention. Patients who are taking antiresorptive drugs must receive special care from dental surgeons and doctors, and receive the necessary oral treatments before starting drug therapy.

MeSH Keywords: Bisphosphonate-Associated Osteonecrosis of the Jaw • Bone Density Conservation Agents • Osteoporosis

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Background

Bisphosphonates are synthetic analogs of endogenous pyrophosphate. They are part of a group of antiresorptive drugs widely used for treating bone diseases and injuries, including multiple myeloma, Paget's disease, osteoporosis, fibrous dysplasia, malignant hypercalcemia, bone metastasis from breast cancer, and other diseases related to bone resorption [1]. In spite of the benefits of bisphosphonates, there are adverse effects, one of which is bisphosphonates-related osteonecrosis of the jaw (BRONJ) [2]. It is important to point that BRONJ is now considered a subclassification of medication-related osteonecrosis of the jaw (MRONJ).

The exact mechanism underlying osteonecrosis of the jaw (ONJ) is still uncertain. However, the association between the bisphosphonates and this injury is thought to be due to a reduction in bone turnover in response to inflammatory and infectious conditions, since the pharmacodynamics of bisphosphonates act on bone cells, including immune cells such as macrophages, affecting the functions of these cells as well as bone recovery [3,4]. Due to its physiological and anatomical characteristics, the maxilla bone is more prone to infection than other bones of the body [2].

Local traumas caused by malocclusion, iatrogenic problems, poorly adapted prosthesis, dental infections, and surgical procedures such as tooth extractions are risk factors that further the development of ONJ in patients taking antiresorptive drugs [2].

Among the iatrogenic problems, osteoporosis induced by corticoids is the most common. It is related to secondary osteoporosis after menopause, and around 40% of patients receiving corticoids will be affected by generalized osteoporosis after the menopause period. If corticoids are taken simultaneously with antiresorptives, the risk of developing ONJ is greatly increased [5]. It is worth pointing out that the use of drugs for the treatment of systemic, chronic, inflammatory, and autoimmune diseases is increasing along with the expansion of the older population. It is expected that the population of elders over 60 years of age will increase by 11% to 22% by the year 2050 [6], and the use of antiresorptives is expected to increase along with this expansion, leading to a substantial rise in ONJ [5].

The present work reports a case of ONJ associated with zoledronic acid. We performed a series of exodontia in the patient, who had been taking intravenous bisphosphonates for 7 years. We aim to enforce the importance of dental follow-up for patients who use antiresorptive drugs, and to describe how to prevent and diagnose necrotic bone lesions in the early stages.

Case Report

A 52-year-old woman came to the dentist for extraction of teeth 24, 25, and 26. She was taking the antiresorptive zoledronic acid (Zometa®). The zoledronic acid (Zometa 4 mg) was administered by intravenous infusion, with injections of 4 mg every 6 months for 7 years. She had been receiving the zoledronic acid for the prevention of osteoporosis resulting from estrogen deficiency related to breast cancer, from which she had recovered in 2012. The patient had undergone mastectomy on the left breast, and left axillary emptying as well. She had been a smoker for more than 30 years (5 cigarettes per day). The clinical examination revealed chronic inflammatory periodontal disease and the presence of necrotic bone between tooth 25 and tooth 26, with no symptoms of pain, and she related no history of exposure to radiation. The panoramic radiograph showed a small radiolucent nondelimited area, and the extraction of teeth 24, 25, and 26 was advocated, along with removal of the necrotic area (Figure 1). The blood laboratory test results (blood counts, coagulogram, and blood glucose levels) were normal and the CTX (C-Terminal Telopeptides Type I Collagen) was 210 ng/mL. After the extraction of the teeth, the lesion, which had a diameter of 1.5 cm, was removed (Figure 2). The drug therapy used was: 500 mg amoxicillin for 7 days (antibiotic), 100 mg nimesulide for 5 days (anti-inflammatory), 500 mg metamizole for 3 days (analgesic), and topical application of chlorhexidine 0.12%. After the extraction, 300 mg clindamycin was prescribed for 10 days. The patient has stopped taking zoledronic acid and is stable. She has been followed for 6 months without any recurrence of the disease.

Discussion

MRONJ is characterized by a necrotic bone area caused by poor blood supply [7], presenting for more than 8 weeks in patients who took or are still taking antiresorptive drugs and with no history of exposure to radiation on the head and neck region [8].

