

CLINICAL VIGNETTE

A 74-Year-Old Female with a Refractory Oral Ulcer

William Martin, MD and Olga Popel, MD, MBA

Case Summary

A 74-year-old female presented to rheumatology for evaluation of a refractory oral ulcer posterior to her right lower molars. She was diagnosed with undifferentiated connective tissue disease 30 years prior, based on positive anti-nuclear antibody (ANA), recurrent pericarditis, and arthritis/arthralgias. She improved on hydroxychloroquine for nearly 20 years. Eight years prior she developed a rash thought secondary to the hydroxychloroquine which was stopped. Her arthritis symptoms had been subsequently managed with NSAIDs. She developed a painless oral ulcer 2 months prior to presentation. The ulcer extended to exposed bone. X-ray was negative and her dentist and periodontist felt the ulcer was related to her connective tissue disease. It did not improve with topical triamcinolone paste, or a course of oral methylprednisolone.

Other past medical history included osteoporosis, cervical and lumbar degenerative disc disease, right knee osteoarthritis, and squamous cell carcinoma. Family and social history were non-contributory. Medications included celecoxib, tramadol, calcium, cholecalciferol, lansoprazole, and denosumab. On presentation, she was afebrile, with blood pressure 175/72, pulse 58, and RA oxygen saturation 97%. Physical exam noted a 1-centimeter mucosa ulceration posterior to the right lower molars. There was no synovitis on joint examination, and no rashes or alopecia. Laboratory evaluation was unremarkable other than borderline lymphopenia (absolute lymphocyte count 1,270 per microliter). Comprehensive metabolic panel, double stranded DNA antibody, C3, C4, sedimentation rate, and c-reactive protein, were all normal.

She was referred to an oral pathologist who documented osteonecrosis of bone adjacent to the ulceration. She was diagnosed with medication-related osteonecrosis of the jaw (MRONJ), secondary to denosumab, and was started on pentoxifylline and was advised to avoid further anti-resorptive therapy.

Discussion

MRONJ is characterized by non-healing exposed or necrotic bone in the maxillofacial area. It is a known risk in patients taking antiresorptive osteoporosis agents, including denosumab. MRONJ can present as jaw pain, tooth/periodontal infection, toothache, bone erosion, osteomyelitis, osteitis, or gingival ulceration. The risk of developing MRONJ is higher on intravenous (IV) antiresorptive therapy with denosumab than for oral therapy.¹ The incidence of MRONJ in patients

receiving denosumab was 28.3 per 10,000 patient years, compared to 4.5 in patients receiving an oral bisphosphonate.² The risk is also higher in cancer patients, who receive these treatments at higher doses and more frequent intervals than patients taking antiresorptive therapy strictly for osteoporosis management.³ Other risk factors for developing MRONJ secondary to denosumab include: invasive dental procedures (e.g. dental implants, tooth extraction, oral surgery); poor oral hygiene; use of dental appliances⁴; longer duration of therapy⁵; concurrent use of certain treatments, such as angiogenesis inhibitor therapy, chemotherapy, systemic steroids, immunosuppressants, erythropoietin, and hormone therapy; ill-fitting dentures; diabetes; anemia; hyperthyroidism; dialysis³; and tobacco use.⁶

Unfortunately, few high quality studies have been published comparing methods to prevent MRONJ.⁷ A Cochrane review from 2017, which was updated in 2022, did not find conclusive evidence to support any specific preventive strategy.⁸ However, as periodontal disease and dental extraction are two of the greatest risk factors for MRONJ, it is appropriate to optimize oral health and use root-retentive measures in dental procedures whenever possible. Routine screening of at-risk patients has also been recommended in international consensus statements.⁹ Denosumab is cleared by the reticuloendothelial system and has a half-life of approximately 26 days, whereas bisphosphonates bind to hydroxyapatite in bone and can have a persistent effect lasting up to 10 years. It is estimated that after 9 months without denosumab, patients are not at risk for developing MRONJ. However, patients taking bisphosphonates, particularly for an extended duration of 5 years or more, have a more prolonged risk.¹⁰ Patients taking denosumab for osteoporosis are advised to undergo dental procedures 3-4 months after the last denosumab dose, and to resume denosumab 6-8 weeks later. The goal is to avoid rebound bone loss and vertebral fractures that can occur after cessation of denosumab.¹¹

