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CASE REPORT

Medication Related Osteonecrosis of the Jaw: A Case Report and Review of Literature

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse reaction caused by the use of antiresorptive antiangiogenic medication. The most commonly affected areas are posterior regions of mandible and maxilla. However, a simultaneous occurrence in both jaws is rarely observed. We present an interesting case of MRONJ affecting both jaws. A 47-year-old female presented with pain and swelling in the left posterior region of the mandible. The patient's medical history was significant for breast cancer with ongoing bisphosphonate therapy. Cone-beam computerized tomography (CBCT) confirmed the presence of an extraction socket at the site of complaint. There was evidence of a diffuse sclerotic bone reaction in the maxillary posterior region bilaterally. The mandible showed presence of diffuse sclerotic bone only in the left para-symphysis and posterior region in addition to association with a periosteal bone reaction in the left para-symphysis region. Considering these findings and a history of exposure to bisphosphonate medication, the final diagnosis was conclusive of MRONJ. Management was aimed at suppressing the symptoms of pain and infection. The present case study reinforces the importance of correlating clinical and radiographic findings. Early diagnosis of MRONJ may lead to a more conservative treatment approach, greatly improving the patient's prognosis.

Key words: Bisphosphonate; Breast cancer; Cone-beam CT; MRONJ

Introduction

Primary solid tumors, especially those originating in the breast, or the prostate commonly metastasize in the bone often predisposing the patients to complications such as bone loss, pain and fractures.[1] Besides this, diseases such as osteoporosis, giant cell tumor of the bone, hypercalcemia of malignancy and Paget disease of bone also commonly lead to such bone complications. Bisphosphonates, denosumab and zoledronic acid are some of the commonly prescribed medications to avoid or reduce the severity of these bone complications. Furthermore, it has been found that in individuals with bone metastases, a lack of prophylactic use of these medications could leave them susceptible to requiring radiotherapy for reducing bone pain and even experiencing pathologic fractures. Bisphosphonates are small molecules that latch onto the hydroxyapatite-binding sites on bone surfaces.[1–4] As a result of the action of the osteoclasts on the affected bone, the bisphosphonate molecules are released which then cause apoptosis of the osteoclast by binding to the farnesyl pyrophosphate synthase within them disrupting intracellular signaling. This helps to prevent further resorption thereby minimizing bone complications and are therefore considered to be effective antiresorptive drugs. Additionally, it has been found that these bisphosphonate molecules have a very short half-life although they remain accumulated within the bone matrix resulting in its effects to last for over three years post last administration, particularly in osteoporosis condition.[5]

First reported in 2003, Medication Related Osteonecrosis of the Jaw (MRONJ) is an adverse reaction to drugs that prevent bone complications such as bisphosphonates, denosumab, zoledronic acid and some others.[1] The condition was initially termed Bisphosphonate Related Osteonecrosis of the Jaw until 2014, when the American Association of Oral and Maxillofacial Surgeons changed

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the name to MRONJ, due to association of the condition to other antiresorptive and antiangiogenic agents such as denosumab. MRONJ is considered to be a multifactorial condition with no complete evidence for its pathogenesis, although some reports suggest a likely harmonious play between the local trauma or infection and the reduced bone turnover post exposure to medications such as bisphosphonates.[6] It most commonly manifests as painful bone exposure in the maxillofacial region and is more prevalent in patients prescribed on high cumulative doses of these medications.[1] However, the safe threshold of these medications below which MRONJ can be prevented is yet unknown. Some recent studies suggest that local dental and periodontal infections can precede the necrosis of bone while some animal and clinical studies are suggestive of involvement of such infections in the development of MRONJ. Furthermore, a study conducted on patients having MRONJ also showed abundance of total bacteria levels at the site of the jaw lesion despite treating with doxycycline and metronidazole.[7]

