Idiopathic Incidence of MRONJ in Patients on Denosumab

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Abstract

Background and Objectives: Osteonecrosis of the jaw (ONJ) has been reported in patients taking bisphosphonates (BPs) for conditions such as osteoporosis, Paget disease, and hypercalcemia of malignancy. Denosumab, a monoclonal antibody against the receptor activator for nuclear kappa B ligand (RANKL), has been recently approved as a safer alternative antiresorptive agent. However, shortly after its release ONJ has been reported in patients taking denosumab. The aim of this study is to present a case of an idiopathic incidence of osteonecrosis of the jaw related to denosumab. In addition, we are providing a critical review of current literature on denosumab-related osteonecrosis of the jaws.

Materials and Methods: A comprehensive and critical review of literature was conducted on PubMed and Medline using the keywords “denosumab”, “osteonecrosis of the jaw”, “anti-RANKL”, and “MRONJ”. Only confirmed denosumab-related ONJ with no history of BPs and in English language were included in the presented study.

Results: Our review of literature identified a total of 18 cases. The majority of cases were reported in posterior mandible of male patients receiving denosumab for treatment of prostate cancer. The most common rendered treatment approach included systemic antibiotics, chlorhexidine (CHX) rinse, discontinuation of denosumab, and surgical debridement.

Conclusion: Denosumab-related ONJ appears to be independent of the duration of denosumab therapy. A combination of systemic antibiotics, CHX rinse, discontinuation of denosumab therapy, and surgical debridement were the most commonly rendered treatments.

Keywords: Osteonecrosis of the jaw, Denosumab, Anti-RANKL, MRONJ, Drug holiday

Introduction

Denosumab is an immunoglobulin (Ig) G2 monoclonal antibody with antiresorptive properties and has been primarily used in the treatment of osteoporosis, BP-resistant hypercalcemia of malignancy, and in the prevention of skeletal-related events (SRE) in patients suffering from metastases of solid tumors [1]. These conditions typically reflect an imbalance in bone remodeling that is characterized by a shift in equilibrium towards an increased osteoclastic activity and therefore bone resorption. Formation, differentiation, function, and activity of osteoclasts are regulated by a variety of physical and chemical stimuli [2]. RANKL, activates osteoclast differentiation by binding to pre-osteoclast RANK cell-surface receptors leading to differentiation of osteoclasts and increase bone resorption [3-5]. Denosumab exerts its antiresorptive action by binding to RANK-L and preventing the formation of the RANKL-RANK- complex, therefore inhibiting the differentiation and maturation of osteoclasts [1,6-9]. In previous studies, denosumab has been reported to have fewer adverse effects with a lower risk for renal toxicity, pyrexia, and arthralgia when compared to BPs [6,9]. Although denosumab presents with a less side effects compared to BPs, several cases of denosumab-related ONJ have been reported since its initial use in 2010 [4,9].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) defined ONJ as necrotic, exposed bone of maxillofacial region persisting for more than eight weeks in patients with an exposure to antiresorptive or antiangiogenic agents and no history of radiotherapy to head and neck [10]. The same authors also introduced the term medication related ONJ (MRONJ) to replace terms such as bisphosphonate-related ONJ (BRONJ), as a growing number of evidence indicated ONJ could result from other antiresorptive or antiangiogenic agent. According to the AAOMS, a diagnosis of MRONJ can be derived by satisfying the following criteria: 1) current or previous treatment with antiresorptive or antiangiogenic agents, 2) exposed bone or bone that can be probed through an intraoral orextraoral fistula in the maxillofacial region that has persisted for more than eight weeks; and 3) no history of radiation therapy to the jaws or obvious metastatic disease to the
with a pale-yellow appearance. The surrounding gingival tissue had a 1.0 cm large defect of hard, immobile, non-tender exposed bone affecting the lingual cortical plate in the area of mandibular left second and third molars. Clinical examination revealed a 3.0 cm × 1.0 cm large defect of hard, immobile, non-tender exposed bone and subjected to analysis (Table 1).

### Case Presentation

An 88-year-old African American male was referred to our department for the evaluation and treatment of exposed bone affecting the lingual cortical plate in the area of mandibular left second and third molars. Clinical examination revealed a 3.0 cm × 1.0 cm large defect of hard, immobile, non-tender exposed bone with a pale-yellow appearance. The surrounding gingival tissue was non-tender and lacked any evidence of erythema or purulent discharge (Figure 1). The patient’s medical history was positive for hypertension, chronic kidney disease, and prostatic cancer that were diagnosed in 1988. According to the patient’s records, the treatment regimen for the prostatic cancer included radiotherapy, Leuprolide, Enzalutamide, and monthly (every 4 weeks) subcutaneous injections of 120 mg denosumab. The patient did not have any history of bisphosphonate usage or radiotherapy to head and neck. His dental history revealed extractions of mandibular left first molar 41 months before the incidence of ONJ. The records also indicated that the patient was receiving denosumab therapy while undergoing extractions. Radiographic investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2).