Bisphosphonates are widely used for the treatment of bone lesions, mostly by postmenopausal women [9]. Antiresorptive use has increased in recent years due to new molecular targets and immunological drugs used for oncologic treatment. There has been a corresponding significant increase in MRONJ [10], which decreases the quality of life in these patients [8]. The antiresorptive drugs are classified into 5 classes, according to the principal agent: bisphosphonates, estrogen, selective estrogen receptor modulators, calcitonin, and denosumab. The bisphosphonates are among the most frequently used first-line antiresorptives and are recommended for patients with osteoporosis and people at high risk of fracture [11]. However, the decrease in bone turnover makes the recovery of bone from injuries difficult. The third-generation bisphosphonates (nitrogenous

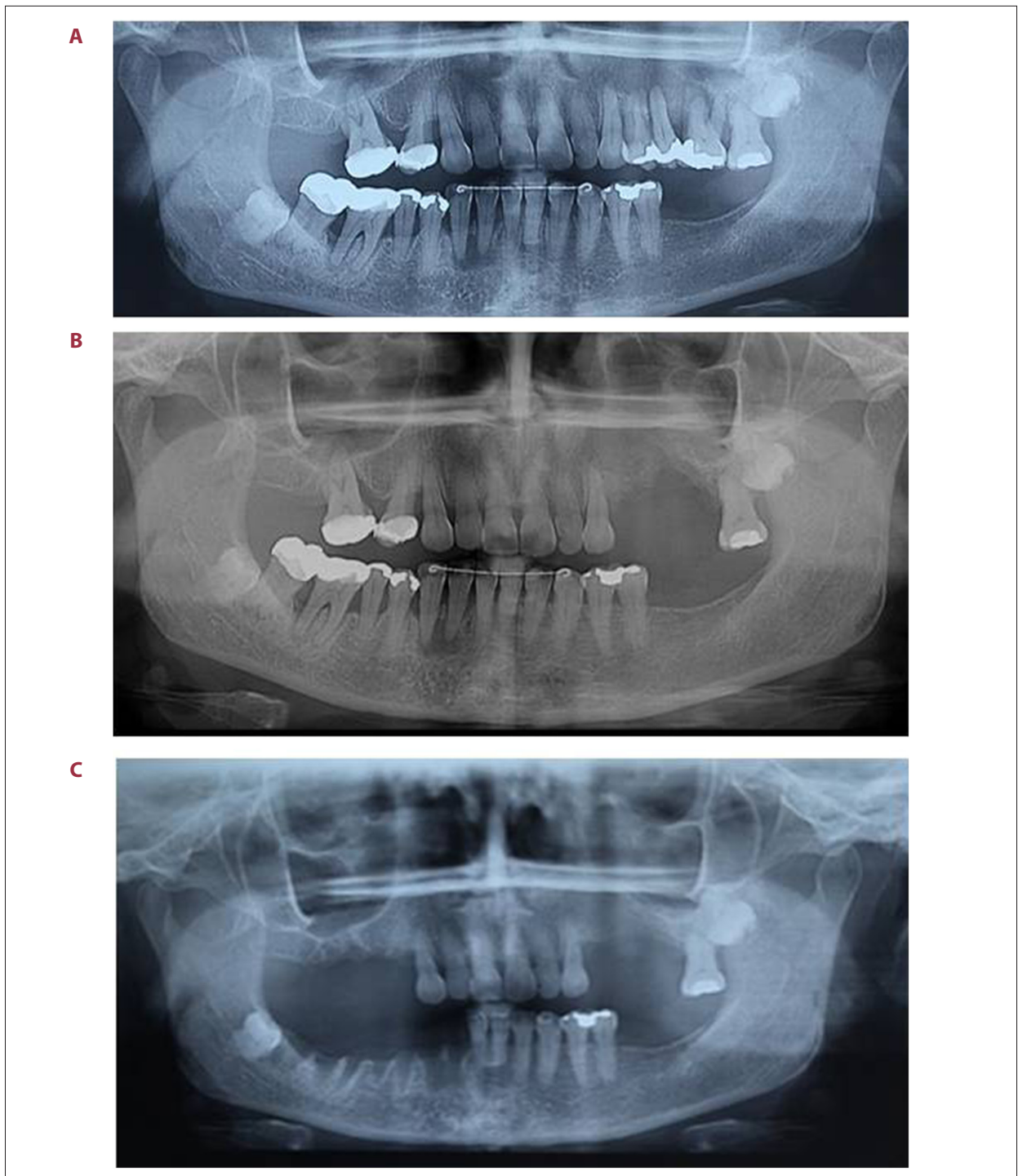


Figure 1. (A) Initial panoramic radiography, showing a radiolucent nondelimited area in the region of the 24, 25, and 26 teeth. (B) Panoramic radiography after the extraction of the teeth. The radiolucent area was recovered. (C) Control panoramic radiography; the lesion did not recur.