Dental procedures such as tooth extractions or periodontal surgery that expose the bone in the maxilla or mandible can trigger MRONJ.[8] Thus, dentists play a pivotal role in treatment of patients who have a history or are currently on medications such as bisphosphonates to help with the prevention and early diagnosis of MRONJ. In accordance with this, the American Society of Clinical Oncology and Cancer Care Ontario made the following recommendation: "A dental assessment is recommended, where feasible, before commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with before starting treatment, if possible."[1] As MRONJ can be multifactorial, its symptoms can vary and can often also be asymptomatic.[6] In general, increasing the awareness and establishment of a good physician-dentist communication regarding the prevention and treatment of MRONJ can substantially reduce the risk of severity of the condition.[1] MRONJ although commonly associated with exposed bone, there are about 30% of cases that occur without bone exposure.[9] In such situations, radiographic evaluation can play a significant role in the early diagnosis of MRONJ. Anatomical imaging techniques such as panoramic radiographs, computed tomography (CT), cone-beam computed tomography (CBCT), and magnetic resonance imaging (MRI) are amongst the most commonly used imaging techniques to help diagnosis of MRONJ.[9]

Case Report

A 47-year-old female presented with pain and swelling in the left posterior region of the mandible. Additionally, numbness and tingling of the lower left lip was also reported. Her medical history was significant for breast cancer with ongoing bisphosphonate therapy without any prior history for exposure to radiation. The patient revealed a history of tooth extraction 3 months ago in the same region. Upon oral examination of the region of complaint, the dentist found an unhealed extraction socket with exposed bone in association with the extracted tooth 35 and recommended a panoramic radiograph. She was then referred to the Division of Oral and Maxillofacial Radiology at the School of Dentistry at University of Mississippi Medical Center where a maxillofacial Cone-beam CT (CBCT) extending from the level of sphenoid sinus to the inferior border of the mandible was performed for further evaluation.

Radiographic findings: Oral and radiographic examination confirmed the presence of almost all the teeth except the four third molars, right upper and lower second molars and left lower second premolar. Besides, generalized mild to moderate periodontal bone loss was also observed for the teeth present. Both the panoramic radiograph as well as the CBCT confirmed the presence of an extraction socket and exposed bone at the site of the missing tooth in the mandibular left posterior region of the mandible (tooth 35). The panoramic radiograph showed evidence of widening of the PDL space with possible furcation involvement in the left mandibular and bilateral maxillary posterior regions (Figure 1) which was further confirmed on the sagittal view of the CBCT evaluation (Figure 2). Additionally, the bone surrounding the extraction site of tooth 35 appeared to be comparatively denser and more radiopaque indicating diffuse sclerosis in the region (Figure 2). Furthermore, the axial view revealed similar diffuse sclerosis of the bone bilaterally in the maxillary posterior regions along with disruption of the palatal cortical plate at the site of tooth 26 (Figure 3). On the other hand, the axial view of the mandible showed presence of diffuse sclerotic bone only in the left para-symphysis and posterior region in addition to association with a periosteal bone reaction in the left para-symphysis region (Figure 3). In addition to these features, maxillary tori were observed in the midline as well as in the posterior regions. The soft tissue in the region of the adenoids revealed the appearance of a small radiopaque entity and is likely suggestive of a nasopharyngeal tonsillith. The soft tissue of the maxillary sinuses appear to be thickened which is likely suggestive of mucositis. Additionally, the floor of the right maxillary sinus in the region of the apex of tooth number 15 appeared to be disrupted. Furthermore, a radiopaque, dome-shaped mass was found to be located on the floor of the right maxillary sinus and is suggestive of mucus retention pseudocyst. Besides these findings, the ostiomeatal complexes and the visualized portions of the airway appeared to be patent. The bone pattern and jaw morphology (other than mentioned above) were found to be within the range of normal.

Diagnosis and management: Based on the above findings, MRONJ, Osteoradionecrosis, and Osteomyelitis were considered in the differential diagnosis. Considering a history of exposure to bisphosphonate medication, the final diagnosis was conclusive of MRONJ. Management of the condition involved performing curettage and debridement at the extraction site in addition to hyperbaric oxygen therapy. Management primarily aimed at alleviating pain and suppressing the symptoms of infection through use of antibiotic mouth rinses and systemic Doxycycline antibiotic therapy.

