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Case Report

Tooth Extractions and Removable Denture as Triggering Factors for the Development of Bisphosphonate Induced Jaw Osteonecrosis - Case Report and Literature Review

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Abstract

Bisphosphonate - Related Osteonecrosis of the Jaw - BRONJ is a severe complication in the treatment with bisphosphonate among patients with removable dentures. Bisphosphonates are pharmaceutics that are more and more frequently implemented in the treatment of various diseases. One of the severe aggravations with this therapy is mandibular and/or maxillary necrosis. Factors triggering its development could be uncomplicated tooth extraction and/or poorly adjusted removable dentures. This paper presents a case of bisphosphonate-related mandibular osteonecrosis in a 71-year old patient with cancer after intravenous (IV) administration of zoledronic acid and tooth extractions. The authors present their treatment plan with the schedule of following postoperative controls for this particular case. Based on the cited references we propose a preventive protocol primarily to be implemented in extraction cases.

Keywords: Bisphosphonate; BRONJ; Dental Prosthetic Treatment; Tooth Extraction; Total Denture

Abbreviations

BRONJ: Bisphosphonate-Related Osteonecrosis of the Jaw; BP: Bisphosphonate; AAOMS: American Association of Oral and Maxillofacial Surgeons

Introduction

Antiresorptive agents such as bisphosphonate (BP) and monoclonal antibodies are used to treat benign and malignant osseous diseases. BPs target osteoclasts, thereby inhibiting bone resorption and subsequent bone loss, currently are considered the cornerstone for the treatment and prevention of bone metastases of solid tumors and osteoporosis [1]. The use of these drugs has increased in recent years as have their complications also, especially bisphosphonate-related osteonecrosis of the jaw (BRONJ) [2,3].

BRONJ is an important condition seen most commonly in oncology patients receiving high-dose intravenous bisphosphonates [4]. It was first described in 2003 by Marx [5] and it was defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2007 [6]. Although the first publications were over a decade ago, the pathophysiology of the disease is not fully elucidated yet [7]. Factors like potency of BPs, biology of jaw bone, antiangiogenic property of BPs and soft tissue toxicity in combination with present infection, other drugs, pre-existing pathologies, compromised immune response and dentoalveolar trauma may lead to development of BRONJ [8]. The high potency BP drugs, e.g. the zoledronic acid (Zoledronat), are also linked with high rate of BRONJ [9,10].

According to Ruggiero., *et al.* (2009) [11] BRONJ symptoms are as follows when three following characteristics are present: a) the

bone has been exposed to the oral cavity, despite treatment for more than eight weeks; b) the patient is being treated or has been treated with BP; c) the patient has no history of radiation therapy to the jaws.

Due to the severity of BRONJ and the treatment consequences dentists should consider an adequate extraction technique and medication protocol including appropriate postoperative prosthetic treatment.

The great number of patients on BP therapy, the severity of the BRONJ as complication triggered by simple tooth extraction or by not properly adjusted removable prosthesis underline the importance of the disease for the general dental practitioner.

The present case of BRONJ outlines the etiological factors that lead to the development of the disease, the treatment protocol and the follow up including prosthodontic rehabilitation.

Case Presentation

A 71-year old female edentulous patient was referred due to non-healing ulcers in the mouth within region of teeth number 33 and 34 after tooth extraction. Her main complaints were pain when wearing her complete acrylic-resin dental prosthesis on lower jaw.

Anamnesis and the presented epicrisis revealed a bone-metastasizing rectosigmoid carcinoma as a concomitant disease. It was diagnosed and surgically treated in April 2012 for the first time, followed by four chemotherapeutical series with various preparations (Capecitabine, FolFO, Cetuximab, Bevacizumab). Bisphosphonate therapy was administered after the detection of bone metastases with 4 mg Zoledronate (Zometa®) IV at each fourth week from July 2016 to May 2017.

In March 2017 the last remaining two teeth on the lower jaw, numbers 33 and 34, were extracted by a general dental practitioner. In January of 2018, five months after the start of the antiresorptive therapy and ten months after the extraction, the dentist removed a small bone fragment from the same region where the previous extraction surgery had been done. The patients had not a denture rebasing consequently and she complained about a suboptimally adjusted removable prosthesis.

