



## Bisphosphonate-Induced Osteonecrosis of the Maxilla Resembling a Persistent Endodontic Lesion

Hossein Mosaferi<sup>a</sup>, Mahta Fazlyab<sup>b,c</sup>, Sanaz Sharifi<sup>d</sup>, Sepideh Rahimian<sup>a\*</sup>

<sup>a</sup> Oral and Maxillofacial Radiology Department, Shahid Beheshti University of Medical Sciences, Dental School, International Branch, Tehran, Iran; <sup>b</sup> Department of Endodontics, Dental Branch, Islamic Azad University of Medical Sciences, Tehran, Iran; <sup>c</sup> Iranian Center for Endodontic Research, Research Institute of Dental Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; <sup>d</sup> Oral and Maxillofacial Radiology, Dental School, Jondy Shapoor University, Ahvaz, Iran

### ARTICLE INFO

Article Type:

Case Report

Received: 14 Jul 2015

Revised: 23 Jul 2015

Accepted: 12 May 2015

Doi: 10.7508/iej.2016.01.013

\*Corresponding author: Sepideh Rahimian, Oral and Maxillofacial Radiology Department, Shahid Beheshti University of Medical Sciences, Dental School, International Branch, Tehran, Iran.

Tel: +98-21 22413897

E-mail: sepidehra@yahoo.com

### ABSTRACT

A 52-year-old Caucasian woman suffering from pain in the anterior maxillary region, presented to the clinic. Examination revealed a draining sinus tract in the buccal vestibule of the maxilla in the left anterior segment and expansion in the middle of palate. On conventional radiographic examination the lesion was initially assumed to be a periapical problem related to the incisors but subsequently it was diagnosed to be a bisphosphonate osteonecrosis. **Conclusion:** Acquiring a comprehensive medical history from the patients, conducting the clinical vitality tests and most importantly being familiar with the non-odontogenic lesions that can be side effects of specific medications are important requirements for reaching a correct diagnosis.

**Keywords:** Bisphosphonate; Breast Cancer; Osteonecrosis; Periapical Pathosis

### Introduction

Many malignancies have tendency to involve the surrounding/distant bone structures as in 75% of the patients with breast cancer, bone metastases occur [1]. The metastatic lesions are sometimes accompanied by skeletal morbidity and severe pain. Prevention of these complications subsequent to cancer diagnosis is very important [2].

Medicines from bisphosphonate group are used for treatment of metabolic bone diseases (e.g. Paget disease), osteoporosis, multiple myeloma, etc. [3, 4] and are considered as the standard modality in prevention of skeletal complications in patients with bone metastases [5]. The mechanism of action is through inhibition of osteoclastic bone resorption and prevention of tumor cells proliferation and angiogenesis [3].

Intravenous zoledronic acid (zoledronate) was the first introduced bisphosphonate for treatment of bone metastases after the breast carcinoma [2] and was approved for prevention of skeletal lesions in patients with multiple myeloma or bone metastases of any solid tumor [5, 6]. However, during the past years, bisphosphonates, especially intravenous preparations, are held responsible for osteonecrosis of the jaws (ONJ) [3]. ONJ was