Discussion

Breast cancer is one of the most prevalent cancers worldwide, and one of the most common adverse events experienced by patients without bone metastases is cancer treatment-induced bone loss (CTIBL).[10] Moreover, patients with advanced-stage breast cancer may develop bone metastases and can have a high incidence for CTIBL ranging from about 60%–75%. Bisphosphonates are the main class of antiresorptive drugs used to prevent bone complications in such situations and act by preventing the osteoclast-mediated bone resorption.[2,5] Moreover, in patients with breast cancer without bone metastasis, bisphosphonates have also been used as an effective adjuvant therapy.[11] However, aside from its benefits they can cause severe side effects in the form of bone destruction and bone necrosis. MRONJ is an adverse reaction to such antiresorptive medication drugs.[1] The duration of exposure and dosage of these medications are additional factors that can influence the onset of MRONJ, which is associated with significant morbidity and a disruption in the patient's quality of life, posing a challenge to its treatment. Besides bisphosphonates, some other medications such as denosumab and zoledronic acid have also been known to cause MRONJ. However, it has been found that the incidence of MRONJ in patients taking bisphosphonates is higher than that for other medications.[12] In keeping with that, MRONJ has been commonly reported as a long-term complication of bisphosphonate medication for more than a decade now.[13] The complete mechanism of MRONJ is not well understood and is often considered to be multifactorial. Over the years MRONJ is associated with several risk factors amongst which malignant disease (100 times greater risk) and use of intravenous bisphosphonates are the most common.[14] Furthermore, it has been found that the risk of MRONJ development increases post bone involving invasive dental procedures such as

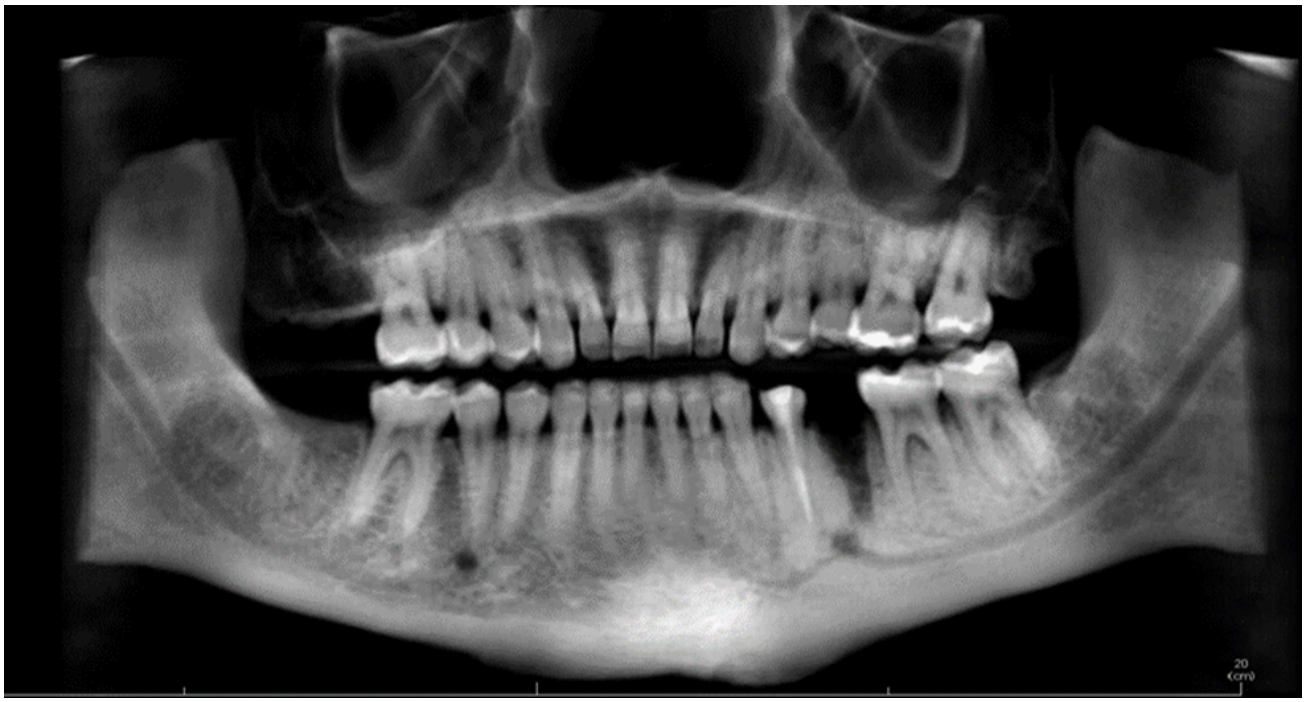

Figure 1. Panoramic radiograph depicting extraction socket at the site of missing tooth 35 and evidence of widening of the PDL space with possible furcation involvement in the left mandibular and bilateral maxillary posterior regions.

