

A Case Report of Ibandronic Acid Induced Non-Exposed BRONJ Involving the Maxillary Sinus

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ABSTRACT

Background: The aim of this case report is to present an interesting case of bisphosphonate-related osteonecrosis of the jaw, involving the maxilla and the maxillary sinus, as a result of per os administration of ibandronic acid.

Methods: A female patient, 62 years old, was referred to the Department of Dentoalveolar Surgery, Surgical Implantology and Radiology, School of Dentistry, Aristotle University of Thessaloniki, Greece, complaining about pain in the first quadrant. Her medical history revealed per os bisphosphonate administration for the past four years. Subsequently, the cone-beam computed tomography examination revealed a small sequestrum of bone, surrounded by radiolucency, in proximity with the sinus floor. The clinical examination didn't reveal any pathological clinical signs.

Results: Based on the radiological examination, a surgical approach was implemented to remove the necrotic bone, irrigate the alveolar process and the sinus with saline, and finally achieve primary closure, after which, the patient healed uneventfully. The osteonecrosis was attributed to the bisphosphonate administration.

Conclusions: Bisphosphonate-related osteonecrosis of the jaw without obvious or with minor implication of gingival tissues is a diagnostic challenge indicating an early stage of this adverse reaction. Imaging is critical for the early detection of those cases. After careful choice of the case the proper surgical intervention could be effective to eliminate a future advancement of bone destruction. The prevention of osteonecrosis of the jaw can be achieved through the provision of adequate education to dental medicine practitioners, medical doctors, and patients.

Keywords: bisphosphonate-associated osteonecrosis of the jaw; ibandronic acid; jaw; maxilla; maxillary sinus.

Accepted for publication: 22 December 2023

To cite this article:

Fotopoulos I, Zisis V, Lillis T, Mourouzis P, Andreadis D, Pouloupoulos A, Dabarakis N.

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J Oral Maxillofac Res 2023;14(4):e5

URL: <http://www.ejomr.org/JOMR/archives/2023/4/e5/v14n4e5.pdf>

doi: [10.5037/jomr.2023.14405](https://doi.org/10.5037/jomr.2023.14405)

INTRODUCTION

Osteoporosis is a chronic condition, characterized by a reduction of the bone density [1]. Bisphosphonates (BPs) are prescribed to prevent this process and the occurrence of fractures [2]. BPs exhibits an affinity for hydroxyapatite crystals, enabling their incorporation into the bone matrix [2]. Osteoclasts may absorb BPs and undergo apoptosis, as a result. The subsequent interruption of the bone remodeling ranges from 1 to 10 years [3]. BPs can be categorized based on their action pattern, specifically as either nitrogenated or non-nitrogenated. Nitrogen-containing BPs, such as pamidronate, alendronate, risedronate, ibandronate, and zoledronate, are predominantly utilized due to their higher potency [1]. The absorption of BPs is influenced by various factors, including the patient's gender, age, and bone resorption rate. Additionally, the route of administration plays a significant role, as the oral absorption of BPs is less than 1% compared to the endogenous route, which can achieve a 50% absorption rate [3-4]. The suppression of osteoclastic activity, combined with its anti-angiogenic effects, contributes to the development of hypovascularization [3-4]. Along with the impairment of T cell activity, bisphosphonate-related osteonecrosis of the jaw (BRONJ) arises. The development of BRONJ is linked to invasive dental procedures like tooth extraction, inflammatory and/or infectious conditions, advanced age, and the dosage and duration of treatment with BPs [2]. The administration method is significantly associated with the occurrence of BRONJ, with a higher frequency observed when drugs are administered intravenously (ranging from 1.6 to 14.8%) compared to oral administration (ranging from 0.001 to 0.01%) [5-8]. Therefore, the incidence of BRONJ due to per os administration is relatively low, however, due to the large number of patients receiving such medication, BRONJ may always be taken into consideration in the differential diagnosis, since many patients are expected to manifest such a complication especially after approximately 3 years of administration [9-10]. The quality of life of the patient may be severely affected, especially in cases of extended necrosis and/or pathological fracture of the jaw [11]. One characteristic that distinguishes BRONJ is the existence of exposed necrotic bone. A number of studies have documented instances of BRONJ occurring in patients who have not been directly exposed to bisphosphonates [12]. However, typical clinical manifestations such as deep periodontal pockets,

purulent drainage with or without sinus tracts, advanced bone loss around affected teeth, as well as swelling and pain, were frequently encountered.

The aim of this study is to present a case of non-exposed, stage 0, bisphosphonate-related osteonecrosis of the jaw, involving the maxilla and the maxillary sinus, as a result of per os administration of ibandronate.

