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Original Article

Medication related osteonecrosis of the jaws: a case serial study

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Abstract: Background/Purpose: This study determined general characteristics of cancer patients who developed medication related osteonecrosis of the jaw (MRONJ). Materials and methods: Demographic and clinical data of 35 cancer patients with MRONJ were retrospectively evaluated. General characteristics were compared between cases with and without complete recovery, to determine factors related to complete treatment response. Results: Seventeen female and 18 male patients (45-82 years) were included. Primary diagnoses were breast cancer (34.3%), prostate cancer (31.4%), or multiple myeloma (14.3%). Most patients (82.9%) used only intravenous zoledronic acid. Median bisphosphonate treatment duration was 36 months (5-120 months) and median time from commencing to stopping medication due to MRONJ progression was 6.5 months (1-84 months). Nearly all patients had a history of surgical procedures (88.6%), or trauma from dentures (5.7%). Half of the patients were treated conservatively (51.4%), and one-third were treated surgically (31.4%). Less than half of the patients recovered completely after treatment (42.9%), and 48.6% improved partially. Conclusion: MRONJ develops with prolonged use of bisphosphonates, but can develop after as little as 5 months of intravenous bisphosphonate treatment. Oncologists and dentists should be aware of this clinical aspect and ensure early determination of lesions when they are still curable.

Keywords: Bisphosphonate treatment, conservative treatment, medication related osteonecrosis of the jaws, surgical treatment

Introduction

Osteonecrosis can be defined as an area of exposed avascular, and dead bone, and may have various etiological causes. Jawbones are more vulnerable to developing osteonecrosis, particularly the mandible, which has a higher bone metabolism and greater bacterial exposure. Major etiological risk factors for development of this disorder are radiation exposure and bisphosphonate treatment [1].

Bisphosphonates are classified as anti-resorptive medications that bind to mineral components outside the osteoclasts and inhibit mineral dissolution by inducing apoptosis of osteoclasts [2, 3]. Hence, they are commonly used for treating diseases such as metastatic solid tumors, multiple myeloma, and hypercalcemia [4]. Despite the significant benefits of these drugs, they can have some serious adverse effects, such as osteonecrosis of the jaw.

Bisphosphonate related osteonecrosis of the jaw was first described in 2003 by Marx, who reported that this condition may be related to nitrogen containing bisphosphonates pamidronate and zolendronate [5]. Subsequently, significant progress has been made in understanding the pathophysiology of this disease [6]. This condition was originally referred to as bisphosphonate related osteonecrosis of the jaw (BRONJ), but in 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended changing the title to medication related osteonecrosis of the jaw (MRONJ). According to the AAOMS position paper, the core characteristics of MRONJ are [7]:

- Current or previous treatment with anti-resorptive or anti-angiogenic agents.
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the

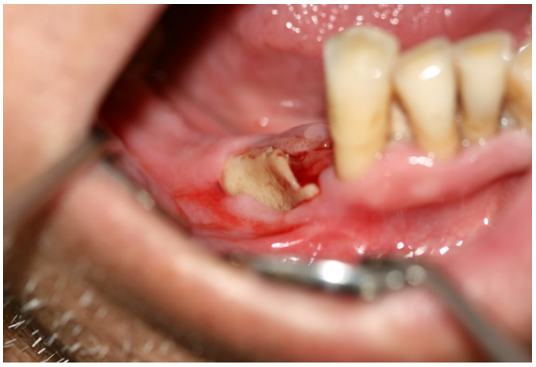

Figure 1. Stage two lesion in a patient with medication related osteonecrosis of the jaws. Intraoral image.

