Spontaneously Developed Bisphosphonate Related Osteonecrosis of the Jaws: Three Cases

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Abstract: *Aim:* The aim of this case report is to present the clinical and radiologic diagnose of the spontaneously developed bisphosphonate-related osteonecrosis of the jaws in the edentulous patients.

Background: Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a common side effect of long term bisphosphonate therapy. It is characterized with the presence of exposed necrotic bone appearing in the jaws of patients treated bisphosphonates never irradiated in the head and neck area. BRONJ lesions may occur spontaneously or at the site of a dentoalveolar procedure. Clinically evident lesions are confirmed through radiographs showing poorly defined radiolucent- radiopaque lesions. At present, no predictable remedy is available for BRONJ.

Case Description: Three edentulous male patients were referred to our clinic for non-healing defect in the posterior region of the mandible. Medical anamnesis revealed prostate carcinoma and the use of zoledronate (Zometa). Clinical examinations showed oval shaped defect or exposed necrotic bone. Digital panoramic radiographs revealed destructive radiolucent area. Biopsy was performed for the exclusion of the metastic disease and revealed inflammation consistent with osteomyelitis. Treatment protocol included systemic antibiotic therapy and conservative surgical treatment.

Clinical Significance: BRONJ should be mentioned that presence of exposed necrotic bone or non-healing oral mucosa in patients with a history of bisphosphonate use without a history of dentoalveolar procedures.

Keywords: Bisphosphonates, Bisphosphonate-related osteonecrosis of the jaws (BRONJ), Jaw, Radiographic finding.

INTRODUCTION

Bisphosphonates (BP) are the most widely used class of antiresorptive drugs and play an important role in concomitant therapy of cancer as well as in treatment of osteoporosis [1-6]. The biological effect of BPs is based on the inhibition of bone resorption and of bone turnover in general that can be documented by suppression of specific serum bone resorption markers. BPs have a very long half-life period and hence accumulate in bone matrix. Furthermore, their degradation in the context of bone remodeling is limited because of their toxic effect on osteoclasts [3,7]. For this purpose, the most common used oral bisphosphonates are alendronate (Fosamax; Merck Co, West Point, PA), risedronate (Actonel; Procter and Gamble), etidronate (Didronel; Procter and Gamble, Cincinnati, OH) and tiludronate (Skelid; Sanofi-Synthe Lab Inc, New York, NY) [8]. More potent bisphosphonates delivered intravenously (iv) are pamidronate (Aredia; Novartis Pharmaceuticals Corporation, East Hanover, NJ) or zoledronate (Zometa; Novartis). They are indicated to stabilize metastatic cancer (primarily breast and prostate) deposits in bone, and to treat the bone resorption defects of multiple myeloma and correct severe hypercalcemia [2,8,9]. Zoledronate is suspected of having antiangiogenetic and antitumoral effects besides its specific inhibition bone turnover. The mechanism is supposed to result from the inhibition of vascular endothelial growth factor, which is involved in the spread of secondary lesions in neoplasia [3].

Despite its great benefits in cancer therapy, iv administration of BPs correlates with bisphosphonate-related osteonecrosis of the jaws (BRONJ) [3,10]. Today, the incidence of BRONJ in patients received iv BPs for the management of malignancy ranges from 0.8% to 12.0% [7,11]. Patients on oral BPs have a considerably lower risk to develop BRONJ when compared to cancer patients receiving iv BPs and ranges from 0.09/100.000 to 73.5 /100.000 patients/years in different studies [7,12,13].

BRONJ is defined as exposed necrotic bone appearing in the jaws of patients treated by systemic iv or oral BPs never irradiated in the head and neck area and that has persisted for more than 8 weeks [5,9,14-17]. The osteonecrosis can develop spontaneously, but it mostly appears after dental surgery or trauma. The disorder is usually painful, but at times the process is asymptomatic [15,17].

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BRONJ is a growing problem and, treatment option is limited and predominantly palliative [7]. Signs and symptoms that may present before the development of clinically detectable osteonecrosis include pain, mobility of teeth, mucosal swelling, erythema, and ulceration [17]. The lesions may occur spontaneously or at the site of a dentoalveolar procedure. In the early phases of BRONJ, radiographic manifestations are not detected; however, as the disease progresses, osteonecrosis of the jaw may become readily identifiable in plain radiographs. When BRONJ is established, a poorly defined osteolytic area is seen along with cortical destruction, loss of cancellous trabeculation, and a decrease in bone density [7,14].