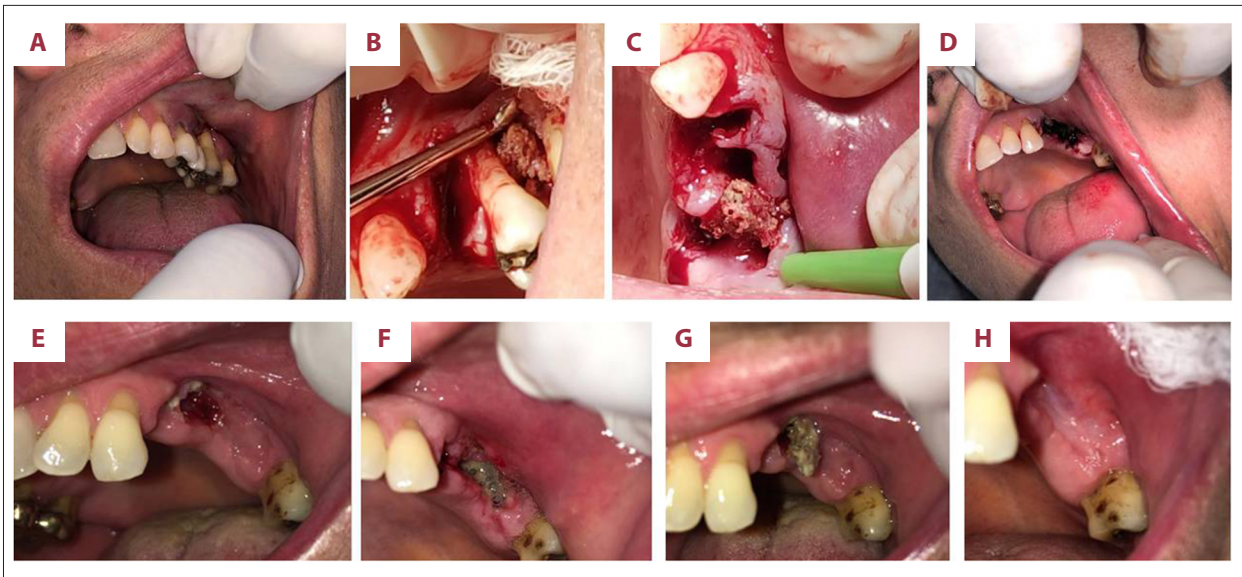


Figure 2. (A) ONJ lesion before the dental extractions. (B) Extraction of the 24, 25, and 26 teeth and necrotic bone curettage. (C) Photograph of the bone sequestration. Note the elastic aspect of the gum. (D) Sutured gum. (E) Presence of necrotic bone after the surgery. (F) Appearance of the area 15 days after the surgery procedure. (G) Appearance of the area 1 month after the surgery procedure, showing bone sequestration. (H) Appearance of the area 6 months after the surgery procedure, showing healing of the total mucosa.

bisphosphonates) are more powerful and have a longer half-life, increasing the risk of BRONJ. Despite a half-life in blood circulation of between 30 and 120 minutes [12], when embedded in the bone, the bisphosphonates remain for up to 10 years [13].

Nifosi et al. reported an increase in ONJ following oncologic treatment. Further, bone diseases such as osteoporosis are more common in postmenopausal women, due to hormonal alterations [10]. Zoledronic acid is a member of the third generation of bisphosphonates. It has a cyclic motif containing 2 nitrogens, one of which is bound to the R2 group; it is this motif that determines the power of the drug [14]. Among all the factors cited previously, Fliefel et al. state that, currently, bacterial infection in the maxillofacial region is a key factor for the development of pathogenesis and progression of ONJ. An infected tooth can develop ONJ on its own, even if it has suffered no local trauma [15]. In our case, we preferred to perform extraction of the teeth despite the risk of developing ONJ. The infection itself was causing the ONJ, and the surgery was the best option in this case, removing the focus of infection.

The risk factors for ONJ include local traumas (tooth extraction, dental implants, and surgical procedures), oral diseases (periodontal diseases, dental cavities, and abscesses), and systemic factors (advanced age, diabetes, tobacco, and corticoid use) [5–16]. In our case, the laboratory test results did not show any abnormality. In the anamnesis, the patient denied the use of corticosteroids, but her tobacco use may have contributed to the development of the disease.

Similar to our case, Graziani et al. showed that there is a direct correlation between ONJ and zoledronic acid. In their study, a group of 14 patients (13 women and 1 man) diagnosed with ONJ had all used zoledronic acid. None of the patients had undergone radiotherapy in the head and neck region and all of them had already been diagnosed with and treated for malignant neoplasm (11 breast cancer, 2 leukemia, and 1 prostate cancer) [17]. Their study reinforces the necessity for dentists and doctors to be aware of the possible adverse effects of anti-resorptive drugs, and to inform the patients about these risks.

We show in our case report that CTX levels cannot be considered a predictive factor for ONJ, since our patient's CTX was 210 ng/mL, which is considered acceptable for surgical procedures. Nevertheless, she presented with ONJ. Salgueiro et al. also concluded that serum CTX levels alone are unreliable as a predictive or preventive measure [18].