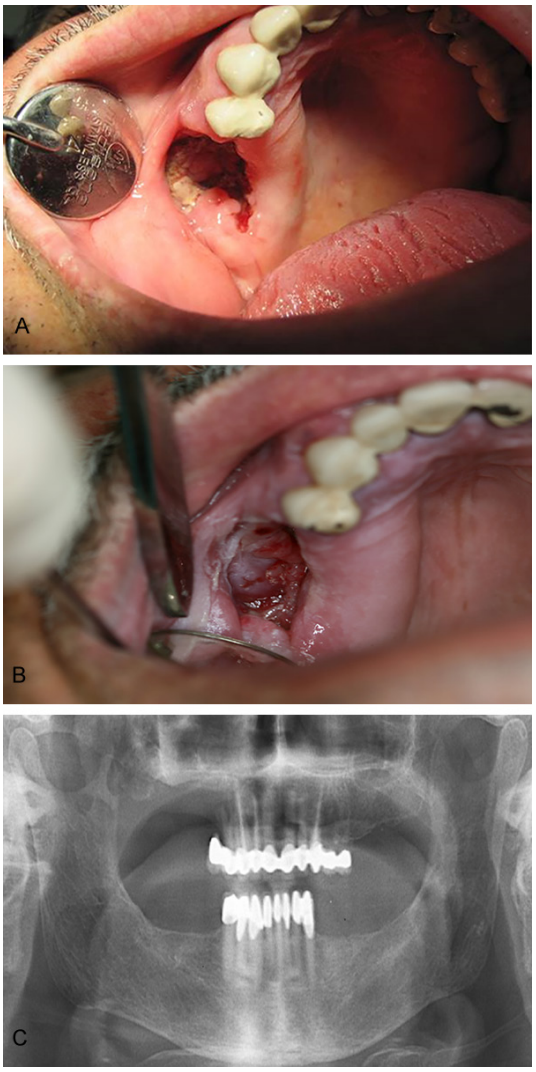

Figure 2. Stage three lesion in a patient with medication related osteonecrosis of the jaws. A. Intraoral image, B. Intraoral image after sequestrectomy, C. Radiographic image after sequestrectomy.

maxillofacial region that has persisted for longer than 8 weeks.

- No history of radiation therapy to the jaws or obvious metastatic disease in the jaws.

Current epidemiological data shows MRONJ occurrence is approximately 0.8-12% of patients taking intravenous bisphosphonate treatment. If the administration route is oral, such as in the treatment of osteoporosis, the risk is 1/100,000; but this risk increases to 1/10,000 if the medication continues for more than 3 years [8, 9].

Major risk factors for MRONJ development in patients under bisphosphonate medication include intravenous administration of drugs and dento-alveolar procedures [10]. Odontogenic inflammatory disease and trauma from ill-fitting prosthetic dentures are also frequent risk factors. Some MRONJ cases could also develop spontaneously. A current AAOMS position paper regarding MRONJ recommends that cancer patients taking intravenous bisphosphonates avoid dental extractions and bone surgery [11].

The aim of this study was to present general MRONJ characteristics, to provide data for prevention and treatment recommendations by evaluating the risk factors.

Materials and methods

Thirty-five cancer patients with MRONJ who were referred to Faculty of Dentistry Department of Oral and Maxillofacial Surgery between July 2007 and December 2012 were retrospectively evaluated. Informed consent was obtained from all patients and approval for the study was obtained from the Local Ethical Committee of Faculty of Medicine (21.07.2016/118).

Patients with osteonecrosis of the jaws (ONJ) using an intravenous bisphosphonate, zoledronic acid, were included in the study if they had bone exposure in the jaws. Patients were referred to the Oral and Maxillofacial Surgery Clinic (OMFS) by the medical oncologist. The following data were collected for each patient: demographics; date of first cancer diagnosis; cancer type; metastasis location; treatment type(s) (operation, radiotherapy, chemothera-

