Original Research Article

Regenerated bisphosphonate related osteonecrosis of the jaws: Clinical data of eleven cases

ABSTRACT

AIMS: Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as the persistence of exposed necrotic bone in the oral cavity for 8 weeks or more in patients with current or previous history of BP use, despite adequate treatment, and no local evidence of malignancy or prior radiotherapy in the maxillofacial region. Complete resolution of symptoms and partial clinical achievement should be the primary goals in the management of BRONJ. The objective of the present study was to describe the clinical data and treatment of 11 patients with completely regenerated BRONJ.

METHODOLOGY: This retrospective study included 11 patients who experienced oral complications after intravenous bisphosphonate therapy. The diagnostic procedure involved clinical and radiological examinations. The patients were treated by irrigation with oral rinses, nonsteroidal anti-inflammatory drugs, long-term antibiotic therapy to resolve the infection, and non-aggressive surgical debridement of soft or hard tissues and sequestrectomy.

RESULTS: Complete healing, defined as the absence of any mucosal breaches and exposed necrotic bone, signs of inflammation and infection, and clinical complaints, was achieved in all patients.

CONCLUSION: Dental professionals should be aware of this potentially serious complication in oral surgery patients receiving long-term treatment with BPs. Although the management of patients with BRONJ is quite challenging since no ideal treatment protocol has been established thus far, discontinuity of bisphosphonate therapy combined with surgical debridement to obtain clear and bleeding margins along with long-term antibiotic therapy administration is the treatment of choice for osteonecrotic lesions of the jaws.

Keywords: BRONJ, management, regeneration, conservative

1. INTRODUCTION

Bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ) was first reported by Marx in 2003 [1]. Since 2003, an increasing number of cases has been reported in the literature. As proposed by the Advisory Task Force of the American Association of Oral and Maxillofacial Surgeons (AAOMS), BRONJ is defined as the persistence of exposed necrotic bone in the oral cavity for 8 weeks or more in patients with current or previous history of BP use, despite adequate treatment, and no local evidence of malignancy or prior radiotherapy in the maxillofacial region [2].

The exact mechanism of BRONJ has not yet been determined. Several hypotheses have been proposed to explain the etiology of BRONJ, such as defects in jaw bone physiologic remodeling or wound healing, osteoclast inhibition, antiangiogenic properties of BPs, BP toxicity to the oral mucosa and mucosal fenestration, and genetic variations [2, 3]. Potential risk factors associated with the development of BRONJ are history of dentoalveolar trauma,

long-term BP use, and intravenous (iv) use of BPs. A history of inflammatory dental diseases and chronic use of steroids with BPs have also been identified as potential risk factors for BRONJ [4, 5].

The treatment alternatives and stages of BRONJ are described in the current guidelines of the AAOMS [6]. BRONJ lesions can be classified into four stages. Stage 0 shows no clinical evidence of necrotic bone, but non-specific clinical symptoms may be present. The clinical features of stage 1 include exposed necrotic bone without mucosal infection. Stage 2 is characterized by exposed necrotic bone and signs of infection (pain, erythema, and purulence). Stage 3 exhibits more extensive necrotic bone, severe infection, and osteolysis, which extends to the inferior border of the mandible or sinus floor [2]. Conservative treatment is recommended for stages 0 and 1; conservative and surgical management for stage 2; and sequestrectomy and surgical resection of the necrotic bone for stage 3 [2, 3, 7].

Complete resolution of symptoms and partial clinical achievement should be the primary goals in the management of BRONJ [8]. In BRONJ patients, it is difficult to establish a defined time-to-healing. The treatment period for each patient is variable and unpredictable.

The purpose of this retrospective study was to describe the clinical data and treatment protocols of 11 patients with completely regenerated BRONJ.

2. METHODOLOGY

This retrospective study included 11 patients with oral complications after iv BP therapy who were referred to Süleyman Demirel University Faculty of Dentistry Department of Oral Maxillofacial Surgery. Approval for the study was obtained from the local ethics committee (Ethical Committee of Süleyman Demirel University Faculty of Medicine, Decision Date/Number: 05.02.2014/20). The diagnosis was made based on the results of clinical and radiological examinations. BRONJ was diagnosed based on a history of iv BP therapy, necrotic bone exposure that did not heal for 8 weeks or more, and no history of radiotherapy in the maxillofacial region.