### Table 1: Data Collection

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Area affected</th>
<th>Procedure performed</th>
<th>Comorbidities</th>
<th>Number of Denosumab Treatments</th>
<th>Hx of BPs</th>
<th>Hx. Of Radiation to Head and Neck</th>
<th>Hx. Of Chemo-therapy</th>
<th>Drug Holiday</th>
<th>Treatment of ONJ</th>
<th>Treatment Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsushita et al. [5]</td>
<td>76</td>
<td>M</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Prostate cancer</td>
<td>24 No No No Yes (1 month prior to tx)</td>
<td>Surgical resection and extraction of affected teeth</td>
<td>Surgical resection</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olata et al. [11]</td>
<td>55</td>
<td>F</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Invasive ductal carcinoma, Unethal carcinoma</td>
<td>1 No No Yes</td>
<td>CHX</td>
<td>No resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Began et al. [12]</td>
<td>55</td>
<td>F</td>
<td>Maxilla</td>
<td>Extraction</td>
<td>Osteogenesis</td>
<td>3 No – – – –</td>
<td>Antibiotics, CHX, Surgical resection</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min You et al. [13]</td>
<td>56</td>
<td>F</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Breast cancer</td>
<td>9 No No Yes No</td>
<td>1. Discontinue denosumab for 3 months only; 2. Abs, CHX, drug holiday for 6 months followed by surgical resection of sequestrum</td>
<td>1. Initial healing with relapse 2. Resolution after 6 months drug holiday and surgical intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohga et al. [14]</td>
<td>64</td>
<td>M</td>
<td>Anterior mandible</td>
<td>Extraction</td>
<td>Colorectal cancer</td>
<td>7 – No Yes No</td>
<td>Discontinued Denosumab, Antibiotic, Antimicrobial mouth rinse</td>
<td>Natural shedding of sequestrum and epithelialization of exposed bone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mogisich et al. [15]</td>
<td>65</td>
<td>F</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Breast cancer, Osteogenesis</td>
<td>– No No Yes –</td>
<td>Osteotomy, Alveoloplasty, and flap closure</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otto et al. [16]</td>
<td>68</td>
<td>F</td>
<td>Posterior mandible</td>
<td>Extraction and Implant placement</td>
<td>Osteogenesis</td>
<td>– No No No No</td>
<td>Discontinuation of denosumab Antibiotics, Surgical resection, Authors do not state</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuprez et al. [17]</td>
<td>58</td>
<td>M</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Osteogenesis</td>
<td>1 No No No –</td>
<td>1. Antibiotics, CHX, 2. Surgical removal and Abs</td>
<td>1. No resolution; 2. Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Povca et al. [1]</td>
<td>58</td>
<td>M</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Prostate cancer</td>
<td>42 No No No No</td>
<td>Discontinuation of denosumab, antibiotics, CHX, surgical resection</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor et al. [18]</td>
<td>60</td>
<td>M</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Prostate cancer</td>
<td>– No No Yes No</td>
<td>Antibiotics, CHX</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Hallora et al. [4]</td>
<td>60</td>
<td>M</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Prostate cancer</td>
<td>7 No No – –</td>
<td>Abs, CHX, followed by surgical removal + debridement</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Hallora et al. [4]</td>
<td>72</td>
<td>M</td>
<td>Posterior maxilla</td>
<td>Extraction</td>
<td>Prostate cancer</td>
<td>6 No Yes – –</td>
<td>Halit of denosumab treatment, surgical removal and soft tissue closure</td>
<td>Oro-anal fistula reduced in size, bony defect remains</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malan et al. [19]</td>
<td>67</td>
<td>M</td>
<td>Posterior mandible and posterior maxilla</td>
<td>Extraction</td>
<td>Prostate cancer</td>
<td>26 No No – No</td>
<td>Discontinuation of denosumab, Antibiotic, CHX, conservative debridement for mandibular lesion—discontinuation of denosumab alone for maxillary lesion</td>
<td>Resolution — Natural shedding of sequestrum and resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diz et al. [20]</td>
<td>73</td>
<td>M</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Prostate cancer</td>
<td>17 No No Yes Yes</td>
<td>Antibiotics, CHX, surgical resection</td>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pichardo et al. [21]</td>
<td>74</td>
<td>M</td>
<td>Posterior mandible</td>
<td>–</td>
<td>Prostate cancer</td>
<td>4 No No Yes No</td>
<td>Antibiotics, surgical resection; authors do not state discontinuation of denosumab</td>
<td>No resolution</td>
<td></td>
<td></td>
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<tr>
<td>Aghalo et al. [22]</td>
<td>26</td>
<td>M</td>
<td>Posterior mandible, bilateral</td>
<td>–</td>
<td>Sacral giant cell tumor</td>
<td>12 No No – No</td>
<td>Discontinuation of Denosumab, Antibiotics, CHX, Surgical resection</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The presented case</td>
<td>88</td>
<td>M</td>
<td>Posterior mandible</td>
<td>Extraction</td>
<td>Prostatic cancer</td>
<td>14 or more No No Yes Yes</td>
<td>Antibiotics, Surgical resection was planned (patient did not present for treatment)</td>
<td>–</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Materials and Methods