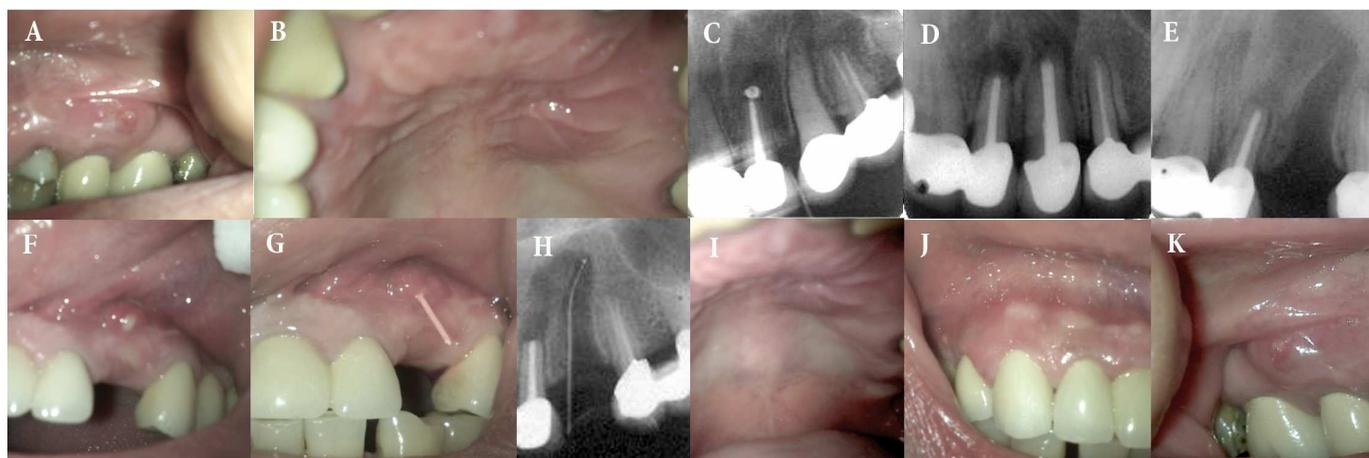
first described in 2003 [7], as the transmucosal exposure of jaw bone for at least eight weeks, in a patient with history of bisphosphonate consumption without any history of radiotherapy in the head and neck region [8]. In most of the cases bone exposure is clinically obvious [9].

Based on retrospective studies, the rate of bisphosphonate-related ONJ is up to 19% in patients with bone metastasis [9] and zoledronate is more dominantly responsible for ONJ [2]. The mandible is more commonly affected than the maxilla with a 2:1 ratio [3, 9]. The present case describes the challenges brought to the clinicians during examination and diagnosis of a bone lesion surrounding the left maxillary canine that was diagnosed as bisphosphonate-related ONJ after many sessions of orthograde and retrograde endodontic treatments.

### Case Report

A 52-year old female with her chief complaint being pain in anterior left maxillary region, was referred to a private maxillofacial imaging center, by a general practitioner.

According to the dentist, she had a history of breast cancer, mastectomy and chemotherapy. During clinical examination of



**Figure 1.** A and B) The presence of sinus tract and swelling in the left lateral incisor and canine in the buccal vestibule and palate; C) Periapical lucency surrounding the left lateral incisor and canine; D) Persistent lesions after orthograde treatment led to periapical surgery; E) Extraction of the canine; F-I) Reoccurrence of the sinus tract and palatal swelling; J and K) Appearance of similar lesions on the right maxillary side

the buccal vestibule in the left lateral and canine region, a draining sinus tract was detected. Also in the middle of palate a firm pediculate expansion was seen (Figures 1A and B). No other clinical sign was present. The canine, like other anterior teeth, was covered with full PFM restoration.

For more evaluation periapical radiography was ordered. The images revealed periapical radiolucency and widening of the periodontal ligament (PDL) surrounding the left lateral incisor and canine (Figure 1C). The teeth were not endodontically treated and considering the clinical and radiographic manifestations, two-session root canal therapy with two-week calcium hydroxide intracanal medication was performed. However, signs and symptoms did not resolve and periapical surgery was indicated (Figure 1D).

After surgery, 500 mg amoxicillin and 250 mg metronidazole was prescribed every 8 h for seven days. During the couple of weeks after surgery the patient reported no complications. However, she returned shortly after the end of antibiotic therapy, due to recurrence of pain and pus drainage. Finally the dentist decided to extract the canine (Figure 1E). Unfortunately, after one week not only the sinus tract re-occurred on the left side of maxilla (Figures 1F to I) but also similar lesions appeared on the right maxillary posterior segment (Figures 1J and K).

The dentist referred the patient to the maxillofacial radiologist for more evaluation. After more assessment of the radiographies the generalized PDL widening in anterior maxilla and sclerosis of trabecular bone was detected (Figure 2A). Also; cone-beam computed tomography (CBCT) imaging was indicated (Figure 2B) which revealed the perforation of the palatal cortex in addition to the sequester formation (Figures 2B and C). Considering the clinical and para-clinical findings and patient's medical history, she was questioned about consumption of additional non-declared medicine. She approved consumption of 4 mg/5 mL intra-venous zometa for the past four years to prevent bone metastasis.