Clinical data, such as sex of the patient, age of the patient, indication for BP therapy, plausible etiology of BRONJ, comorbidities, location of the lesion, duration and cessation of the BP therapy, treatment procedures, and the stage of the lesions, were recorded for all the patients. Staging of the disease was performed according to the definition and staging guidelines of the AAOMS [2]. The clinical data of the patients are shown in Table 1.

59 **Table 1. Data of the patients**

Patient number	Sex/Age	Indication for BPs	Etiology	Comorbidities	Location Mandible(n=6) Maxilla (n=5)	Smoking	Alcohol	Duration of the bisphosphonate therapy (months) (Zoledronic Acid 4 mg/3-4 weeks iv)	Cessation BP therapy (months)	Treatment procedure (surgical)	Follow-up (months)	Stage
1	M/74	Prostat Ca	Tooth extraction	None	3cmx2cm molar socket, maxilla	Yes	No	14	25	Sequestrectomy	18	3
2	F/49	Breast Ca	Tooth extraction	Type II Diabetes	0.8cmx1.2cm premolar alveolar crest maxilla	No	No	48	33	Debridement on soft tissues	27	2
3	M/57	Prostat Ca	Tooth extraction	None	1.2cmx0.4cm molar alveolar crest mandible	Yes	Rarely	40	33	Debridement on soft tissues	21	2
4	M/50	Epitheloid sarcoma	Tooth extraction	None	3cmx1.4cm premolar alveolar crest mandible	Yes	Sometimes	42	42	Sequestrectomy	29	3
5	F/54	Malign melanoma	Tooth extraction	None	1.5cmx2cm molar lingual cortex mandible	No	No	20	10	Sequestrectomy	5	3
6	M/51	Multiple mylelom	Apical disease	None	3x2 mm maxillary premolar	Yes	No	18	10	Debridement on soft tissue	6	2
7	F/56	Multiple mylelom	Tooth extraction	None	1 cm molar alveolar crest maxilla	No	No	36	21	Sequestrectomy	18	3
8	F/55	Breast Ca	Tooth extraction	None	1 cm molar alveolar crest maxilla	Yes	No	18	20	Debridement on soft tissue	10	2
9	M/82	Prostat Ca	Tooth extraction	Type II Diabetes	1 cm x0,5 cm mandible molar	Yes	No	48	40	Debridement on soft tissue	6	2
10	F/75	Breast Ca	poorly-fitting dentures	None	1 cm molar alveolar crest mandible	No	No	32	19	Debridement on soft tissue	8	2
11	M/62	Prostat Ca	Tooth extraction	None	1x0,5 cm molar alveolar crest mandible	Yes	No	12	22	Sequestrectomy	12	3

The treatment protocol included conservative therapy consisting of daily oral antimicrobial rinses (chlorhexidine 0.12%, benzydamine hydrochloride, and analgesics (nonsteroidal anti-inflammatory drugs, NSAIDs). Systemic antibiotic therapy (500-mg amoxicillin with 125-mg clavulanate orally 2 times daily or 300-mg clindamycin orally 3 times daily in cases of allergy to Penicillium) was indicated when signs of infection were present. Antibiotic therapy was administered for at least 14 days and continued until all the signs of infection had subsided. After elimination of the infection, surgical therapy in combination with conservative therapy was considered for all the patients. Surgical treatment involved surgical debridement up to macroscopically healthy bone (that showed an altered color until there was sufficient bleeding from the surrounding surfaces) for stage 2 lesions (Figure 1) and sequestrectomy (Figure 2) for stage 3 lesions. The sharp edges of the bone were removed to avoid damage to the soft tissue. It was mandatory that primary wound closure of the mucoperiosteal flaps was performed without tension. Oral antibiotics, antiseptic mouth rinses, and NSAIDs were administered for 10 days after surgery.