A systematic PubMed and Medline search was conducted using the keywords “denosumab”, “osteonecrosis of the jaw”, “anti-RANKL”, and “MRONJ”. Confirmed reports of denosumab-related ONJ with no previous history of BPs and in English language were included in the presented study. Clinical data of interest, such as age at presentation, gender, race, area affected, rendered treatment, follow up period, and outcome of treatment were collected, tabulated, and subjected to analysis (Table 1).

### Case Presentation

An 88-year-old African American male was referred to our department for the evaluation and treatment of exposed bone affecting the lingual cortical plate in the area of mandibular left second and third molars. Clinical examination revealed a 3.0 cm × 1.0 cm large defect of hard, immobile, non-tender exposed bone with a pale-yellow appearance. The surrounding gingival tissue was non-tender and lacked any evidence of erythema or purulent discharge (Figure 1). The patient’s medical history was positive for hypertension, chronic kidney disease, and prostatic cancer that were diagnosed in 1988. According to the patient’s records, the treatment regimen for the prostatic cancer included radiotherapy, Leuprolide, Enzalutamide, and monthly (every 4 weeks) subcutaneous injections of 120 mg denosumab. The patient did not have any history of bisphosphonate usage or radiotherapy to head and neck. His dental history revealed extractions of mandibular left first molar and retained root of second molar 41 months before the incidence of ONJ. The records also indicated that the patient was receiving denosumab therapy while undergoing extractions. Radiographic investigation using an orthopantogram showed ground-glass appearance and loss of trabeculation associated with the involved area (Figure 2). Considering the anamnestic data and findings of initial workup, the differential diagnosis included denosumab-related ONJ, osteomyelitis, and metastases related to previous malignancy. To establish a definitive diagnosis a biopsy of the involved hard tissue was performed. The histopathologic analysis was positive for necrotic jaws [10].
bone consistent with osteonecrosis. There was no evidence for any malignant involvement. Treatment included systemic antibiotics with Amoxicillin 500 mg every eight hours for seven days and referral to a local hospital for surgical intervention. Multiple attempts to schedule the patient for surgery failed and follow up was not possible.

**Results**

We identified a total of 18 cases diagnosed with MRONJ due to denosumab since its initial release in 2010 (Table 1). Most of the cases were reported in patients receiving denosumab for the treatment of prostate cancer (50%; 9), followed by breast cancer, and osteoporosis with 22% (4/18) and 17% (3/18) respectively. In two cases (11%) the underlying condition for denosumab treatment was not reported. The data shows a predilection for male gender (61%; 11) with a male-to-female ratio of 1.8:1. The posterior mandible is the most commonly involved site (78%; 14), followed by posterior maxilla (17%, 3), and anterior maxilla (11%, 2). In one report the posterior maxilla and mandible were affected simultaneously. The most common dental procedures identified as initiating factor for MRONJ was dental extraction (72%; 13). In four cases the authors (22%) did not report the procedure that caused MRONJ [4,11-21,22]. The most commonly encountered clinical presentations were pain, purulent discharge, delayed wound healing, and exposure of necrotic bone. The race was infrequently reported (17%, 3) with four Asian, three Caucasian, and one Black patients. In 56% (10/18) the race was not reported. The treatment regimen rendered most commonly included a combination of systemic antibiotics, CHX rinse, discontinuation of current denosumab therapy, and surgical resection.