Clinical examination revealed intraoral mucosal lesions in the region of tooth number 33 (10 mm) and teeth number 45 - 47 (15 mm). The exposed mandibular surface was rough and necrotic.

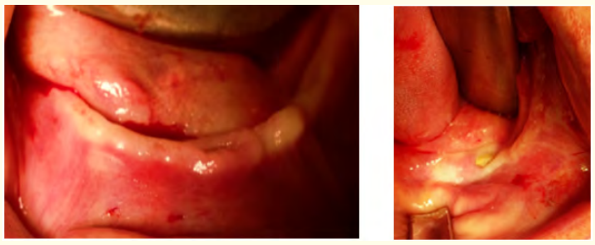

Figure 1A and 1B: *Pictures showing intraoral preoperative condition.*

3D image examination by Cone Beam Computed Tomography (CBCT) revealed disorders in the cortical lamina and spongy jaw structures corresponding to osteonecrosis. We observed diffuse destruction of the trabecular structure (osteolytic changes) of the cancellous bone and erosion of the cortical bone with surface irregularity. The reconstructed 3D image clearly pictured sharp bone edges in the related regions as well.

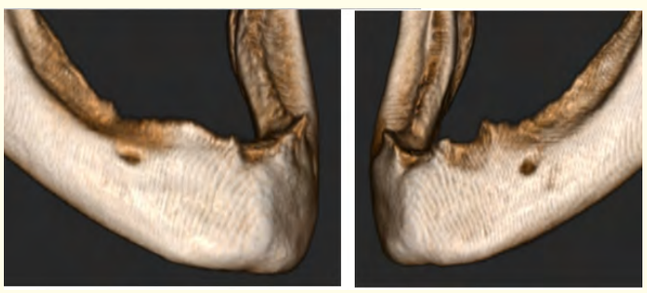

Figure 2A and 2B: *Images presenting the bone surface before the operation.*

One week after the initial examination the patient was operated under general anesthesia with nasal intubation. The inflamed modified mucosa edges were excised during the operation. An adequate muco-periosteal was mobilized in order to expose the diseased bone and two partial box-type resections were performed in the involved regions. The necrotic bone regions were removed and the remaining surface of jaw showed no visual pathological changes in color, blood supply and structure. Rotational cutting instruments under continuous saline solution irrigation as well as a Piezosurgery® (Mectron-Italy) were used for this procedure. The sharp and traumatic edges were therefore eliminated. After mobilization of the adjacent tissues the mucosal defect was closed by a multi-lay-

ered suture without any tension after preparation of a buccal mucosal transpositional flap. The respective two excised bone pieces measuring with 45 x 11 x 9 mm and 9 x 7 x 4 mm were sent for histological examination which confirmed the primary diagnosis: drug-induced bone necrosis.

The peri- and postoperative implemented drug therapy in the following five days Cefuroxime 3 x 750 mg IV, and after the patient was discharged from the hospital the antibiotic therapy was continued with Cefuroxime 3 x 500 mg, P.O., for another 10 days. The patient was instructed to use chlorhexidine (0,1%) containing mouth wash in the morning and evening as well as after every food intake for the first three weeks. After the three-week period a new non-alcoholic, non-chlorhexidine mouthrinse was recommended. The promoted good oral hygiene was optimally maintained for the whole follow-up.

Strictly fluid diet and absolute refraining from patients using the denture on the operated jaw was recommended for the first three weeks after the surgery. The postoperative healing period was uneventful and the non-absorbable sutures were removed. In the fourth postoperative week we referred the patient back to her general dentist for adjustment and soft acryl-based relining of the existing prosthesis with soft material and she was able to use it without any restriction. Since using the well-fitting denture, the mucosa was checked at every follow-up visit for an even minor trauma or denture soreness. In case of mucosa erythema the prosthesis was immediately readjusted, polished and new denture-refraining for three days was oriented.

The postoperative follow-up protocol was as follows: 1) The first six days after the operation, patient was observed every day. 2) The second and the third week, patient was seen two times a week. 3) The fourth week, patient was followed up once a week; 4) The second and the third month, patient returned once a month; and 5) After the third month, patient was seen every three month. Six months after the surgery at the last patient visit no mucosa dehiscence was observed, nor dental soreness or mucosal lesions.