CASE DESCRIPTION AND RESULTS

A female patient, 62 years old, was referred, on July 9th, 2022, to the Department of Dentoalveolar Surgery, Surgical Implantology and Radiology, School of Dentistry, Aristotle University of Thessaloniki, Greece. The referred patient's chief complaint was nonspecific pain and discomfort at the first quadrant. Before the examination, the patient provided written informed consent. This form was approved by the School of Dentistry, Aristotle University of Thessaloniki and was in accordance with the Helsinki Declaration for research and patient's ethics. Subsequently, the patient was examined thoroughly. Her medical history revealed osteoporosis and BP administration for the past four years, ibandronate 150 mg (Bonviva® - Roche Registration Ltd.; Welwyn Garden City, Hertfordshire, UK), once per month, in particular. The clinical examination demonstrated an oral fistula with exudate upon pressure, at the area of the first upper molar which could not be explained by an odontogenic cause. The dental history revealed that the patient had an extraction of the specific tooth four months ago. The initial clinical condition is displayed in Figure 1. A periapical radiograph was performed showing non healed alveolar bone, and radiolucent process extending to the floor of right sinus. After excluding dental infection, cone beam computed tomography (CBCT) was ordered for further investigation of the case.



Figure 1. Initial condition of the area under investigation.

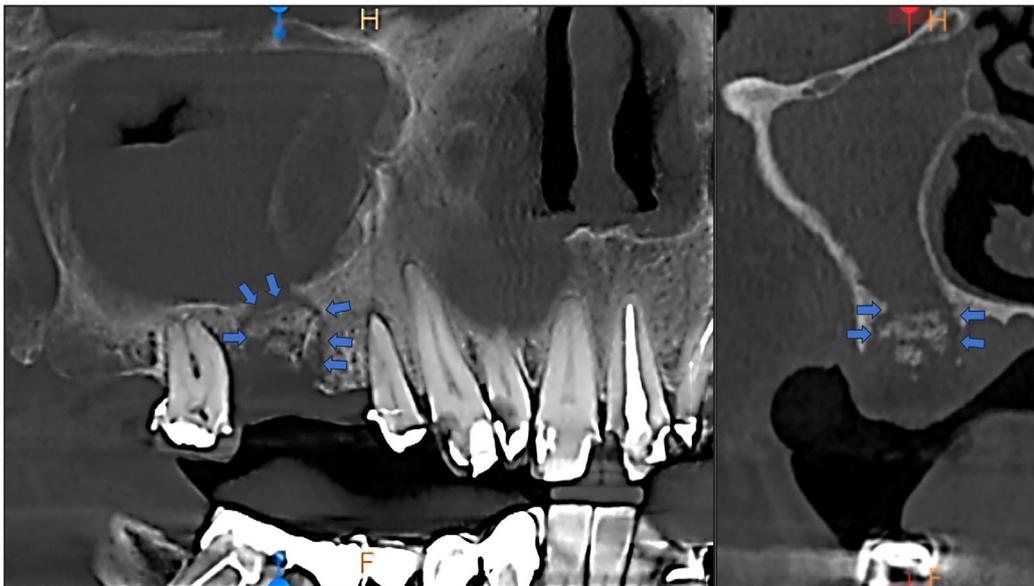


Figure 2. Initial cone-beam computed tomography examination. Blue arrows indicate the bone lesion. Almost complete opacification of the sinus is visible.

The CBCT revealed a round bony sequestrum at the area of the right upper first molar and almost complete radiopacification of the maxillary sinus (panoramic image of CBCT). The portrayed borders of the sinus floor were discontinuous, revealing a communication between the necrotic bone and the sinus cavity (cross-sectional image of CBCT) (Figure 2). The osteolysis extending beyond the alveolar crest of the maxilla was considered to be associated with the observed chronic sinusitis (almost complete opacification of sinus). The clinical and radiological examination combined with patient's medical history of oral bisphosphonate administration for the past 4 years (Bonviva® ibandronate 150 mg, once per month) led to stage 0 medication related osteonecrosis of jaw diagnosis affecting the sinus (classification by American Association of Oral and Maxillofacial Surgeons [AAOMS]) [13].

A surgical approach was implemented to remove the bony sequestrum. After raising a full-thickness mucoperiosteal flap a piece of devitalized bone, well-separated from the surrounding vital bone, was revealed. Following diligent curettage of the lesion, the bony defect and the sinus was irrigated with saline, and finally primary closure was achieved. The stepwise surgical intervention is depicted in Figure 3. Postoperatively, the patient received amoxicillin/clavulanic acid (500/125 mg - Augmentin® GlaxoSmithKline; London, UK) for 7 days.

After 5 months, the patients remained free of symptoms and a second CBCT was carried through to examine the bone healing and the closure of the sinus. The CBCT showed regeneration of new bone at the site of the defect, restoration of the sinus floor and the remission of mucosal inflammation (Figure 4).

