Journal of Dental Sciences 19 (2024) 2428–2429

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Correspondence

Medication-related osteonecrosis of the jaw in a patient with rheumatoid arthritis with suspected involvement of methotrexate and tocilizumab

KEYWORDS
Bisphosphonate;
Medication-related osteonecrosis of the jaw;
Methotrexate;
Rheumatoid arthritis;
Tocilizumab

There are few reports of non-bisphosphonates as a causative agent of medication-related osteonecrosis of the jaw (MRONJ), an intractable disease,[1] and there is a lack of information and evidence. In this report, we describe a case of MRONJ that developed in a patient with a history of bisphosphonate (BP) use but who also used two new drugs that have recently been reported as possible triggering agents for osteonecrosis of the jaw.[2,3]

A 59-year-old female patient had a left mandibular molar implant placed in 2012, and she has been under continuous maintenance treatment since then. At the age of 68 years, oral bisphosphonates were prescribed for the treatment of osteoporosis in the order of alendronate (1 month), risedronate (9 months), and ibandronate (5 months), over a total period of 15 months. Treatment for rheumatoid arthritis (RA) was started at age 69 years, with oral methotrexate (MTX: once/daily) and injectable tocilizumab (once/weekly). Three years after the start of RA treatment, the patient complained of discomfort in the left mandibular molar region. Intraoral findings showed yellowish-white exposed bone without spontaneous pain, and a diagnosis of MRONJ stage 2 was made (Fig. 1).[4] After administration of oral amoxicillin, the sequestrum separated after one month and the area was completely covered with soft tissue after another month. There has been no postoperative recurrence and the patient has continued to do well.

MTX, the anchor drug for RA treatment, inhibits folic acid activation and suppresses proliferation of lymphocytes that produce TNF-α and IL-6, and synovial cells that form the granulation that causes bone destruction. Myelosuppression is one of its side effects, and MTX-associated lymphoproliferative disorders (MTX-LPDs) have been reported in recent years. Thus, cases of osteonecrosis of the jaw have been reported even in the absence of bisphosphonate drugs.[2] The biological tocilizumab is an IL-6 receptor inhibitor. Tocilizumab treatment increases osteocalcin and type I collagen C-terminal telopeptide, which are bone formation markers, while decreasing deoxypyrinodine, a bone resorption marker, and inhibiting bone metabolism turnover. It also has an inhibitory effect on angiogenesis[5] and is therefore considered to be a risk factor for MRONJ development.

In the present case, it is suspected that tocilizumab suppressed bone metabolic turnover and angiogenesis under immunosuppressive condition by MTX, possibly

