Letter to the Editor

MEDICATION-RELATED OSTEONECROSIS OF JAW

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INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) primarily occurs as a complication of bone antiresorptive treatment in specific bone treatment modalities. It was first identified in 2003 as a bisphosphonate (BP) treatment complication. Denosumab is a molecule with a particular mode of action. This molecule inhibits bone resorption by suppressing osteoclast function. BPs have a strong affinity for hydroxyapatite crystals and remain in bone for years. The pathogenesis of MRONJ is not fully explained and appears multifactorial.

Hypotheses include impaired jaw bone vascularization due to antiangiogenic effects, altered bone remodeling, direct toxicity of BPs for soft tissue, specific infections, vitamin D deficiency, reduced salivation, constant jaw micro-traumas, and genetic factors. Patient education about oral cleanliness and maintenance becomes essential. Diagnosing and resolving any dental infection during antiresorptive treatment is essential to avoid harmful effects. Histological analysis of the resected bone is mandatory to rule out degenerative transformation.

When discussing antibiotics as a treatment form in this situation, the amoxicillin group of drugs may be considered for a brief interval. Oxygen in the hyperbaric mode has also been found to be a supportive therapy.

Osteonecrosis of the jaws is often known by historical names like "phossy jaw" due to its whitish appearance, which resembles phosphorus. It has been a subject of interest in oral and maxillofacial pathology since the 19th century (1-5).

Medication-related osteonecrosis of the jaws (MRONJ) primarily occurs as a complication of bone antiresorptive treatments. It was first identified in 2003 as a bisphosphonate (BP) treatment complication. MRONJ is not exclusive to bisphosphonate. Other enzyme inhibitors have been reported in this context. Many terminologies depicting this clinical

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condition have been mentioned in previous literature. Higher risk in MRONJ is identified as a significant adverse event associated with bisphosphonates (BP) and denosumab, primarily occurring in an oncological context (6-8).

Risk

The risk of developing MRONJ is significantly higher in cancer patients compared to osteoporosis patients. The prevalence of MRONJ in cancer patients receiving high doses of intravenous (IV) BP is noted to be less than 1%. The overall risk for MRONJ among cancer patients exposed to these categories of drugs is less than 7%. Patients with multiple myeloma receiving IV ZA (intravenous zoledronic acid) treatment are highlighted as having the highest risk, but there is a low risk in osteoporotic patients (9,10).

Medication and its mechanism of action

The medication works by blocking the enzymatic pathway for bone resorption, which affects bone metabolism. BPs exhibit both in vitro and in vivo antiangiogenic effects. This property is used in osteoporosis and cancer-related conditions such as bone metastases, multiple myeloma, and hypercalcemia of malignancy to reduce osteoporosis-related fractures and improve the quality of life in advanced cancers involving bones. All these groups of medications have a specific effect on the bone metabolic pathway (11-13).

Pathogenesis

The pathogenesis of MRONJ is not fully explained and appears multifactorial. Hypotheses include impaired jaw bone vascularization due to antiangiogenic effects, altered bone remodeling (14), direct toxicity of BPs for soft tissue, specific infections, vitamin D deficiency, reduced salivation, constant jaw micro-traumas, and genetic factors. In vivo, antiangiogenic effects of BPs may contribute to MRONJ by impairing post-interventional healing due to reduced blood vessel formation. Tooth extraction is a common triggering factor. However, MRONJ can also appear spontaneously (15).

Clinical features

The American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria are often used for diagnosis. Characteristics include exposed bones persisting for more than two months with no other significant medical history in addition to these treatment methods. It is essential to differentiate this status from conditions like osteoradionecrosis, osteitis, malignancies, osteomyelitis, and fibro-osseous disease. There are a few other signs, like pain, altered neurosensory function, loosening of teeth, local swelling, infections, or halitosis.

Radiographic appearance

Radiographic findings include subperiosteal bone deposition, osteolysis, changes in trabecular pattern and densely woven bone. Histological examination is not mandatory for MRONJ diagnosis but is typically performed after surgical resection. Necrotic non-viable bone, necrosis, fibrosis of marrow spaces, hypocellularity, hypovascularity, fibrotic mucosa, and periosteum are present. Potential complications include repeated infections, fistulae, and pathologic fractures. In a few cases, spontaneous healing is seen, often after eliminating the bony sequestra (16).

It has been reported that panoramic radiography can provide an immediate view of the lesion. However, this method is not advantageous in detecting early bony changes and other features of MRONJ, such as fragmentation of bone and sinus communication (17).