**Discussion**

The involved pathophysiology MRONJ has not been fully established yet; however, proposed mechanisms thought to play a role in causing MRONJ include altered bone remodeling, inhibition of osteoclastic bone resorption, inhibition of angiogenesis, and microtrauma [10]. Several local factors such as dento-alveolar surgery, infections, trauma, and systemic factors such as medications, breast cancer, lung cancer, prostate cancer, multiple myeloma, chemotherapy have been implicated as predisposing factors [9,10,23]. MRONJ has been traditionally associated with BPs and more recently with the usage of denosumab or other antiresorptive/antiangiogenic agents. The overall incidence of MRONJ in patients taking denosumab ranges from 0.9% to 5% [7,24,25]. To our knowledge 18 cases of MRONJ due to denosumab therapy have been reported in English literature. (Table 1) Patients with history of denosumab as well as BPs were excluded from the study due to limitations in determining the individual contribution of the drugs to the development of MRONJ. The age ranges from 26 to 88 years with a mean age of 62.5 years. Most cases (94%; 17) present at age of 50 years or above with a peak incidence in the 6th and 7th decade. Reports of MRONJ in female patients were largely related to conditions such as osteoporosis or breast cancer. In male patients, most of the authors reported history of denosumab therapy related to prostate cancer (82%; 9/11). The posterior mandible appears to be at greatest risk for MRONJ with 78% of cases presenting with MRONJ in this area. (Table 1) This is consistent with previous reports in the literature [1,9]. The posterior mandible has denser bone, is less vascularized, and subjected to more masticatory forces and therefore bone remodeling. The most commonly described surgical intervention to trigger MRONJ were dental extractions which was reported in 72% (13/18) of the cases. Trauma due to ill-fitting removable or full denture has been described as a predisposing factor [1]. In our review none of the cases has been linked to an ill-fitting denture. The effects of denosumab on bone remodeling abate faster after discontinuation when compared to BPs. Both, Denosumab and BPs, are considered two pharmacologically different types of antiresorptive agents. Denosumab inhibits bone resorption by selectively interfering with the interaction between RANKL and the receptor activator of nuclear factor-kappa B which is essential in the formation, activation, and survival of osteoclasts. BPs inhibits bone resorption by decreasing the activity level of farnesyl diphosphate synthetase, an enzyme important for the cytoskeletal maintenance, vesicular transport, ruffling, migration, and adhesion of osteoclasts. In addition, BPs are deposited and stored in mineralized bone for a prolonged period of time with a half-life time ranging between 10 and 14 years [26]. In contrast, denosumab is not deposited in bone, exhibits a faster onset of activity within six hours, and is eliminated more rapidly from the system when compared to bisphosphonates [4,19]. Due to the reversible character of denosumab authors have proposed a drug holiday prior to any dental surgery as a preventive measure [10,27]. In the presented study 13 cases (72%) provided information about the current status of denosumab therapy; five authors (28%) did not provide enough information on the denosumab regimen. Only in one instance the authors reported MRONJ despite initiating a drug holiday of six months before extractions [20]. Considering the lack of a drug holiday in the majority of cases, we agree with other authors in recommending a drug holiday prior to any dental surgery to minimize the risk for MRONJ [16]. However, the value of such a drug holiday remains unclear and underlines the need for further investigation. There is evidence suggesting that the initiation of denosumab therapy shortly after dental procedures may also increase the risk for MRONJ. Matsushita et al. presented a case of MRONJ in a patient receiving...
initial denosumab therapy three weeks after performing extraction [5]. Considering this, patients may benefit by extending the drug holiday for some time after surgical procedures to decrease the risk for developing osteonecrosis. However, further investigation is needed to evaluate this hypothesis and the appropriate time for reinitiating denosumab. A definitive or standard treatment protocol for MRONJ has not been established yet. Different treatment approaches have been suggested including antibiotic therapy, antimicrobial rinses, drug holiday, and surgical interventions. Several authors have described spontaneous resolution of sequestrum and healing after discontinuing Denosumab alone without any other interventions [10,14,18,19]. Ohga “et al.” reported a case of MROMJ related to denosumab after extraction in an Asian female treated for colorectal cancer with 120 mg denosumab injections every 4 weeks with a total of seven administrations [14]. Spontaneous shedding of sequestered bone and resolution 7 months after discontinuing denosumab was observed. Similar reports were made by Melan “et al.” and Taylor “et al.” stating that discontinuation of denosumab alone without surgical intervention lead to natural shedding of sequestrum after 11 and 15 months respectively [18,19].

**Conclusion**

MRONJ due to denosumab presents with a relatively rare occurrence. Conservative surgical resection in conjunction with systemic antibiotics, CHX rinse, and discontinuation of current denosumab therapy has been shown to be the most commonly used approach. A drug holiday to be started before and extended after surgical intervention may play a role in decreasing the risk for MRONJ.

**References**