Treatment of MRONJ includes both operative and non-operative management, with the goal of curative therapy and improved quality of life. Treatment strategies are often patient-specific and depend to some degree on the stage/severity of osteonecrosis. Non-operative therapy focuses on reassurance, patient education, pain control, and control/prevention of secondary infection to allow for sequestration of exposed, necrotic bone. Sequestration refers to separation of devitalized bone from surrounding healthy bone during necrosis. Three-

dimensional imaging is important for fully staging necrotic lesions and identifying fully formed sequestra, that can help minimize invasiveness of surgical procedures.¹¹

Stage 1 lesions involve asymptomatic patients with no infection/inflammation with exposed and necrotic bone, or fistula that probes to bone. These patients are typically managed with improved oral hygiene and topical chlorhexidine to remove biofilm from the necrotic bone surface. Surgery may be avoided if there is adequate quality of life and lack of disease progression.^{7,12} A recent randomized controlled trial of Stage II patients demonstrated benefit from a tocopherol and pentoxifylline protocol with both mucosal and radiographic healing.¹³

Stage 2 lesions are like stage 1, however must be symptomatic, with evidence of infection/inflammation. These patients may not respond to local wound care and may require systemic antibiotics. Surgery may be needed if symptoms remain refractory to non-operative measures. Stage 3 lesions have similar features to stage 2, with any of the following additional features: exposed necrotic bone extending beyond the region of alveolar bone, pathological fracture, extraoral fistula, oronasal/oronasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor.^{7,11} Another randomized controlled trial reported benefit from teriparatide treatment in the rate of resolution of MRONJ lesions.¹⁴

Patients with stage 1, 2, or 3 lesions, undergoing non-operative treatment, should be closely monitored for clinical or radiographic progression, which would warrant early surgical intervention. For patients with more advanced disease at presentation, should have operative resection of MRONJ without prolonged non-operative management.¹¹ Although there is some controversy regarding operative and non-operative management of MRONJ, operative treatment has demonstrated improved quality of life, maintenance of mucosal coverage, and timely resumption of anti-resorptive therapy for all stages of MRONJ.¹⁵