Prevention protocol

Doctors should delay antiresorptive therapy until dental treatment is completed, including replacing or modifying ill-fitting dentures. Routinely checking oral hygiene is necessary to assess the risk. Diagnosing and resolving any dental infection during antiresorptive treatment is also a requirement.

Tooth extraction must be performed. Individual risk estimation for tooth extraction, considering parameters related to the patient, has to be well evaluated in advance, and the planned procedure can then be executed. Temporary discontinuation of therapy has been previously recommended for osteoporosis patients before and after invasive dental surgery, but current evidence on altering MRONJ risk is inconclusive.

If root fragments or crowns are present in the oral cavity, they should be addressed to curb the risk after the therapy is underway. The placement of dental implants is contraindicated. No evidence supports discontinuing IV BP therapy before invasive dental treatment (18).

Denosumab is associated with a faster reversal of antiresorptive effects compared to BPs. The potential for a six-month drug holiday before invasive dental procedures is suggested, but evidence is lacking in the literature.

Surgical procedures should be performed with caution, associated with antibacterial mouthwash before and after surgery, along with prophylactic oral antibiotics. Quadrant-by-quadrant procedures with a two-month delay between them, minimizing trauma, achieving primary closure, and minimizing vasoconstrictor use are recommended (19).

Treatment

Conservative therapy is the primary approach, aiming to control pain and infection and minimize the progression of bone osteonecrosis. While conservative therapy may not completely resolve the lesion, it can provide long-term relief from symptoms. The objectives include controlling pain and infection. Efforts are made to minimize the progression of bone osteonecrosis.

Discontinuation of antiresorptive treatment is mandatory in the development of MRONJ. Regardless of the disease stage, improving oral hygiene and patient education are mandatory. The initial stage is related to symptoms like unexplained pain, altered neurosensory function, and unexplained tooth loosening. Features of radiography vary and need to be appropriately evaluated (6).

Establishing clinical diagnosis and stage with instrumentation of advised protocol for lesions standing on for over two months is of paramount importance. Surgical removal of necrotic bone sequestrum should be considered, preferably without exposing uninvolved bone. With the advancements in the surgical field, surgery is now possible at any disease stage.

When conservative methods fail, surgery becomes the only option to preserve the important bony structure for susequent structural and functional rehabilitation. Histological analysis of the resected bone is mandatory to rule out malignant transformation.

Antibiotic therapy of the penicillin group, such as amoxicillin and clavulanic acid, is the first-line treatment for infections (20). Oxygen in the hyperbaric form has been tried along with several other methods.

CONCLUSIONS

Osteonecrosis of the jaws depicts fatality and leads to a poor quality of life. The medications and the pathways associated with MRONJ must be studied in depth. Retrospective analysis of the cases and histopathological correlation may contribute to a better treatment outcome. The topic of osteonecrosis is explored by dental surgeons and oral specialists.

REFERENCES

1. Minervini G, Franco R, Marrapodi MM, Fiorillo L, Cervino G, Cicciù M. The association between parent education level, oral health, and oral-related sleep disturbance. An observational crosssectional study. *European Journal of Paediatric Dentistry*. 2023;24(3):218-223. doi:https://doi.org/10.23804/ejpd.2023.1910
2. Inchingolo F, Tatullo M, Marrelli M, et al. Clinical trial with bromelain in third molar exodontia. *European Review for Medical and Pharmacological Sciences*. 2010;14(9):771-774.
3. Inchingolo F, Tatullo M, Pacifici A, et al. Use of dermal-fat grafts in the post-oncological reconstructive surgery of atrophies in the zygomatic region: clinical evaluations in the patients undergone to previous radiation therapy. *Head & face medicine*. 2012;8(1). doi:https://doi.org/10.1186/1746-160x-8-33
4. Kün-Darbois JD ., Fauvel F. Medication-related osteonecrosis and osteoradionecrosis of the jaws: Update and current management. *Morphologie*. 2020;105(349). doi:https://doi.org/10.1016/j.morpho.2020.11.008
5. Minervini G, Franco R, Marrapodi MM, Almeida LE, Ronsivalle V, Cicciù M. Prevalence of temporomandibular disorders (TMD) in obesity patients: A systematic review and meta-analysis. *Journal of oral rehabilitation*. 2023;50(12):1544-1553. doi:https://doi.org/10.1111/joor.13573
6. Ghidini G, Manfredi M, Giovannacci I, et al. Medication-related osteonecrosis of the jaw: risk factors in patients under biphosphonate versus patients under antiresorptive-antiangiogenic drugs. *Minerva Dental and Oral Science*. 2017;66(4). doi:https://doi.org/10.23736/s0026-4970.17.04056-0
7. Lund T, Gundesen MT, Vangsted AJ, et al. In multiple myeloma, monthly treatment with zoledronic acid beyond two years offers sustained protection against progressive bone disease. *Blood cancer journal*. 2024;14(1). doi:https://doi.org/10.1038/s41408-024-01046-2
8. Qi C, Sun Q, Xiao D, et al. Tetrahedral framework nucleic acids/hyaluronic acid-methacrylic anhydride hybrid hydrogel with antimicrobial and anti-inflammatory properties for infected wound healing. *International Journal of Oral Science/International journal of oral science*. 2024;16(1). doi:https://doi.org/10.1038/s41368-024-00290-3
9. Lončar Brzak B, Horvat Aleksijević L, Vindiš E, et al. Osteonecrosis of the Jaw. *Dentistry Journal*. 2023;11(1):23. doi:https://doi.org/10.3390/dj11010023
10. Zhao L, Lai Y, Jiao H, Huang J. Nerve growth factor receptor limits inflammation to promote remodeling and repair of