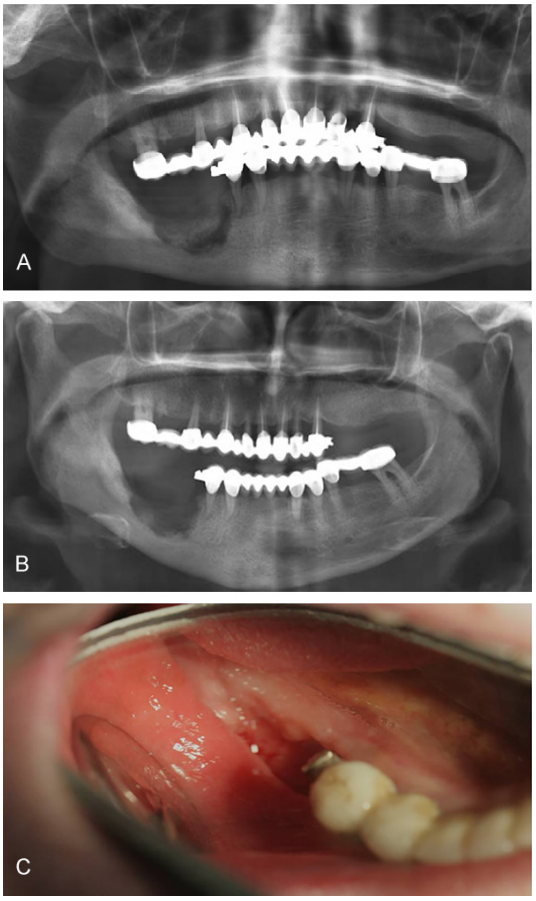

Figure 3. Stage three lesion in a patient with medication related osteonecrosis of the jaws. A. Radiographic image before sequestrectomy, B. Radiographic image taken two weeks after sequestrectomy, C. Intraoral image taken two weeks after sequestrectomy.

py); accompanying systemic diseases; indication for IV bisphosphonate therapy; dose and frequency of bisphosphonate therapy; duration; cessation of bisphosphonate; location and diameter of any bone exposure; previous treatments for exposed bone; whether any surgical or nonsurgical dental procedure was performed at the location of exposed bone (for example, dental extraction, debridement, placement of biomaterials) prior to bone exposure; treatment protocol and duration of follow-up applied by the OMFS, and the healing status (with or without complete recovery). Each patient underwent oral examination, noting the size and location of the exposed bone as well as signs and presence of secondary infection. Disease stage was determined by the OMFS using the criteria given in the AAOMS Position Paper on Medication related Osteonecrosis of the Jaws-2014 Update (**Figures 1** and **2**) [7].

Case definition was as used by Marx et al. [10]: presence of exposed bone in the maxilla or mandible that persisted for more than 8 weeks in a patient who had received systemic bisphosphonate, but had not received local radiation therapy to the head and neck region.

The treatment included nearly all the current therapeutic protocols for osteomyelitis with conservative (antibiotics) and surgical (debridement-sequestrectomy) procedures (**Figure 3**). For patients who were treated surgically, the removed bone specimens were pathologically evaluated. Surgical outcome data, including postoperative complications, infection, use of antibiotics, and recurrence of MRONJ, were collected.

The treatment protocol included conservative therapy consisting of daily oral antimicrobial rinses (chlorhexidine 0.12%), benzydamine hydrochloride, and analgesics (nonsteroidal anti-inflammatory drugs, NSAIDs), and systemic antibiotic therapy (825 mg amoxicillin with 125 mg clavulanate orally, twice daily, or 300 mg clindamycin orally, four times daily in cases of allergy to penicillin) was indicated when infection signs were present. Antibiotics were administered for at least 14 days and continued until all infection signs had subsided. After eliminating the infection, surgical therapy combined with conservative therapy was considered for all the patients in Stage 2 and 3. Surgical treatment involved surgical debridement up to macroscopically healthy bone (which showed a change in color until there was sufficient bleeding from the surrounding surfaces) for stage two lesions and sequestrectomy for stage three lesions. Bone sharp edges were removed to avoid damage to the soft tissue. Primary wound closure of the mucoperiosteal flaps without tension was mandatory. Oral antibiotics, antiseptic mouth rinses, and NSAIDs were administered for 10 days after surgery. Patients who underwent debridement or sequestrectomy were given partial dentures as an obturator, with soft lining material facing the exposed bone site. Drug regimens were advised for MRONJ patients who experienced pain and inflammation.