Discussion

Four principal theories for BRONJ etiology are well established in the literature: 1) BPs inhibit osteoclast activity, thereby reducing the rate of bone turnover, which results in compromised bone wound healing; 2) Bone healing is compromised but the lack of primary mucosal closure over areas of exposed bone is the key factor in the development of BRONJ; 3) Bone healing is compromised but factors specific to the oral cavity such as bacterial aggression or exposure to saliva are key factors in the development of BRONJ; 4) BPs exert an antiangiogenic activity by a transient reduction of growth factors circulating levels after its infusion [12,13].

Even though the absence of consensus on the pathophysiology, a 4-stage classification system, based on clinical findings, was presented in the scientific literature.

ONJs stages/ phases	Features/Aspects
Stage 0	Absence of bone exposure
Stage 1	Osteonecrosis with bone exposure, asymptomatic and without signs of infection
Stage 2	Osteonecrosis with bone exposure and clinical signs of infection
Stage 3	Osteonecrosis with infection and presence of pathological fracture, extraoral fistulae or bone

Table 1: *Table adapted from Ruggiero., et al. (2009) by Azoubel., et al. (2017) [14].*

Since three-dimensional imaging correlates well with the actual intraoperative findings, the imaging diagnosis has a high importance for assessment of necrotic bone tissue [15]. The CBCT can illustrate bone surface in the suspect area, therefore imaging is an essential part of the clinical assessment of BRONJ patient and might be an additional tool for tracking the progression of the disease [16]. In patients with BRONJ, CT can diagnose osteolytic and osteosclerotic regions, depending on the stage of the disease. More dense bone characterizes the necrotic area and more lytic areas illustrate the infected regions with pus and soft tissue swelling [17].

The AAOMS on Medication-Related Osteonecrosis of the Jaw in 2014 [7] described the radiographic findings: a) Alveolar bone loss or resorption not attributable to chronic periodontal disease; b) Changes to trabecular pattern-dense bone and no new bone in extraction sockets; c) Regions of osteosclerosis involving the alveolar bone or surrounding basilar bone; d) Thickening or obscuring of the periodontal ligament (thickening of the lamina dura, sclerosis, and decreased periodontal ligament space).

These nonspecific findings, which characterize this unexposed variant of BRONJ, can occur in patients with a history of disease stage 1, 2, or 3 who have healed and have no clinical evidence of exposed bone.

A retrospective study with 119 patients showed distribution of BRONJ with bone exposures (68.1%) in the mandible alone, 33 (27.7%) in the maxilla, and 5 (4.2%) occurred in both jaws [18]. Another retrospective study with 320 patients revealed that BRONJ triggered by tooth extraction occurred more frequently in the mandible than the maxilla [19].

Tooth extraction is a well-known risk factor for BRONJ development but an increasing of non-extraction-triggered forms has been reported in the literature [20]. The relationship between preexisting dental health and development of BRONJ-precipitating events included not only dental extractions (55%) but dental implants (2.9%), periodontal disease (41%), trauma related to intubation or poorly fitting dentures (17%) [21].

Kyrgidis*., et al.* [22] showed results indicating that history of tooth extraction during zoledronic acid treatment and the use of dentures increased the risk of developing jaw necrosis. In our case report both triggering factors such as tooth extraction and poorly fitting denture were present.

Tooth extraction in patients receiving BPs can be performed in a safe and predictable way, even in high-risk patients, when performed accordingly to the established guidelines. It is not the tooth extraction by itself, but rather the prevailing infectious conditions that may be a key risk factor for the development of BRONJ [23].