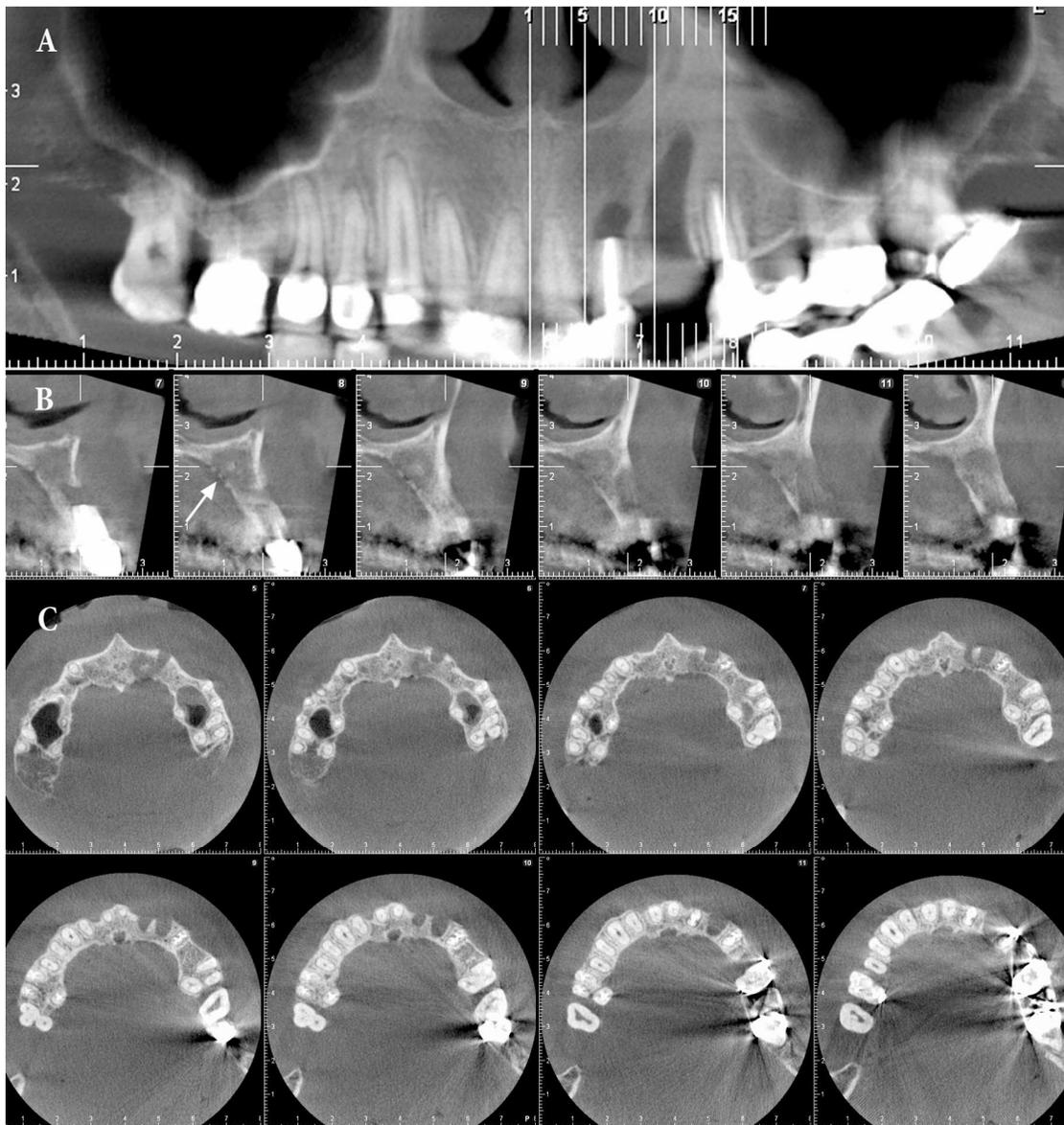
As a result the primary diagnosis was bisphosphonate-related ONJ and the patient was referred to an oral-maxillofacial surgeon in order to take a biopsy. Histological assessment showed areas of necrotic bone with signs of infection and also regions with increased bone turnover which was compatible with ONJ and confirmed the final diagnosis. The patient was referred for treatment.