Statistical analysis

Categorical data were presented as frequency and percent, and numerical data were presented as mean and standard deviation, or median

Table 1. Demographic and clinical characteristics of patients according to treatment response

	None/Partial Recovery	Complete Recovery	p
Age (years)	61.5 (45-80)	56 (49-82)	0.582
Bisphosphanate duration (month)	36 (5-84)	24 (5-120)	0.119
Time since bisphosphanate stop (month)	7 (1-24)	6 (1-84)	0.638
Longest diameter of lesions (cm)	2.5 (0.5-5)	1.2 (0.5-3)	**0.006**
Gender			
Female	10 (50.0)	7 (46.7)	0.845
Male	10 (50.0)	8 (53.3)	
Systemic Disease			
Present	5 (25.0)	4 (26.7)	0.911
None	15 (75.0)	11 (73.3)	
Localization			
Maxilla	8 (40.0)	3 (20.0)	**0.039**
Mandible	12 (60.0)	8 (53.3)	
Maxilla and Mandible	0 (0.0)	4 (26.7)	
Stage			
Stage 1	2 (10.0)	4 (26.7)	0.297
Stage 2	12 (60.0)	9 (60.0)	
Stage 3	6 (30.0)	2 (13.3)	
Treatments			
Conservative	2 (10.0)	4 (26.7)	0.151
Surgery Debridment/Sequestrectomy	18 (90.0)	11 (73.3)	
Smoking status			
Non-user	13 (65.0)	10 (66.7)	0.458
Smoker	7 (35.0)	5 (33.3)	

Data are presented as median (minimum-maximum) or number (%), where appropriate.

and minimum maximum, as appropriate. Comparisons between categorical variables with and without complete recovery were analyzed using chi-square tests for independence and the Mann-Whitney-U test for non-normally distributed numerical data. All analyses were two-tailed, and statistical significance was set at $p < 0.05$. SPSS 21 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses in this study.

Results

This study included 17 female (48.6%) and 18 male (51.4%) patients, with mean ages 56.5 ± 7.9 years and 63.9 ± 9.8 years, respectively. Primary diagnoses of patients were breast cancer (12 patients, 34.3%), prostate cancer (11 patients, 31.4%), multiple myeloma (five patients, 14.3%), with the remaining diagnoses being angiosarcoma, renal cancer, tongue cancer, epithelioid sarcoma, colon cancer, malign melanoma, and gastric cancer (each patient, 2.9%). Twenty-two patients had metastatic diseases (62.9%). Nine patients had systemic diseases, such as asthma, diabetes, hypertension, cardiac disease, depression, hyperlipidemia, hyperthyroidism, and goiter. Ten patients were active smokers (28.6%) and two patients were ex-smokers (5.7%).

The majority of patients used intravenous zoledronic acid (n = 29; 82.9%), and one patient used ibandronic acid (2.9%). Of those patients that used zoledronic acid, three patients also used disodium clodronate (8.6%), one ibandronic acid (2.9%), and one alendronate (2.9%). The median time of medication use in the patient group was 36 months (5-120 months). Nine patients continued to use their medications until MRONJ progression, and the median time from stopping the treatment to the development of MRONJ in the remaining patients was 6.5 months (1-84 months).

MRONJ lesions were localized in the mandible (20 patients, 57.1%), maxilla (11 patients, 31.4%), and in both the mandible and maxilla (four patients, 11.4%). The median of the largest diameter of the lesions was 2 cm (0.5-5 cm).

MRONJ was classified as stage 1 in 17.1% of patients, as Stage 2 in 60.0%, and as stage 3 in 22.9%. Evaluation of MRONJ lesion etiological factors showed that only one patient had no history of risk factors (2.9%). Tooth extraction had been performed in 31 patients (88.6%), trauma from prosthetic dentures was present in two patients (5.7%), and periodontal disease in one patient (2.9%).