ONJ treatment must be performed rapidly, as the ONJ can severely evolve and affect the patient's quality of life. Murilo et al. presented a case of a 52-year-old female patient who complained of recurrent infection and maxilla bone exposure. Similar to our case, she used the drug zoledronic acid for treating osteoporosis for 5 years. Due to late treatment of the lesion, she developed an oro-antral communication with extension of the lesion to the cranial base, as observed on computerized tomography [19].

During the initial clinical evaluation, the need for periodontal scraper treatment, radicular straightening, and exodontics was determined, with a view to restoring the patient's health. These procedures must be carried out as a necessary preventive measure against induction of osteonecrosis associated with the use of zoledronic acid. The literature shows that the control of the infection is of fundamental importance to protect against the process of osteonecrosis. In addition, the presence of infectious processes in the oral cavity promotes the release of inflammatory mediators. Finally, the presence of microorganisms (bacteria) in the oral cavity increases the risk of bacteremia in the patient, in view of the fact that these bacteria can access the bloodstream through the connective tissue exposed in the periodontal pocket. The work protocol adopted by our group considered the request for panoramic radiography after the initial clinical evaluation. We understand that panoramic radiography is an important complementary examination which is helpful in decision making regarding diagnosis, prognosis, and treatment plan. Corroborating these initial clinical findings, in the present clinical case report, all the clinical dental procedures done routinely by professionals in our group indicated that the patient expressed low complexity. Therefore, an image examination with greater wealth of details, like computerized tomography, was not requested. Socioeconomic aspects were also crucial for this decision, in view of the financial condition of the patient. Patient treatment was started without any suspicion of the presence of osteonecrosis in the jaw; the injury was only observed at the time of performing the tooth exodontics for numbers 24, 25, and 26. After the performance of these exodontics and during the patient's follow-up phase, we requested new radiography to follow the healing process.

In our case, the patient developed the ONJ after the extraction of the teeth, precipitated by the invasive procedure, which was necessary for the treatment. The lesion did not have serious complications, due to the fact that we were aware of the risks of ONJ; we treated the lesion at the early stage with a small bone sequestration, and the patient did not have residual. She is stable after 1 year.

Patients who are taking antiresorptive drugs are not indicated for osseointegrated implants because of the high risk for developing ONJ. However, surgical removal of implants is possible: a study including 15 patients with peri-implant MRONJ describes the surgical treatment and removal of the implants. They concluded that surgical treatment for peri-implant MRONJ has great results, with complete healing in 86.7% of the cases, and 100% success for maxillary MRONJ [20]. Removable prosthodontics is the best option for dental replacement in these patients. It is important to make sure that the removable prosthodontics do not cause lesions in the soft tissue, however. ONJ is a condition that needs to be under control,

and patients need to be aware of the risks, maintaining good dental hygiene and staying on top of dental follow-up.

We, as doctors, must advocate multidisciplinary treatment. The correct approach would be an assessment of the oral environment prior to treatment with antiresorptive medication, as well as follow-up visits with the dental surgeon throughout the drug therapy and after its suspension. When established, the diagnosis of MRONJ faces many difficulties; for example, the CTX, which is a serum marker of bone resorption, can be altered by several factors. Therefore, it serves only as an aid in preparing the diagnosis and not as a conclusive examination. As to medication, there is no need to suspend medication and there would be no guarantee of prevention of MRONJ, since its effects continue for a long period in the body. Furthermore, antiresorptive medication is effective and important in the treatment of comorbidities.

After the literature review and the clinical analysis, we adopted the following protocol for infection control: antibiotic prophylaxis at pre-, trans- and post-operative timepoints. At the preoperative timepoint, we gave systemic antibiotics 60 minutes before the procedure began. At the trans-operative timepoint, infection was controlled with antiseptic mouth rinse. At the post-operative timepoint, we employed topical application of 0.12% chlorhexidine soaked in gauze twice per day, as well as antibiotic therapy for 7 days after the procedure. By lowering the risk of infection, the possibility of developing ONJ decreases considerably. The patients should be followed up, as the ONJ can occur even years after the surgery.

Conclusions

Antiresorptive drugs can lead to osteonecrosis of the jaw (ONJ) as a serious adverse effect. The development of ONJ depends on a number of factors, such as infection and local trauma, necessitating awareness of preventive procedures. For the clinician, special attention to the medical history and infection control are warranted. It is important for patients taking or planning to take bisphosphonates to receive regular oral health checkups, and to receive any necessary treatment prior to the use of the drug. It is important to understand that we can prevent cases of ONJ; this is the aim of the present study, to show clinicians how we were able to prevent or decrease the risk of the disease.

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