osteoarthritic joints. *Nature communications*. 2024;15(1). doi:https://doi.org/10.1038/s41467-024-47633-6

11. Huang N, Wang P, Gong P, Huang B. The Progress in Reconstruction of Mandibular Defect Caused by Osteoradionecrosis. *Journal of Oncology*. 2023;2023:1-12. doi:https://doi.org/10.1155/2023/1440889
12. Rasteniene R, Simenaite G, Zaleckas L, Aleksejuniene J. Non-odontogenic maxillofacial infections – a 17-years retrospective cohort study. *Oral and maxillofacial surgery*. 2023;28(1). doi:https://doi.org/10.1007/s10006-023-01162-6
13. Shin JW, Kim JE, Huh KH, et al. Radiological manifestations and clinical findings of patients with oncologic and osteoporotic medication-related osteonecrosis of the jaw. *Scientific reports*. 2024;14(1). doi:https://doi.org/10.1038/s41598-024-59500-x
14. Piattelli A, Scarano A, Piattelli M. Detection of alkaline and acid phosphatases around titanium implants: a light microscopical and histochemical study in rabbits. *Biomaterials*. 1995;16(17):1333-1338. doi:https://doi.org/10.1016/0142-9612(95)91049-5
15. Ciobanu GA, Camen A, Ionescu M, et al. Risk Factors for Medication-Related Osteonecrosis of the Jaw—A Binomial Analysis of Data of Cancer Patients from Craiova and Constanta Treated with Zoledronic Acid. *Journal of Clinical Medicine*. 2023;12(11):3747. doi:https://doi.org/10.3390/jcm12113747
16. Polyane Mazucatto Queiroz, Karolina Castilho Fardim, Luiz A, Ricardo Alves Matheus, Pereira L. Texture analysis in cone-beam computed tomographic images of medication-related osteonecrosis of the jaw. *Imaging science in dentistry*. 2023;53(2):109-109. doi:https://doi.org/10.5624/isd.20220202
17. Christoph Klingelhöffer, Manja Klingelhöffer, Steffen Müller, Ettl T, Ulrich Wahlmann. Can dental panoramic radiographic findings serve as indicators for the development of medication-related osteonecrosis of the jaw? *Dentomaxillofac Radiol*. 2016;45(5):20160065-20160065. doi:https://doi.org/10.1259/dmfr.20160065
18. Pan J, Liu JY. Mechanism, prevention, and treatment for medication-related osteonecrosis of the jaws. *Hua Xi Kou Qiang Yi Xue Za Zhi = Huaxi Kouqiang Yixue Zazhi = West China Journal of Stomatology*. 2021;39(3):245-254. doi:https://doi.org/10.7518/hxkq.2021.03.001
19. Akashi M, Wanifuchi S, Iwata E, et al. Differences between osteoradionecrosis and medication-related osteonecrosis of the jaw. *Oral and Maxillofacial Surgery*. 2017;22(1):59-63. doi:https://doi.org/10.1007/s10006-017-0667-5
20. Wang Z, Xu J, Wan J, Zhang W, Wang Y, Du Y. Vascular Analysis of Soft Tissues Around the Bone Lesion in Osteoradionecrosis, Medication-Related Osteonecrosis, and Infectious Osteomyelitis of the Jaw. *The Journal of craniofacial surgery*. 2022;33(7):e750-e754. doi:https://doi.org/10.1097/scs.0000000000008697