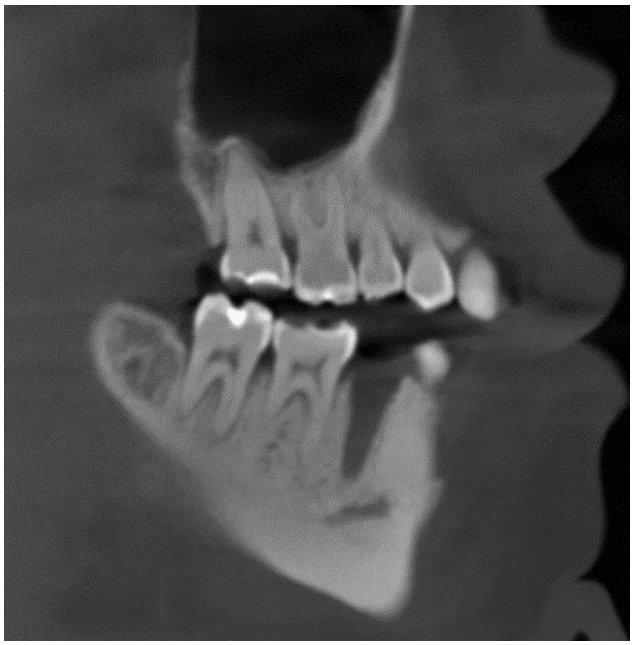

Figure 2. The sagittal view of CBCT showing diffuse sclerosis of bone surrounding the extraction site of tooth 35 and in the left maxilla.

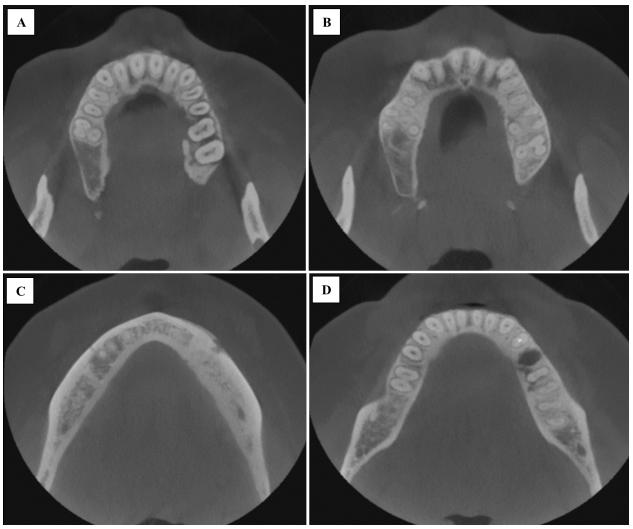

Figure 3. CBCT imaging A. Axial view of shows sclerosis of maxillary bone and disruption of the palatal cortical plate on left side. B. Axial view of maxilla showing sclerotic bone changes both sides of maxilla. C. Axial view of mandible depicts periosteal bone reaction on the left side of the mandible. D. Axial view of mandible demonstrates extraction socket at the site of tooth 35 with sclerosis of bone and widening of PDL spaces of multiple teeth.

tooth extraction, dental implant, and apical or periodontal surgery.[2] Studies conducted indicate that among patients diagnosed with MRONJ, tooth extraction was the predisposing event, ranging from 62% to 82%.[15,16] Additionally, the risk of developing MRONJ after a tooth extraction in patients with ongoing bisphosphonates therapy ranged from 1.6% to 14.8%.[8] According to literature, there are primarily three factors that qualify for a conclusive diagnosis of MRONJ: a history of or active treatment of an antiangiogenic or antiresorptive medication, lack of history of exposure to radiation in the head or neck region, and exposed bone in the oral cavity persisting for more than eight weeks.[8] The case presented in our study shows a medical history for breast cancer with ongoing bisphosphonates therapy without any history of previous radiation exposure with an oral manifestation of exposed bone in the left posterior region of the mandible three months post tooth extraction in addition to pain, swelling and supportive radiographic findings qualifies it for a diagnosis of MRONJ. Concerning the differential diagnosis, osteoradionecrosis can be ruled out since no radiation therapy was involved in the patient's treatment.[17] Although, osteomyelitis does present with symptoms similar to MRONJ; the patient was on bisphosphonate therapy which helps conclude on a diagnosis for MRONJ.