The objective of the cases presented here was to report the clinical and radiologic diagnose and treatment protocol of the BRONJ spontaneously developed in the edentulous patients treated by systemic BP (zoledronate).

CASE DESCRIPTION

Case 1

A 83-year-old male was referred to our department for a nonhealing bone wound in the posterior region of the mandible. His past medical history included malign melanoma and prostate carcinoma and he had used pamidronate for 5 years period, but he used only zoledronate (Zometa) for one year. Intraoral examination showed exposed necrotic bone on the lingual surface of the right mandibular premolar region (Figure **1**), and then digital panoramic radiograph were taken (Veraviewpocs 2D, J Morita Corp, Kyoto, Japan). The panoramic radiograph showed destruction of the bone (Figure **2**). Biopsy was performed for the exclusion of the metastic disease and revealed inflammation consistent with osteomyelitis. Therefore BRONJ diagnosis was defined. Since discontinuation of zoledronate therapy has not recovered the osteonecrosis of the jaw, systemic antibiotic therapy and conservative surgical treatment aiming the removal of bone necrosis area was applied. Six month after follow up, clinical and panoramic radiographic examination revealed healing (Figures **3**,**4**).

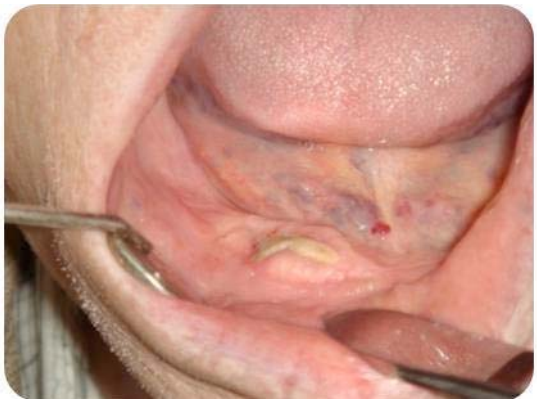


Figure 1: shows the intraoral appearance of exposed necrotic bone on the lingual surface of the right mandible.

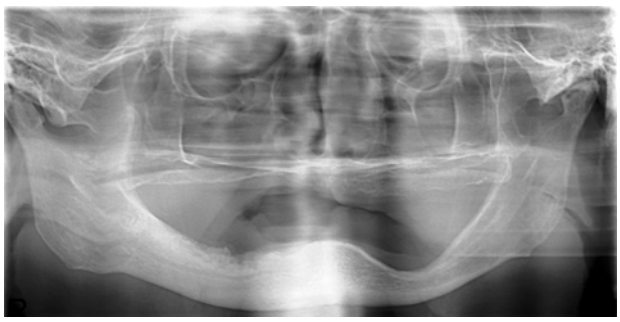


Figure 2: reveals the panoramic radiograph of the irregular radiolucent area on the right edentulous mandible.

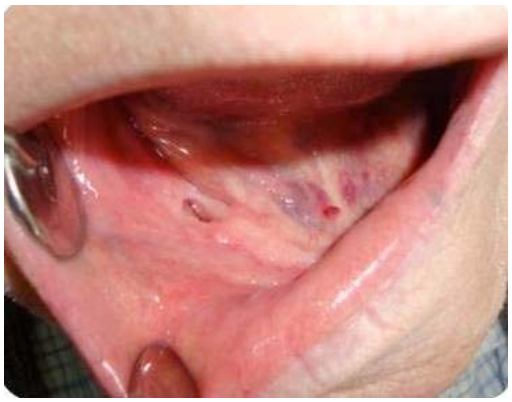


Figure 3: shows the clinical appearance of the defect six month after follow up.

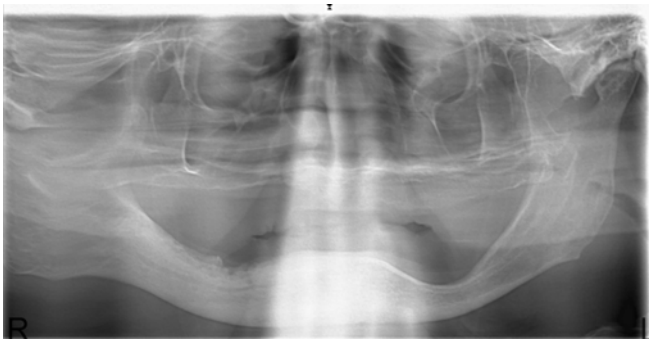


Figure 4: shows the panoramic radiograph six month after follow up.