DISCUSSION

Oral BPs has traditionally been employed in the management of osteoporosis. Individuals who develop osteoporosis are typically found within an age group that also exhibits other systemic chronic diseases, which serve as additional risk factors for BRONJ [2,14-15]. Conditions such as diabetes, hypertension, dyslipidemia, and rheumatoid arthritis have the potential to impact microvascularization, thereby increasing the susceptibility to the development of BRONJ [14-15]. However, this necrosis may be observed even in cases without any medical history like in our case. The posterior area of the maxilla was involved although the mandible is much more frequently affected, at a ratio 2 : 1 compared to the maxilla (most probably to the inherent better vascularization of the maxilla) [16]. The lack of discernible clinical manifestations of BRONJ, particularly the presence of exposed necrotic bone, may result in delayed diagnosis, an extended progression of the disease, and difficulty in achieving successful treatment outcomes [12]. According to estimates, approximately 30% of cases of BRONJ may initially manifest without any observable clinical signs of necrotic bone exposure [12]. According to the prevailing diagnostic criteria established by AAOMS [13], such cases are typically categorized as stage 0 [17]. It is worth noting that they frequently go unnoticed and consequently receive insufficient treatment. Hence, the accurate diagnosis and appropriate treatment protocol for non-exposed BRONJ variants present a significant challenge.

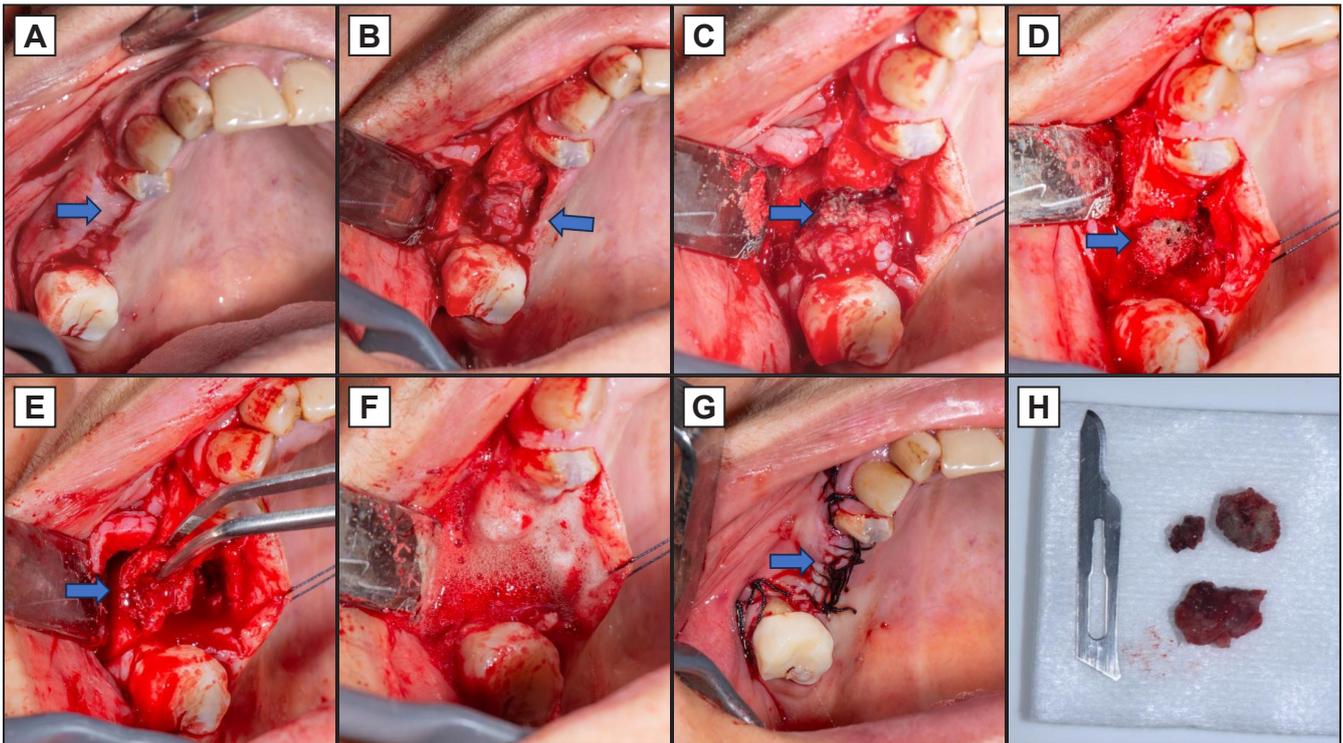


Figure 3. Surgical removal of the bone sequestrum. A = initial incision with scalpel (blue arrow). B = flap elevation (blue arrow). C-D = localization of the necrotic bone (blue arrow). E = removal of the necrotic bone (blue arrow). F = display of the bone deficit. G = sutures placed and primary wound closure (blue arrow). H = display of the bone removed, compared in size to the scalpel that was used in the surgery (blue arrow).