## Discussion

The present report represented the challenging diagnosis of a bisphosphonate-related ONJ that had the clinical profile of a common endodontic lesion with draining sinus tract; after non-surgical and surgical endodontic intervention and persistence of the lesion the general practitioner suspected a non-odontogenic lesion. A revision through patient's medical history (breast cancer and bisphosphonate therapy for prevention of bone metastasis) confirmed the final diagnosis.

The question is if there was a space for prompt diagnosis during the first visits by the dentist. The answer may be positive. The dentist failed to elicit the list of medicines consumed by the patient considering a history of malignancy, mastectomy and chemotherapy. But if the dentist was aware of patient's injection of zometa, could he/she still consider the clinical relevance of it?

Bisphosphonates are analogous to synthetic pyrophosphate that concentrate in areas of bone and thus are powerful inhibitors of osteoclastic activity [3, 10] and have high affinity for hydroxyapatite crystals [3]. They have low intestinal absorption and are excreted through the kidneys without metabolic alteration [11]; as a result they are absorbed into the skeleton without degradation and have the incredibly long half-life of up to 12 years [3, 5]. Bisphosphonates cause resistance to osteoclastic activity [11] and are able to reduce the rate of pathological fractures, bone pain, the need for radiotherapy and surgery in patients with bone metastases [7, 9].



**Figure 2.** A) Generalized PDL widening in anterior maxilla and sclerosis of trabecular bone; B and C) Perforation of the palatal cortex in and sequester formation

As the newer member of this family, amino-bisphosphonates (alendronate, risidronate, pamidronate, zoledronic acid and ibandronate) have several anti-tumor effects, such as induction of cell apoptosis, inhibition of cell adhesion to the extracellular matrix and inhibition of tumor invasion [12, 13].

The use of bisphosphonates in patients with multiple myeloma, primary and metastatic bone malignancies (breast, prostate, lung and renal cell carcinomas) [13], has reduced the skeletal complications, such as pathologic fractures, spinal cord compression, hypercalcemia secondary to malignancies and the need for bone radiotherapy or surgery [3, 14]. Our patient had a history of breast cancer and, although late, mentioned the consumption of intra-venous zoledronic acid for the past four

years. In treatments exceeding 36 months with bisphosphonates the increasing risk of osteonecrosis increases which is more noticeable with the use of zoledronic acid and pamidronate [3].

Bisphosphonates have many oral complications: oral mucosal lesions arising from direct contact injury in cases of oral consumption [3] and induction of avascular osteonecrosis in maxilla and mandible [15]. In the present case, maxilla was involved unilaterally which became bilateral after some time. The only clinical manifestation was the presence of a sinus tract and a periradicular lucency around the crown-restored canine. ONJ has been reported as the exposure of mandibular (65%) or maxillary (26%) bone or both (9%) which is painless in one third of the cases [16] and has a tendency to occur on female patients and in

posterior mandible [3]. In 40% of the cases it occurs spontaneously [7, 15] and bilateral involvement was slightly more common in the maxilla [3]. Clinically, intraoral lesions appear as areas of exposed yellowish hard bone with smooth or ragged borders and extra/intra oral sinus tracts may be present [9]. In our patient only sinus tract was present. In radiographies widening of the periodontal ligament is obvious which can be confusing and lead to misdiagnosis of periodontal issues [16]. We shall say if the dentist had radiographically evaluated the anterior segment, he/she would have detected the generalized PDL widening in our patient. Although this could be also attributed to necrotized crowned anterior teeth. The presence of full restorations challenged conducting pulp vitality tests.