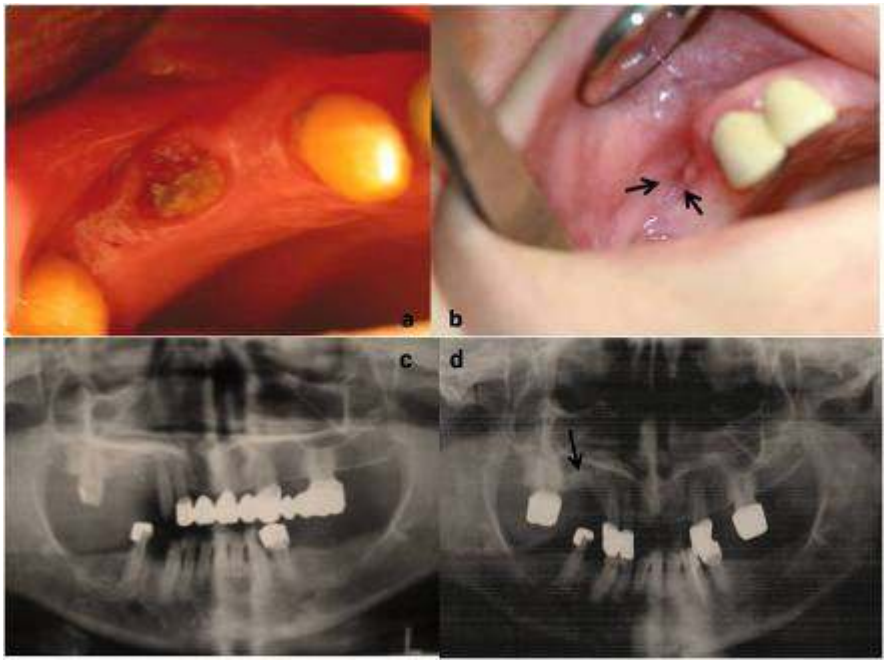

Figure 1 (a) Intraoral image showing Stage 2 BRONJ, (b) Intraoral image after healing, (c) Radiographic image of the patient showing BRONJ, (d) Radiographic image after healing

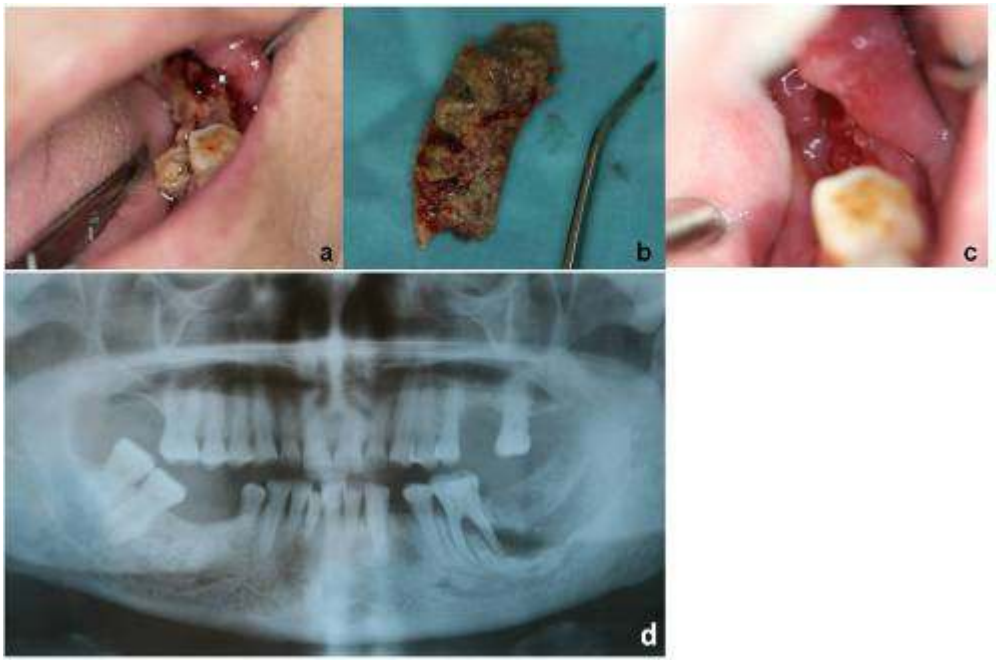

Figure 2 (a) Intraoral image of the sequestra, (b) Image of the sequestra after sequestrectomy, (c) Intraoral image of patient after healing, (d) Radiographic image of the patient at Stage 3

Statistical analyses were carried out using SPSS 18.0 (SPSS, Chicago, IL, USA). The relationship between the number of follow-up months and smoking, comorbidities, and stage and the location of BRONJ were evaluated with the two-sample T-test. $p = 0.05$ was considered to indicate statistical significance.