REFERENCES

1. **Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O’Ryan F; American Association of Oral and Maxillofacial Surgeons.** American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg.* 2014 Oct;72(10):1938-56. doi: 10.1016/j.joms.2014.04.031. Epub 2014 May 5. Erratum in: *J Oral Maxillofac Surg.* 2015 Jul;73(7):1440. Erratum in: *J Oral Maxillofac Surg.* 2015 Sep;73(9):1879. PMID: 25234529.
2. **Everts-Graber J, Lehmann D, Burkard JP, Schaller B, Gahl B, Häuselmann H, Studer U, Ziswiler HR, Reichenbach S, Lehmann T.** Risk of Osteonecrosis of the Jaw Under Denosumab Compared to Bisphosphonates in Patients With Osteoporosis. *J Bone Miner Res.* 2022 Feb;37(2):340-348. doi: 10.1002/jbmr.4472. Epub 2021 Nov 30. PMID: 34787342.
3. **Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O’Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J; International Task Force on Osteonecrosis of the Jaw.** Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res.* 2015 Jan;30(1):3-23. doi: 10.1002/jbmr.2405. PMID: 25414052.
4. **Boquete-Castro A, Gómez-Moreno G, Calvo-Guirado JL, Aguilar-Salvatierra A, Delgado-Ruiz RA.** Denosumab and osteonecrosis of the jaw. A systematic analysis of events reported in clinical trials. *Clin Oral Implants Res.* 2016 Mar;27(3):367-75. doi: 10.1111/clr.12556. Epub 2015 Feb 2. PMID: 25639776.
5. **Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, Scagliotti GV, Sleeboom H, Spencer A, Vadhan-Raj S, von Moos R, Willenbacher W, Woll PJ, Wang J, Jiang Q, Jun S, Dansey R, Yeh H.** Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol.* 2011 Mar 20;29(9):1125-32. doi: 10.1200/JCO.2010.31.3304. Epub 2011 Feb 22. PMID: 21343556.
6. **Yarom N, Shapiro CL, Peterson DE, Van Poznak CH, Bohlke K, Ruggiero SL, Migliorati CA, Khan A, Morrison A, Anderson H, Murphy BA, Alston-Johnson D, Mendes RA, Beadle BM, Jensen SB, Saunders DP.** Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. *J Clin Oncol.* 2019 Sep 1;37(25):2270-2290. doi: 10.1200/JCO.19.01186. Epub 2019 Jul 22. PMID: 31329513.
7. **Bennett B, Tahir H, Solanki K, Ali N.** An Update on medication-related osteonecrosis of the jaw in patients with osteoporosis. *EMJ Rheumatol.* May 2023. Available at: <https://www.emjreviews.com/rheumatology/article/an-update-on-medication-related-osteonecrosis-of-the-jaw-in-patients-with-osteoporosis/>.
8. **Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O.** Interventions for managing medication-related osteonecrosis of the jaw. *Cochrane Database Syst Rev.* 2017 Oct 6;10(10):CD012432. doi: 10.1002/14651858.CD012432.pub2. Update in: *Cochrane Database Syst Rev.* 2022 Jul 12;7:CD012432. PMID: 28983908; PMCID: PMC6485859.
9. **McGowan K, McGowan T, Ivanovski S.** Risk factors for medication-related osteonecrosis of the jaws: A systematic review. *Oral Dis.* 2018 May;24(4):527-536. doi: 10.1111/odi.12708. Epub 2017 Aug 2. PMID: 28656643.
10. **Oral health management of patients at risk of medication-related osteonecrosis of the jaw.** *Br Dent J.* 2017 Jun 23;222(12):930. doi: 10.1038/sj.bdj.2017.539. PMID: 28642516.

11. **Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D.** American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws-2022 Update. *J Oral Maxillofac Surg.* 2022 May;80(5):920-943. doi: 10.1016/j.joms.2022.02.008. Epub 2022 Feb 21. PMID: 35300956.
12. **Hadaya D, Soundia A, Freymiller E, Grogan T, Elashoff D, Tetradis S, Aghaloo TL.** Nonsurgical Management of Medication-Related Osteonecrosis of the Jaws Using Local Wound Care. *J Oral Maxillofac Surg.* 2018 Nov;76(11):2332-2339. doi: 10.1016/j.joms.2018.05.025. Epub 2018 May 29. PMID: 29932939; PMCID: PMC6265090.
13. **Colapinto G, Goker F, Nocini R, Albanese M, Nocini PF, Sembriano S, Argenta F, Robiony M, Del Fabbro M.** Outcomes of a Pharmacological Protocol with Pentoxifylline and Tocopherol for the Management of Medication-Related Osteonecrosis of the Jaws (MRONJ): A Randomized Study on 202 Osteoporosis Patients. *J Clin Med.* 2023 Jul 13;12(14):4662. doi: 10.3390/jcm12144662. PMID: 37510777; PMCID: PMC10380687.
14. **Sim IW, Borromeo GL, Tsao C, Hardiman R, Hofman MS, Papatziomos Hjelle C, Siddique M, Cook GJR, Seymour JF, Ebeling PR.** Teriparatide Promotes Bone Healing in Medication-Related Osteonecrosis of the Jaw: A Placebo-Controlled, Randomized Trial. *J Clin Oncol.* 2020 Sep 10;38(26):2971-2980. doi: 10.1200/JCO.19.02192. Epub 2020 Jul 2. PMID: 32614699.
15. **Giudice A, Barone S, Diodati F, Antonelli A, Nocini R, Cristofaro MG.** Can Surgical Management Improve Resolution of Medication-Related Osteonecrosis of the Jaw at Early Stages? A Prospective Cohort Study. *J Oral Maxillofac Surg.* 2020 Nov;78(11):1986-1999. doi: 10.1016/j.joms.2020.05.037. Epub 2020 Jun 1. PMID: 32615096