Case 2

A 71-year-old male with a 6 year history of treatment of prostate carcinoma with zoledronate (Zometa) was referred to our department. He also had a non-healing defect of the oral mucosa in the right

mandible for 3 months. Clinical examination showed an oval shaped defect in the right premolar mandibular region of the edentulous patient (Figure **5**). Digital panoramic radiograph showed an irregular destructive radiolucent area on the right side and also impacted lower canine tooth on the left side (Figure **6**). Histopathologic examination showed necrotic bone and the presence of filamentous bacteria suggesting actinomyces. No evidence of malignancy was observed. Treatment protocol included systemic anti-biotic therapy and the removal of bone sequestrations. Postoperative follow-up consisted of 6 months and clinical and panoramic radiographic appearance showed healing at the surgical site (Figures **7**,**8**).

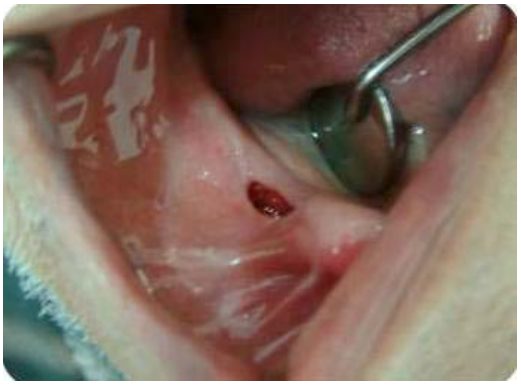


Figure 5: clinical apperance of the oval shaped defect in the edentulous mandible.

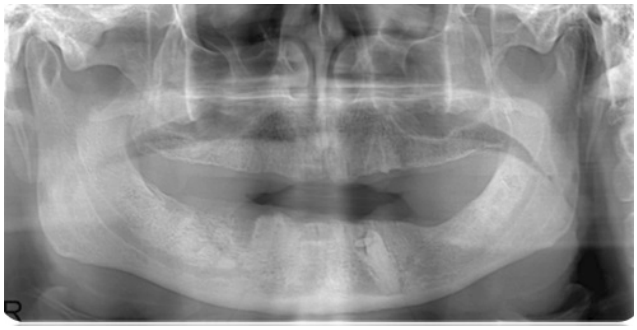
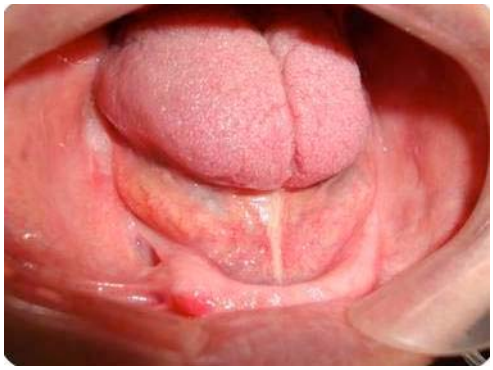


Figure 6: panoramic radiograph revealing irreguler destructive radiolucent area on the right side and also impacted lower canine tooth on the left side.

Case 3

A 58-year-old male was referred to our department for treatment of a non-healing oral mucosa and also a mild pain in the both right and left mandible. Medical anamnesis revealed prostate carcinoma and the use of zoledronate (Zometa) for 3 years. Clinical examination showed an exposed necrotic bone in the both right and left posterior mandible. Panoramic radiographic examination showed a diffuse rarefaction with irregular border on both posterior mandibular region (Figure **9**).



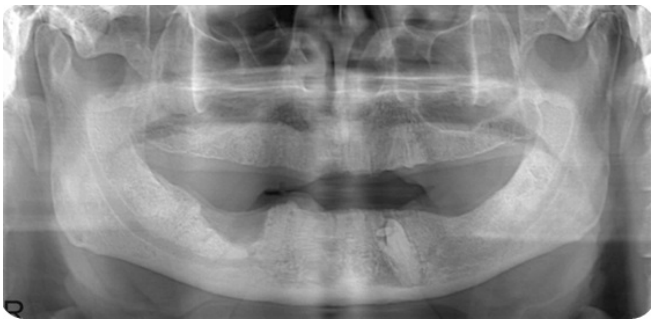


Figure 7 and 8: reveals clinical and panoramic radiographic appearance of the surgical site after 6 months follow up.

Severe ridge resorption on both sides and very close relationship with mandibular canal also noted. BRONJ diagnosis was based on the above criteria. Treatment protocol was the same with the other two patients.