Figure 4. Postoperative cone-beam computed tomography examination. Successful healing and closure of the sinus (blue arrows).

Clinicians frequently fail to detect these necrotic lesions, which lack evident mucosal breakdown, during routine oral examinations, thereby impeding accurate diagnosis [12]. Typically, the pharmacological agents most frequently employed for the management of osteoporosis include alendronate, risedronate, and ibandronate. Risedronate is the most potent, followed by ibandronate, and then

alendronate. Based on their bone-binding affinity, alendronate having the highest affinity, followed by ibandronate, and then risedronate [15]. The existing literature indicates that there is a potential correlation between the duration of oral BP use and the development of BRONJ, specifically in the case of alendronate usage exceeding three years [18-20]. Ibandronate exhibits the lowest frequency of BRONJ,

following a continuous administration period of two years [9-10,21-22]. In the case presented, the patient had received ibandronate for 4 years before BRONJ appeared. The typical surgical intervention has been characterized as highly cautious, involving the use of antibiotics and a preference for refraining from invasive interventions in cases of extensive lesions [14]. However, the disease may advance if left untreated or managed in a conservative manner. Therefore, the preferred approach for treating any stage of BRONJ is the early intervention through surgical resection, as it has been shown to yield improved outcomes and reduced morbidity [23]. In our case, both the relatively early intervention and the successful removal of the necrotic bone were the key for the uneventful healing of the surgical site and primary closure of the sinus. It must always be taken into account, that any surgical intervention may lead to further necrosis, no matter how successful it appears to be in the first postoperative months, thus necessitating the regular clinical and radiological examination. Regarding the discontinuation or not of the drug, the literature doesn't provide a specific golden standard. According to the position paper of the AAOMS [13], it is recommended, based on empirical evidence, to cease the use of oral bisphosphonates for a period of three months prior to and three months following surgery. Nevertheless, multicentric prospective studies have demonstrated that the aforementioned recommendation does not yield any advantages in terms of preventing BRONJ, regardless of whether the bisphosphonates are administered orally or intravenously [7,24]. Furthermore, the BP drug holiday may potentially elevate the likelihood of experiencing a fracture [25]. The low occurrence rate of BRONJ, along with the high probability of successful healing in comparison with the complications of a possible fracture, supports the argument against BP drug holiday [2]. The most significant prognostic factors are the clear medical history and in case of compromised patients, the regular checkups by a physician as well as the application of proper oral hygiene. The elevated level of oral hygiene and the regular checkups by a dentist may prevent any chronic oral infection which may lead to delayed epithelial closure, wound healing and bone necrosis [26]. Furthermore, osteonecrosis

affects exclusively the jaws due to the comparatively elevated rate of bone remodeling in this particular bone, rendering it more susceptible to the impact of bisphosphonates [26].

Recent studies have indicated the utilization of innovative therapeutic approaches, including platelet-rich plasma, hyperbaric oxygen therapy, laser therapy, and parathyroid hormone administration [27]. Nevertheless, the effectiveness of these treatment modalities has not been definitively established [28].

CONCLUSIONS

Bisphosphonate-related osteonecrosis of the jaw without obvious or with minor implication of gingival tissues is a diagnostic challenge indicating an early stage of this adverse reaction. Imaging is critical for the early detection of those cases. After careful choice of the case the proper surgical intervention could be effective to eliminate a future advancement of bone destruction. The primary objective of the treatment is to alleviate pain, eradicate infection, and impede or deter any subsequent advancement. The prevention of osteonecrosis of the jaw can be achieved through the provision of adequate education to dental medicine practitioners, medical doctors, and patients. Given that oral surgery carries the highest potential for osteonecrosis, it is imperative for dental practitioners to possess knowledge regarding the protocols applicable to patients undergoing bisphosphonate treatment.

ACKNOWLEDGEMENTS AND DISCLOSURE STATEMENTS

The authors report no conflict of interest related to this study. Authors declared taking informed written consent for the publication of clinical photographs, from the patient with an understanding that every effort will be made to conceal the identity of the patient. Authors declared to fulfil authorship criteria as devised by International Committee of Medical Journal Editors (ICMJE) and approved the final version.

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To cite this article:

Fotopoulos I, Zisis V, Lillis T, Mourouzis P, Andreadis D, Pouloupoulos A, Dabarakis N.
A Case Report of Ibandronic Acid Induced Non-Exposed BRONJ Involving the Maxillary Sinus
J Oral Maxillofac Res 2023;14(4):e5
URL: <http://www.ejomr.org/JOMR/archives/2023/4/e5/v14n4e5.pdf>
doi: [10.5037/jomr.2023.14405](#)

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