3. RESULTS

The age of the patients ranged from 49 to 82 years, with a mean age 60.45 years. All of the patients had received iv BPs for one of the following oncologic diseases: prostate cancer (36.4%), breast cancer (27.3%), multiple myeloma (18.2%), malignant melanoma (9.1%), and epitheloid sarcoma (9.1%). The etiology of BRONJ development was tooth extraction in 9 cases (81.82%), apical disease in one case (9.09%), and poorly fitting dentures and chronic denture trauma in one case (9.09%). Of the 11 patients, only 2 cases had comorbidities (type II diabetes) (18.18%); the other 9 cases did not have any systemic disease (81.82%; Table 1).

Of the 11 patients (5 women and 6 men) examined in this study, BRONJ was located in the maxilla in 5 cases (45.5%), and mandibular involvement was observed in 6 cases (54.4%). The BRONJ lesions were classified as stage 2 in 6 patients and stage 3 in 5 patients. The duration of BP therapy ranged from 12 to 48 months (mean 29.81 months). BP therapy was discontinued at an average of 25 months (range, 10–42 months). A BP drug holiday had been declared by the medical oncologist. The follow-up period ranged from 5 to 29 months, with a mean follow-up of 14.5 months (follow-up duration indicates the time between the diagnosis of the BRONJ lesion and complete healing. Complete healing is defined as the absence of any mucosal breaches and exposed necrotic bone, signs of inflammation and infection, and clinical complaints with re-epithelialization (Figures 1, 2, and 3).

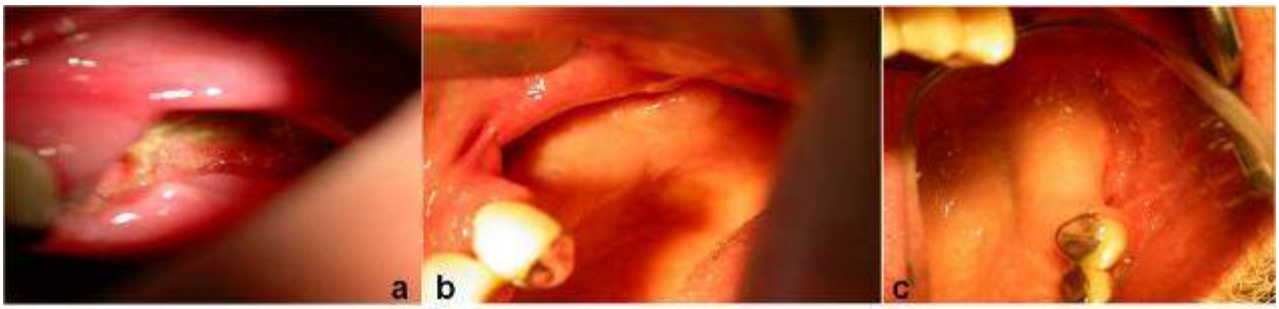

Figure 3 (a) Clinical image of the Stage 2 BRONJ, (b) and (c) Intraoral images after healing

The relationship between the number of follow-up months and smoking status, comorbidities, and stage and the location of BRONJ was not statistically significant ($p > 0.05$) (Table 2).

Table 2. The relation between follow-up time (Complete healing) and smoking,

		Follow-up (months)			
		n	Mean	St. Deviation	P
Smoking	Yes	7	14,57	8,52	0,990
	No	4	14,50	10,00	
Comorbidities	None	9	14,11	7,96	0,742
	Type II Diabetes	2	16,50	14,80	
Stage	2	6	13,00	8,85	0,542
	3	5	16,40	8,85	
Location	Maxilla	5	15,80	8,14	0,682
	Mandible	6	13,50	9,57	

4. DISCUSSION

Bisphosphonates are used in the treatment of metabolic diseases of the bone (Paget's disease and osteoporosis); hypercalcemia of malignancies; and metastatic bone disease resulting from breast cancer, multiple myeloma, and prostate cancer [4, 8, 9]. BPs inhibit osteoclast function and block the formation of lytic bone lesions. The profound inhibition of osteoclast function inhibits normal bone turnover and local micro damage from normal mechanical loading or injury (tooth extraction) can not be repaired [2,3]. In this study, all the patients had been administered iv BPs for metastatic bone diseases. BPs are efficacious drugs, with few side effects due to their high affinity for bone and minimal metabolism [10].

