Medication-related osteonecrosis of the jaw: A multifaceted diagnostic challenge. Mini review

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Abstract: Medication-related osteonecrosis of the jaw (MRONJ) may present a challenge to the dental clinician due to the many presentations that it can have. This condition can be caused by multiple medications including bisphosphonates, RANKL ligand inhibitors and antiangiogenic drugs. Cases were reported in multiple sites of both the maxilla and mandible, including the hard palate, mylohyoid area, and the buccal plate. The risk factors for this condition include the use of a combination of antiresorptive medications, trauma, periodontal disease, immunosuppression, dental trauma, dental extractions, and bone manipulations. Spontaneous MRONJ have been reported in about half of the cases. Conventional radiographs are not conducive to a diagnosis, underscoring the importance of a three-dimensional modality in the diagnosis of MRONJ. The multifaceted diagnostic challenges of MRONJ are underscored in this mini review. (*Am J Dent* 2022;35:109-112).

Clinical significance: MRONJ can have diverse presentations and a lengthy multisite involvement. Therefore, long-term follow up for patients with history of use of antiresorptive medications is recommended.

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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a severe bone reaction that consists of progressive bone destruction in the maxillofacial region, which includes exposed necrotic bone that has persisted for more than 8 weeks with no history of radiation or metastatic disease to the jaws.[1] The main causes are pharmacological agents that are antiresorptive, antiangiogenic, or other immunosuppressive medications.[1,2]

The pathophysiology of MRONJ is not fully elucidated but appears to be multifactorial. There are several hypotheses considering high bone turnover of the mandible, inflammation, infection, the oral microbiome, trauma, immunity, and genetics.[3]

The severity of MRONJ is currently measured through a staging system (0-3). Stages 1-3 are defined by bone exposure in the oral cavity. Stage 0 has no clinical evidence of bone exposure, but radiological findings are present. Early diagnosis is crucial for the treatment of MRONJ.[4]

The duration of time that the patient was taking the medication affects the prevalence, prognosis, and severity of MRONJ.[1,5,6] In addition, the condition can present and persist for years after the use of the medication was stopped. Low plasma concentration of zoledronic acid can be observed up to 28 days post-dose.[7] Although the half-life of zoledronic acid in serum is days, it can remain in bone, preferentially those with high turnover rates like the mandible.[8] This may be due to the mandible experiencing daily bone remodeling around the periodontal ligaments.[8] For this reason, discontinuing the drug for several months before extractions will have little effect because the bisphosphonates would have already been incorporated into the bone.[9] After bisphosphonates bind to the bone, they are not released again until the bone to which they bind is resorbed.[10]

Only a few cases of MRONJ have cited involvement of both the maxilla and mandible in the same patient over a period of 2 years[11,12] (Fig 1A,B). Bone exposures may occur in multiple sites of the mouth, both synchronous and asynchronous, with different clinical presentations, such as varying sizes of bone exposures and the presence of sinus tracts (Fig 1C). New appearances may occur for extended periods of time in the maxilla and the mandible even years after cessation of the drug.