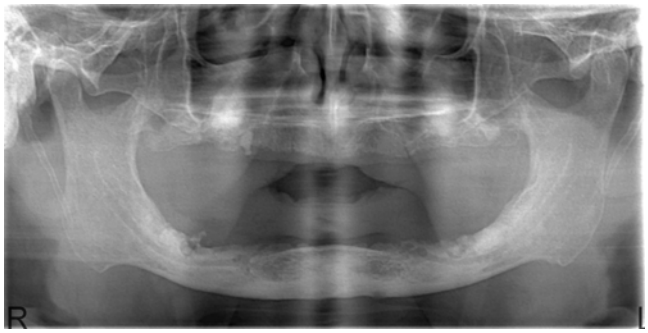


Figure 9: shows the diffuse rarefaction with irregular border on both posterior mandibular region.

DISCUSSION

BPs are known to be very potent bone resorption inhibitors. Bone necrosis is considered dose- and timedependent due to the long half-life of BPs in the bone [7]. Zoledronate (Zometa) is a nitrogen-containing BP, which accumulates in the mineralized bone matrix and remains there for a long time. This fact may affect the development of avascular bone necrosis [18-20]. In literature there is no definition of the minimum duration of the use of oral BPs for developing BRONJ. The risk for developing BRONJ increases when the duration of oral BP therapy exceeds 36 months [5,11].

BRONJ is defined as “necrotic bone exposed in maxillofacial region lasting for more than eight weeks in BPs-treated patients who have not undergone head and neck radiation therapy” [7,11,19]. These lesions can be asymptomatic or present with pain, purulent discharge, swelling, tooth mobility, and paresthesia. In this case presentation, three patients referred to the nonhealing oral ulceration or defect of posterior mandibular region. On the medical anamnesis, all three patients revealed zoledronate (Zometa) therapy for the prostate carcinoma; and interestingly, all patients were male and edentulous.

The precise mechanism of BRONJ still remains unclear [5]. Most patients report a history of previous dental extractions or other local trauma. Mucosal trauma attributable to dentures and also endodontic treatment have been discussed as further trigger factors. Wearing a denture in the initial occurrence site of BRONJ have influenced the prognosis of BRONJ, especially in patients wearing mandibular dentures. However, spontaneous occurrence has been mentioned [1,2,5,18,20]. In this report, all three patients were edentulous. Since there was no detected any trauma, BRONJ lesions could be considered spontaneously developed.

Diagnosis of BRONJ is very clear, directed by anamnesis, the history of oncologic pathology, and/or administration of BPs. Clinically evident lesions are confirmed through radiographs showing poorly defined radiolucent- radiopaque lesions [7]. Similarly, our patients revealed irregular radiolucent areas on the digital panoramic imagings. Early osteonecrosis restricted to small areas of bone exposure (<1 cm) may be undetectable in panoramic radiographs; however, signs of bone destruction arising from this process may be recognized in computed tomography [7,17,21]. In addition, magnetic resonance imaging may also provide visualization of useful features in the early stage of BRONJ [21]. Therefore, there is a need for prospective studies of patients to compare the imaging modalities of BRONJ lesions.

In the literature BRONJ is said to be resistant to therapy and may lead to serious loss of bone. At present, no predictable remedy is available for BRONJ. Treatment should eliminate and control pain, as well as preventing progression of bone exposure [7]. Recommendations range from strictly conservative management to extended surgical interventions [3,17,20]. Therefore, patients are treated palliatively with antibiotics, antimicrobial mouth rinses, debridement of necrotic bone, hyperbaric oxygen therapy and ozone therapy. Lazarovici *et al*. [20] proposed that patient management should be excluded routine diagnostic bone biopsies. If the condition progresses to a state of recurrent infections, tooth loss and jaw fracture can occur, further reducing the patient’s quality of life [17,19]. In patients who used BPs and did not experience osteonecrosis, preventive measures should be taken, since osteonecrosis may appear up to one decade after the start of bisphosphonate therapy. Patient should be advised to undergo thorough oral examination every 3 months [7].

CONCLUSION

The still-accumulating evidence suggests that all types of BP increase the risk of BRONJ incidence. Although extensive bony involvement can appear as poorly defined radiolucent- radiopaque lesions on panoramic radiographs, it could be usually inconclusive in the early stages of BRONJ. Most patients report a history of previous dental extractions or other local trauma; but spontaneous occurrence should be mentioned. Prevention of BRONJ might be aided by oral care before and after BP administration.

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