The incidence of BRONJ in patients taking iv BPs for metastatic bone diseases ranges between 0.7% and 6.7% [2]. BRONJ is found in both the sexes; however, more cases have been reported in women than in men, probably due to the large number of breast cancer patients with BRONJ [4].

It is believed that discontinuity of BP therapy combined with surgical debridement to obtain clear and bleeding margins along with long-term antibiotic therapy administration is the treatment of

choice for osteonecrotic lesions of the jaw. Discontinuity of BP therapy is a decision that rests with the oncologist, rather than the surgeon. The disease status of the patient from the oncologist's point of view is crucial to the decision to terminate BP therapy in order to treat BRONJ [2]. In the present study, a drug holiday for all the patients had been declared by the medical oncologist, and the mean cessation of BP therapy was 25 months (range, 10–42 months).

In the present study, lesions were located in the maxilla in 5 cases while 6 cases showed mandibular involvement. In several previous studies, BRONJ lesions reportedly occurred more frequently in the posterior lingual region of the mandible than in the maxilla [2, 8, 11]. However, the location of the lesion did not influence the treatment outcome [11]. In our study, the relationship between location and follow-up duration was not statistically significant, which is similar to the results of recent studies.

The management of patients with BRONJ is quite challenging since no ideal treatment protocol has been suggested thus far [11, 12]. Complete resolution of symptoms and partial clinical achievement should be the primary goals in the management of BRONJ [11]. Complete healing is rarely achieved. Most authors agree on conservative treatment strategies, which lead to reduction in symptoms and decrease in the frequency of infectious complications [8, 12]. All the lesions encountered in this study were treated by irrigation with oral rinses, NSAIDs, long-term antibiotic therapy to avoid related infections, and nonaggressive surgical debridement of soft or hard tissues and sequestrectomy. Addition of the several conservative treatments such as minimally invasive procedures, oral hygiene education, and administration of antibiotics along with 0.12% chlorhexidine antiseptic mouth wash or more aggressive procedures such as debridement of bone sequestrum and subtotal resection of the affected bone followed by prolonged antibiotic therapy and the long-term cessation of BP therapy, minimally invasive surgery combined with ozone therapy or platelet-rich fibrin membrane combined with surgical treatment with primary closure rendered the patients asymptomatic and stable [8, 11-15].

Although some reports have indicated that radical removal of all of the necrotic bone with primary closure can provide good healing in patients who had failed to heal with conservative management [7, 16, 17], it has been reported that extensive and radical surgical resections rarely result in long-term successful wound closure and have sometimes led to worsening of the disease. Therefore, surgery should be considered only in limited symptomatic cases when conservative treatment has failed [8, 11]. According to the guidelines of the AAOMSs, "The treatment objectives for patients with an established diagnosis of BRONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone osteonecrosis." These guidelines suggest that a surgical approach is indicated only in patients with advanced stages of BRONJ (surgical resection for stage 3 disease and debridement for stage 2 disease) [2]. Lerman, et al. [13] reported that BRONJ is a relapsing-remitting condition and, as such, the period that each patient stays in each stage and time-to-healing is variable and unpredictable.

Many BRONJ patients have comorbidities such as diabetes, anemia, and systemic use of corticosteroids. These systemic conditions have been variably reported to increase the risk of BRONJ and delay healing. Although Tsao, et al. [18] reported that tobacco use was not associated with BRONJ in a sample of cancer patients exposed to zoledronate, some authors also reported an increased risk for BRONJ among cigarette smokers [2]. It is well known that cigarette smoke hinders healing by inducing angiogenesis, collagen metabolism, or osteoblastic activity [19]. In the present study, the relationship between the follow-up duration and smoking and comorbidities was not statistically significant ($p > 0.05$). Of the 11 patients, only 2 patients had comorbidities and 7 patients were smokers. However, this study only recruited 11 patients, and the small number of the patients in this retrospective study is a limitation that needs to be considered.

5. CONCLUSION

Dental professionals should be aware of this potentially serious complication in oral surgery patients receiving long-term treatment with BPs. It is thought that BRONJ can be managed by

cessation of BP therapy for a considerable duration, according to the oncologist's decision, along with conservative treatment and surgical debridement/sequestrectomy, as needed.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

"All authors hereby declare that all experiments have been examined and approved by the Ethical Committee of Süleyman Demirel University Faculty of Medicine, Decision Date/Number: 05.02.2014/20 and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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