https://doi.org/10.1016/j.jds.2024.07.024

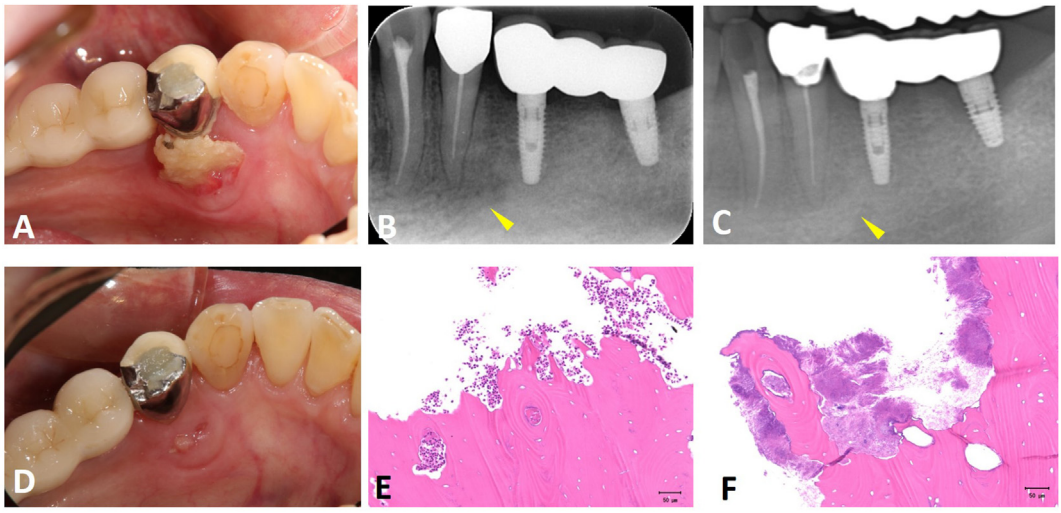

Figure 1 Radiographs and clinical photographs of this case. (A) Hard tissue isolated on lingual mucosa of #34 in chronic periapical periodontitis (2024). Diagnosed as MRONJ stage 2 based on clinical symptoms. (B) Preoperative radiograph. Diffuse bone resorption at the root apex of #34 (arrowhead). (C) Sequestrum removal and post-antibiotic treatment periapical radiograph with healing of the bone lesion (arrowhead). (D) One month after removal of sequestrum. The patient had healed well and reported no discomfort. (E) Histopathology specimen of excised hard tissue. Neutrophil infiltration was observed around the sequestrum, which obscured the laminar structure of the bone tissue (× 20 hematoxylin-eosin stain). (F) Adhesions of bacterial clumps are seen around bone tissue lacking osteocytes (× 20 hematoxylin-eosin stain).

modifying BPs-derived MRONJ exacerbation. Considering the short duration of bisphosphonate use (15 months), the influence of MTX and tocilizumab is presumed to be substantial. Furthermore, given that tocilizumab has recently been approved as an effective treatment for patients with severe COVID-19 and is known to significantly reduce the risk of death, its indication for use is expected to expand. In the future, not only osteoporosis but also rheumatoid arthritis and COVID-19 will be recognized as diseases requiring vigilance for the development of MRONJ. Future research should further investigate unknown drugs suspected of causing MRONJ to address this evidence gap.

Acknowledgements

This research was supported by JSPS KAKENHI grant number JP23K16235.

References

1. Amano K, Sugauchi A, Yamada C, Kogo M, Iida S. Osteonecrosis of the jaw in two rheumatoid arthritis patients not treated with a bisphosphonate. *Acta Med Okayama* 2023;77:111–6.
2. Henien M, Carey B, Hullah E, Sproat C, Patel V. Methotrexate-associated osteonecrosis of the jaw: a report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2017;124:e283–7.
3. Roh T, Jo H, Kim JY. Maxillary bone necrosis in post-COVID-19 patients: possibility of medication-related osteonecrosis of jaws (MRONJ) induced by tocilizumab. *J Craniofac Surg* 2024;35:e454–7.
4. 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;80:920–43.
5. Shinriki S, Jono H, Ueda M, et al. Interleukin-6 signalling regulates vascular endothelial growth factor-C synthesis and lymphangiogenesis in human oral squamous cell carcinoma. *J Pathol* 2011;225:142–50.

Keisuke Seki
Department of Comprehensive Dentistry and Clinical Education, Nihon University School of Dentistry, Tokyo, Japan
Division of Dental Education, Dental Research Center, Nihon University School of Dentistry, Tokyo, Japan

Atsushi Kobayashi
Norihito Takahashi
Nihon University School of Dentistry Dental Hospital, Tokyo, Japan

Atsushi Kamimoto*
Department of Comprehensive Dentistry and Clinical Education, Nihon University School of Dentistry, Tokyo, Japan
Division of Dental Education, Dental Research Center, Nihon University School of Dentistry, Tokyo, Japan

*Corresponding author. Department of Comprehensive Dentistry and Clinical Education, Nihon University School of Dentistry, 1-8-13, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan.
E-mail address: kamimoto.atsushi@nihon-u.ac.jp (A. Kamimoto)

Received 23 July 2024
Final revision received 24 July 2024
Available online 31 July 2024