Poorly defined radiolucencies with moth-eaten borders, with or without radiopaque sequestra can be seen in advanced cases [3, 9], which was not detected in routine radiographies of the present case. Even surface colonization of the exposed bone by organisms of dental plaque such as *Actinomyces* can be detected by culturing, which is hard to distinguish from a true suppurative infection such as osteomyelitis [3]. Among the routine signs of ONJ including pain, swelling, fever, purulent secretion and oroantral sinus tracts [15], our patient presented only the last two signs.

There are many medical conditions that can alter the procedure of routine dental treatments. The fact that if the patient's problem was diagnosed earlier periapical surgery would not be chosen, emphasizes on the necessity of meticulous history taking before diagnosis and treatment.

## Conclusion

Although diagnosis of this case was particularly challenging, it was finally achieved. Taking a comprehensive history, especially from medically compromised patients and a complete list of patients' medicines in addition to pulp vitality tests can help the clinician avoid "tunnel vision" during evaluation of the patient. This will provide the keys to successful diagnosis and treatment.

## Acknowledgment

The authors wish to thank the patient for her cooperation.

Conflict of Interest: 'None declared'.

## References

1. Harvey HA, Cream L. Biology of bone metastases: causes and consequences. *Clin Breast Cancer*. 2007;7 Suppl 1:S7-S13.
2. Lacerna L, Hohneker J. Zoledronic acid for the treatment of bone metastases in patients with breast cancer and other solid tumors. *Semin Oncol*. 2003;30(5 Suppl 16):150-60.
3. Woo S-B, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Annals of internal medicine*. 2006;144(10):753-61.

4. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol*. 2005;23(32):8219-24.
5. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, Apffelstaedt J, Hussein MA, Coleman RE, Reitsma DJ, Chen BL, Seaman JJ. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer*. 2003;98(8):1735-44.
6. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, Apffelstaedt J, Hussein M, Coleman RE, Reitsma DJ, Seaman JJ, Chen BL, Ambros Y. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J*. 2001;7(5):377-87.
7. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61(9):1115-7.
8. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws AAoO, Maxillofacial S. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg*. 2007;65(3):369-76.
9. Walter C, Al-Nawas B, Grotz KA, Thomas C, Thuroff JW, Zinser V, Gamm H, Beck J, Wagner W. Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. *Eur Urol*. 2008;54(5):1066-72.
10. Russell RG, Bisaz S, Fleisch H, Currey HL, Rubinstein HM, Dietz AA, Boussina I, Micheli A, Fallet G. Inorganic pyrophosphate in plasma, urine, and synovial fluid of patients with pyrophosphate arthropathy (chondrocalcinosis or pseudogout). *Lancet*. 1970;2(7679):899-902.
11. Russell RG, Croucher PI, Rogers MJ. Bisphosphonates: pharmacology, mechanisms of action and clinical uses. *Osteoporos Int*. 1999;9 Suppl 2:S66-80.
12. Santini D, Vespasiani Gentilucci U, Vincenzi B, Picardi A, Vasaturo F, La Cesa A, Onori N, Scarpa S, Tonini G. The antineoplastic role of bisphosphonates: from basic research to clinical evidence. *Ann Oncol*. 2003;14(10):1468-76.
13. Mashiba T, Mori S, Burr DB, Komatsubara S, Cao Y, Manabe T, Norimatsu H. The effects of suppressed bone remodeling by bisphosphonates on microdamage accumulation and degree of mineralization in the cortical bone of dog rib. *J Bone Miner Metab*. 2005;23 Suppl:36-42.
14. Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clin Prostate Cancer*. 2005;4(1):31-7.
15. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med*. 2005;353(1):99-102; discussion 99-.
16. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg*. 2005;63(11):1567-75.

Please cite this paper as: Mosaferi H, Fazlyab M, Sharifi S, Rahimian S. Bisphosphonate-induced Osteonecrosis of the Maxilla Resembling an Infectious Endodontic Lesion. *Iran Endod J*. 2016;11(1):67-70. Doi: 10.7508/iej.2016.01.013