Six patients were treated conservatively (17.1 %), 22 were treated surgically (62.9%), and 7 were treated by sequestrectomy (20%). After appropriate treatment, three patients showed no improvement (8.6%), 17 showed partial improvement (48.6%) and 15 recovered completely (42.9%).

Demographic and clinical data for the patient groups (with and without complete recovery) are compared in **Table 1**. Age (p = 0.582), bisphosphonate treatment duration (p = 0.119), and time since stopping medication (p = 0.638) were similar between the patient groups.

However, the median longest diameter of lesions was significantly different between patient groups (p = 0.006), and patients who made a complete recovery had significantly smaller median lesion diameters than those who did not (1.2 and 2.5 mm, respectively). The relationship between the localization of the MRONJ and healing status were statistically significant (0.039). All of the lesions located in both the maxilla and the mandible showed complete healing. Gender (p = 0.845), presence of systemic disease (p = 0.911), primary cancer site, history of past surgeries, metastatic disease (p = 0.069), treatment modalities (p = 0.151), and smoking status (p = 0.458) were also not statistically different between these patients with or without complete recovery.

Discussion

Medication related osteonecrosis of the jaws is a serious adverse effect that may develop while treating patients with bisphosphonates. Primary indications for bisphosphonate treatment include osteoporosis, control of bone metastases, and malignant hypercalcemia [11]. The current study investigated the general MRONJ characteristics and treatment results for a sample of cancer patients who were treated with intravenous bisphosphonates. Approximately one-third of the MRONJ patients had breast cancer, one-third had prostate cancer, and nearly half of the remaining patients had multiple myeloma. Treatment outcomes showed that demographic and clinical characteristics of patients with and without complete remission were similar, and the only significant difference between the patients with or without complete recovery was the size and the localization of the osteonecrozis.

Zoledronic acid significantly inhibits osteoclastic activity, and is widely used for osteoporosis prevention and treatment. Long term use of this drug is related to decreased bone turnover and reparative ability, which eventually causes disabled repair of bone microdamage [12]. Osteonecrosis of the jaws commonly occurs with prolonged use of zoledronic acid [13].

General characteristics of patients with bisphosphonate related osteonecrosis of the jaws were recently evaluated by Filleul et al. [14], including 2,400 cases, and found that the predominant gender was female and the main underlying diseases were multiple myeloma and breast cancer. These outcomes were confirmed in a subsequent study [11]. Nevertheless, for the MRONJ patients in the current study, gender distribution was similar (51.4% male and 48.6% female), primary disease distribution was similar to previously results, and breast cancer was the most frequent underlying disease.

Management of skeletal events in breast cancer patients and of bone metastases include application of bisphosphonates to reduce the frequency and prolong the time to development bone related events [15]. Previous reports have shown that approximately one-fifth of all ONJ patients are breast cancer patients taking bisphosphonates [16]. On the other hand, Hoff et al. evaluated 4096 patients taking intravenous bisphosphonates, and reported that only 1.2% of patients with breast cancer and 2.4% of patients with multiple myeloma developed ONJ [17]. They also found that ONJ risk could reach 3.8% in patients who were treated with monthly zoledronic acid. However, a subsequent study found this risk was less than 0.7% in patients administered zoledronic acid on a biyearly basis [13]. Intravenous bisphosphonates are antiresorptive drugs used to manage cancer-related conditions including the hypercalcemia of malignancy, skeletal-related events associated with bone metastases in the context of solid tumors such as breast cancer and prostate cancer, and the management of lytic lesions in the setting of multiple myeloma [7]. The majority of patients in this study had breast or prostate cancers, or multiple myeloma, consistent with previous

studies. Although more than half the patients had metastatic diseases, which had spread to the skeleton in the majority, patients without metastatic lesions and malignant hypercalcemia were also prone to MRONJ development. Prolonged use of bisphosphonates is known to be a significant risk factor for osteonecrosis, but the current study shows that the treatment duration could be as short as 5 months for development of MRONJ lesions.