Alveolectomy compared to non-alveolectomy procedure seems to attenuate the risk of MRONJ after dental extractions [24]. This risk tends to decrease with adjusted extraction protocols [25]. Ferlito., *et al.* [26] proposed an extraction protocol that provided antibiotic prophylaxis and surgical extraction of interested teeth, accompanied by the removal of the adjacent alveolar bone. A total of 71 extractions in 34 patients were performed with this approach. The follow-up was 12 months. No signs of inflamed tissue or necrotic exposed bone in any patients were observed. Matsumoto., *et al.* [27] included in the extraction protocol the wound closure as a factor as well. In that way tooth extractions in patients receiving Denosumab can be performed in an appropriate manner. During surgery, bone edges were smoothed off and all wounds were closed using a double-layered technique. This study indicated that proper wound closure to avoid secondary infection may be effective for the prevention of BRONJ even in high-risk patients. Campisi. *et al.* [28] also recommended mucoperiosteal covering of post-extraction sites. Ristow., *et al.* [29] advocated that the double-layer closure techniques enable a mechanically stable, well-vascularized covering of the bone defect and demonstrated good clinical outcomes.

The second factor in this case report was related to the removable denture. Osteonecrosis can occur early during the drug intake regime and simply from minor mucosal trauma [30]. Wearing a denture in the initial occurrence site of BRONJ was shown to influence the prognosis of BRONJ, especially in mandibular denture-wearing patients [31]. In Walter., et al. [32] study all patients with BRONJ had had a previous dental surgical procedure or suffered from denture pressure sores. Therefore, close cooperation among medical doctors prescribing BPs and oral and maxillofacial surgeons or highly skilled dentists in this field seems to be reasonable. The avoidance of ulcers by dental prosthesis is part of preventing on of such complications [33].

It is indispensable that general dentists and specialists be trained in differential pathology diagnosis and multidisciplinary approach involving dental clinician, OMF surgeon, periodontist, prosthodontist, oncologist, endocrinologist and oncologic surgeon [14]. Extractions, when necessary, must be performed by expert dentists and follow-up must occur until the complete socket healing [34].

Kyrgidis., *et al*. [22] suggested early referral by oncologists for dental evaluation for every patient to be treated with BP. Several methods have been implemented to try to regulate soft tissue and bone healing and they are but not limited to: a) medication, b) surgical resection, c) hyperbaric oxygen, d) laser biostimulation, e) autologous platelet-rich plasma [35].

Reviewing the international literature about the treatment of BRONJ there is a support for an osseous resection of the diseased bone extended to the healthy osseous tissue. A resection performed with ultrasonic device is recommended due to its the minor trauma and more osseous protective effect [36]. The extension of the resection can be intraoperatively evaluated using a polarographic fine needle or fluorescence-guided probe, respectively [37,38]. Furthermore an adequate soft tissue closure including a tension-free multilayer coverage is essential for long term results. In addition, refractory disease can be successfully managed with a more aggressive resection, specifically, a segmental resection of the mandible after a marginal resection of the mandible where refractory disease developed [39]. Due to the high success rate of osteotomy and primary wound closure, it should be checked for every patient suffering from BRONJ if osteotomy is a viable treatment option [40].

Following the recommendation from the German S3 Guideline [15] the surgical protocol for this case was as follows: 1) Treatment with anti-microbiological rinsing; 2) Resection of the entire necrotic bone and smoothening of any sharp bone edges; 3. Coverage of the remaining bone by usage of a bi-layered wound closure.

Our surgical protocol is similar to the one used by Wilde., et al [41]. The authors reported high success case rate (88%) and because of this high success rate it seems that patients with BRONJ might be benefitted from this approach. Treatment of BRONJ might require more careful and extensive surgical procedures rather than curettage under local anesthesia [42]. Eguchi., *et al.* [43] advocate that surgical treatment is more effective than non-surgical treatment for stage II BRONJ.

Conclusion

The implementation of preventive surgical and medication protocol even at non-complicated tooth extractions plays an essential role in reducing BRONJ risk. This procedure should include alveoplasty and full covering of the occurring post-extraction defects with adjacent tissues (flaps). Intense antibiotic therapy is administered until the removal of the non-absorbable sutures by the second or third weeks after surgery.

We recommend absolute refraining from patients using the denture on the respective operated jaw until the full post-operative wound healing.

After this period a new denture or precise adjustment and rebasing of the old one, aiming an atraumatic pressure distribution might be indicated.

The frequent and regular post-operative follow-up is a key factor to timely diagnosing and possibly eliminating of eventual BRONJ recurrence.

Conflict of Interest

The authors declare no conflict of interest.

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