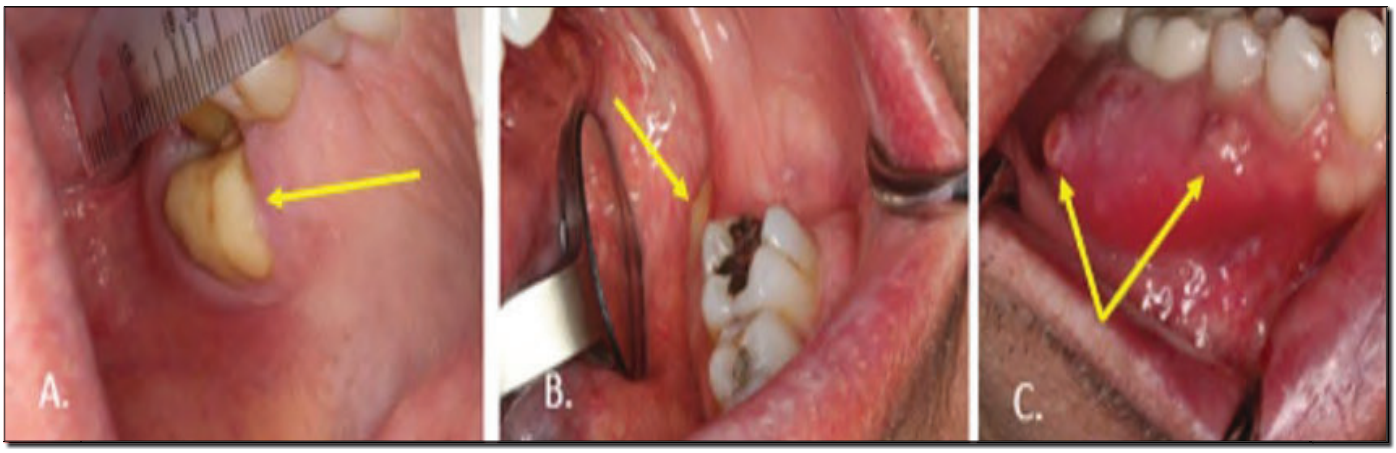

Fig. 1. **A.** 12 × 0.5 cm area of exposed one in the maxillary right palate with minor inflammation. **B.** 3 × 2 mm of bone exposure on the posterior portion of the left mylohyoid line. **C.** Soft tissue with abscess-like of the gingiva of tooth #29-#31 (ADA system).

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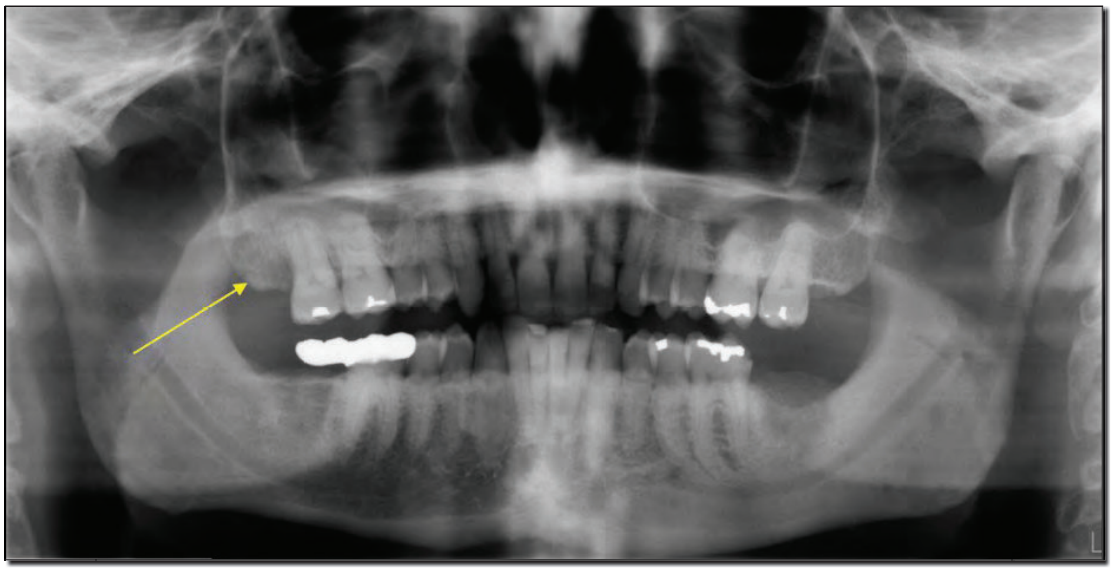

Fig. 2. Pantomograph not showing radiolucency or radiopacity in the upper right.

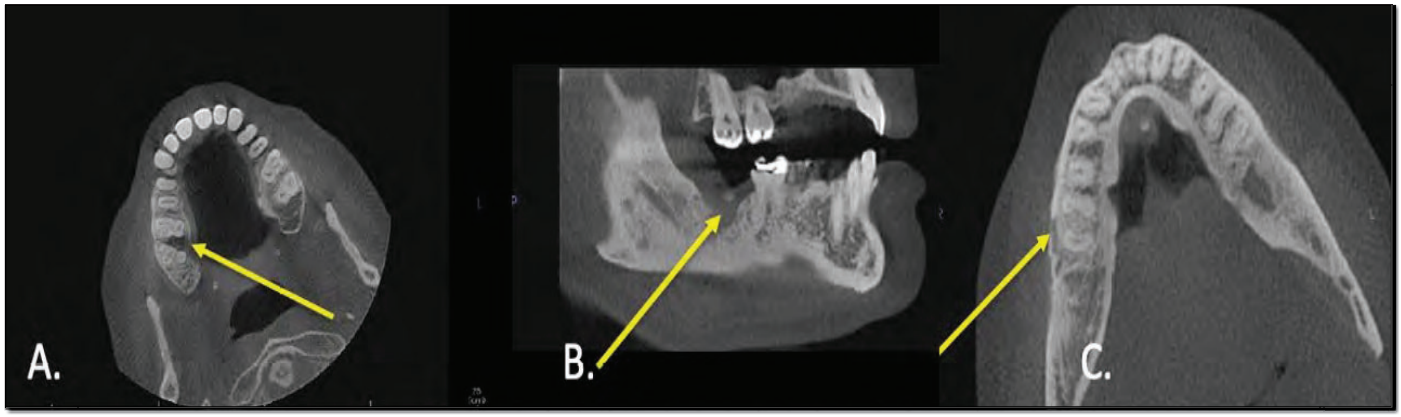

Fig. 3. MRONJ site on CBCT. **A.** Mixed density on the palatal region of tooth #3 (ADA system). **B.** Mixed radiolucency and radiopacity in the region of missing tooth #18 (ADA system). **C.** Bone resorption and perforation of the cortex of the mandible in the region of tooth #29 to #31 (ADA system).