Panoramic radiographs and CBCT have been routinely used for

diagnosis of MRONJ.[2,9,18] Commonly panoramic radiographs used for diagnosis of MRONJ have shown signs of osteonecrosis ranging from increased trabecular bone density, non-healing extraction sockets, sequestrum formation with radiopacity surrounding the necrotic bone, thickening of the lamina dura, cortical border of the mandibular canal and maxillary sinus floor, enlargement of the periodontal ligament space, periosteal reaction, and the appearance of a pathological fractures. In addition to these, CBCT diagnosis of MRONJ can show more detailed features such as osteosclerosis and osteolysis, irregularities and destructions at the borders of cortical bones, cortical bone perforation and sequestrum formation. In our study, a combination of panoramic radiograph and CBCT findings were used for the diagnosis of MRONJ. The findings indicated presence of exposed bone in association with the extraction socket in addition to widening of the PDL space with possible furcation involvement and diffuse sclerosis in the region of tooth number 35. Additionally, diffuse sclerosis was also seen bilaterally in the maxillary posterior region of the jaw with disruption of the palatal cortical plate in the region of tooth number 26. MRONJ most commonly affects the posterior region of either the mandible or the maxilla while a simultaneous presentation in both jaws is a rarity. A thorough literature search found that only 4.5% of the cases show involvement of both maxilla and mandible similar to what was observed in our study.[19]

Staging of MRONJ plays an important role especially for the purpose of treatment planning.[20] MRONJ has been classified into several stages starting from zero up to three by the American Association of Oral and Maxillofacial Surgeons (AAOMS) based on the disease associated symptoms and the corresponding treatment options.[2] The stage 2 condition comprises of exposed and necrotic bone or fistulae that probe to the bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage. Conservative treatment in the form of use of antimicrobial mouthwash and systemic antibiotic is a reliable method and is commonly the first line of treatment advised in most MRONJ cases. Immediate treatment besides this involves adequate pain control measures combined with debridement to reduce soft tissue irritation and suppress infection. Based on this classification the case presented in our study can be diagnosed as a stage 2 MRONJ condition. In keeping with this diagnosis, the management of the condition in the present case study was primarily aimed at alleviating pain and suppressing the symptoms of infection through use of topical antibiotic mouth rinse and systemic antibiotic therapy. Additionally, curettage and debridement was performed at the extraction site along with hyperbaric oxygen therapy (HBOT). Previously, it has been shown that HBOT in MRONJ cases can help reduce edema and swelling, enhance wound healing, stimulate stem cell mobilization, and reduce the suppression of bone regeneration resulting from the use of bisphosphonate medication.[8] It is noteworthy, as a final observation, that due to the complexities associated with the diagnosis and treatment of MRONJ, prevention becomes paramount. Opting for a multidisciplinary approach is crucial, necessitating the education and awareness of healthcare professionals regarding MRONJ. Consequently, when contemplating the use of bone-modifying agents, dental assessments should take precedence, provided the patient's systemic condition allows. The overall general and oral health of the patient will play a pivotal role in mitigating the risk of MRONJ.[5,8]

Conclusion

MRONJ is a rare but serious condition caused by the use of antiresorptive or antiangiogenic medications. The current study highlights an interplay between bisphosphonate cancer therapy and the development of MRONJ leading to morbidity and adversely affecting the quality of life of the suffering patients. It further reinforces the importance of correlating clinical findings with radiographic imaging for timely diagnosis of MRONJ which can help improve the prognosis and treatment outcomes. Dental professionals play an important role in the prevention, early diagnosis, and management of MRONJ, especially in patients receiving medications such as bisphosphonates. As invasive dental procedures pose a high risk for development of MRONJ, dental examinations should be recommended before initiating bisphosphonate therapy. Finally, increasing the awareness and establishment of good physician-dentist communication regarding the prevention and treatment of MRONJ can substantially reduce the risk of severity of the condition.

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Author Contributions

A.P, P.T, N.B, B.D. and M.R. wrote the manuscript. R.J. diagnosed the condition. J.L, and R.J. participated in the study design and coordination and approved the final manuscript. All authors read and approved the final manuscript.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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