For the current study, 88.6% of patients had a history of tooth extraction, and the second most frequent risk factor was trauma from dentures (5.7%). ONJ risk posed by surgical procedures on jaws have been reported previously to range between 0.09% and 0.34% in the case of oral bisphosphonate use [18], and AAOMS updated this estimate to 0.5% in 2014 [7]. On the other hand, MRONJ risk after tooth extraction in patients treated with intravenous bisphosphonates was reported to range between 1.6% and 14.8% in the AAOMS 2014 update [7]. All but one of the current study MRONJ patients used intravenous zoledronic acid, which poses a significant risk for development of necrotic lesions. This excess risk presented as large necrotic lesions with median diameter 2 cm on the jawbones.

Inflammation or infection has long been considered an important component of MRONJ. Early studies identified bacteria, especially the Actinomyces species, in biopsied specimens of necrotic bone removed from patients with MRONJ. It has been shown that bacteria in combination with fungi and viruses, may require more complicated treatment to fight against the multiorganism ONJ-associated biofilm [7, 19]. The most frequently used antibiotics are penicillin, amoxicillin, amoxicillin/clavulanic acid, metronidazole, and/or a combination thereof. Erythromycin, clindamycin, or lincomycin are prescribed if the patient is allergic to penicillin [20]. However, Klingelhöffer et al. [21] reported that it remains unclear whether sufficient prolongation of antibiotic therapy causes this condition or whether the existence of actinomyces is crucial for the surgical outcome. Bermúdez-Bejarano et al. [22] reported that antibiotic therapy is a vital part of conservative management to reduce the symptoms of MRONJ.

In stage II/III MRONJ, the minimum necessary necrotic bone elimination is indicated, and two surgical approaches have been recommended: surgical debridement and sequestrectomy; and segmental resection [23]. Rodriguez-Lozano et al. [23] reported that most authors recommend minimally invasive surgery for MRONJ, and they also reported healing rates of over 50% for minimally invasive surgery. For the current study, 82.9% of patients were treated with minimally invasive surgery, and 42.9% of 35 patients showed complete healing. Klingelhöffer et al. [21] reported that surgery was effective for reducing the MRONJ stage, but not for complete healing. Therefore, surgical treatment should be reserved for patients who suffer from pain and expanding necrosis. The AAOMS guidelines recommend against surgery in general for stage I patients. Only for stage III patients and patients with no response to conservative therapy at stage II should surgical intervention be considered [7].

This study showed that demographic or clinical characteristics of patients with and without complete healing were not significantly different, except for lesion size. As can be anticipated, larger lesions tend to heal less rapidly, but none of the remaining characteristics significantly affected complete recovery. The completely healed lesions had significantly smaller median lesion diameters than partially healed lesions (1.2 and 2.5 mm, respectively). The relationship between the localization of the MRONJ and the healing status was statistically significant. All of the lesions located in both the maxilla and the mandible showed complete healing. Clinically, the diameters of the lesions located in both the maxilla and mandible were found to be smaller than those of lesions with only maxillar or mandibular localization.

It is clear that the pathogenesis of MRONJ is complex and multifactorial. Before starting therapy, the oral cavity should be systematically examined and oral hygiene measures should be initiated. Antiresorptive therapy should be delayed by 2-3 weeks until the extraction wounds have healed, according to the oncologist's decision. Dental professionals should be aware of this potentially serious complication in oral surgery patients receiving antiresorptive therapy. Surgical therapy is especially indicated for patients with MRONJ at stages II and III, in accordance with the actual recommendations of the AAOMS. In stage I disease, non-

surgical treatment represents a promising alternative. Nevertheless, more studies are necessary to clarify the definite significance of surgical intervention.

The major limitation of the current study is its retrospective nature, which limits the available data to existing patient records. Nevertheless, we believe that the study results provide basic information about general MRONJ characteristics, laying the foundation for further studies.

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Disclosure of conflict of interest

None.

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