This mini review presents the multifaceted challenges associated with MRONJ.

Discussion

MRONJ cases may be manifested in many forms and may present a challenge to the dental clinician.[13] Some of the signs used in the staging system can overlap with other dental conditions, leading to a misdiagnosis of periodontal or endodontic lesions that mask MRONJ. It has been previously observed that a nonhealing lesion after conventional root canal therapy, periodontal surgery, and extraction was diagnosed as MRONJ.[14] In addition, periodontal, endodontic disease and MRONJ can be interconnected.[15] Although optimal treatment for MRONJ has not been established, surgical debridement is commonly performed in Stages 1-3.[16] Small sample case series also suggest that preventive treatment such as combination of tocopherol and pentoxifylline can provide effective relief to patient's symptoms.[17,18] The approach modality should be explored on a case-by-case basis, but there is moderate strength recommendation for preventive dental treatment before a patient is scheduled to receive bone-modifying agent therapy for underlying conditions.[19]

Dentoalveolar and periodontal surgery are the major risk factors associated with MRONJ,[20] but it appears that smaller traumatic events can also contribute to bone exposure and many cases may appear spontaneously.

The two-dimensional modality of a conventional pantomograph does not always capture the bone resorption (Fig. 2) and may not be conducive to a diagnosis. The importance of a three-dimensional modality such as a CBCT (Fig. 3) for the diagnosis of MRONJ has previously been demonstrated.[21]

Risk factors for MRONJ can include both systemic and local factors. Systemic factors include age, race, corticosteroid use, diabetes mellitus, tobacco use, immunosuppression and length of therapy.[22,23] Local factors for MRONJ include recent history of trauma, location in the jaw, periodontal disease, anatomy of the maxilla and mandible, and the presence of sinus tracts and deep periodontal pockets that may present even before necrotic bone exposure.[24] Increased age, dental procedures, trauma, periodontal disease, white race, the use of immunosuppressant medications such as dexamethasone, and the use of nitrogen containing IV bisphosphonates for prolonged periods are all risk factors for MRONJ. A combination of different bisphosphonates (pamidronic and zoledronic acid)

Table. Literature review of MRONJ in single vs. multiple sites.

Author	Sites
Kim et al[29]	Mandible only
Drudge-Coates et al[30]	Maxilla only
Fornaini et al[31]	Mandible only
Dunphy et al[11]	Both maxilla and mandible
Bumm et al[32]	Maxilla only
Lyttle et al[33]	Mandible only
Van Camp et al[34]	Mandible only
Javelot et al[12]	Both maxilla and mandible
Bouland et al[35]	Mandible only
Bennardo et al[36]	Maxilla only
Torres et al[37]	Mandible only
Matsuda et al[38]	Mandible only
Dennis et al[39]	Maxilla only
Diniz-Freitas M et al[40]	Mandible only
Kiho et al[41]	Maxilla only
Del Pilar Rodríguez-Sánchez et al[42]	Maxilla only
Gupta et al[43]	Mandible only
Myoken et al[44]	Mandible only

may be more conducive for MRONJ; however, it is unclear at the moment whether synergistic effects would increase the occurrence of MRONJ, but this area should be further explored.[25,26]

Many case reports have demonstrated a solitary presentation of exposed necrotic bone, but few have reported more than one arch or one lesion (Table). Cases of MRONJ can continue to occur for long periods of time following the cessation of antiresorptive medications, presenting as Stage 1 necrotic bone exposures without infection, to Stage 2 infected bone with abscess or fistulas and experience of pain and advanced Stage 3 with severe bone perforation.[27,28] Sometimes, the lesions present as sinus tracts that appear too far from the apex to be of endodontic origin and therefore require evaluation by a periodontist. In many instances MRONJ requires a multidisciplinary approach for proper management of the condition, involving the specialties of Oral Medicine, Oral and Maxillofacial Radiology, Periodontics, Endodontics, and Oral and Maxillofacial Surgery.

Conclusion

MRONJ related bone exposure can happen in any site of the mouth without a preceding dental procedure. Precautions should be taken when treating patients with history of use of bisphosphonates. Patients can have multiple sites of bone exposure in different arches and areas of the mouth over a long period. The diagnosis and treatment of MRONJ can present a challenge to the dental clinician and a multidisciplinary approach may be necessary for diagnosis and treatment.

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