Acta Med. Okayama, 2023
Vol. 77, No. 1, pp. 111–116

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Osteonecrosis of the Jaw in Two Rheumatoid Arthritis Patients Not Treated with a Bisphosphonate

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Medication-related osteonecrosis of the jaw (MRONJ) is a side effect in patients taking bone-modifying agents (BMAs), which are highly beneficial for treating osteoporosis and cancer. Bisphosphonates are prescribed to treat secondary osteoporosis in patients with rheumatoid arthritis (RA). We recently encountered two unusual cases of intraoral ONJ in RA patients who had not been treated with a BMA and did not have features of methotrexate-associated lymphoproliferative disorder. Their ONJ stage II bone exposures were treated by conservative therapy, providing good prognoses. These cases indicate that ONJ can occur in RA patients not treated with bisphosphonates. Several risk factors are discussed.

Key words: osteonecrosis of the jaw, rheumatoid arthritis, risk factor, bisphosphonate

The jaw bones provide support for dentition and thus play an essential role in maintaining daily oral functions. Bones are not static; rather, they are dynamic tissue in which osteoblasts, osteocytes, and osteoclasts orchestrate bone formation and resorption. This normal active biological metabolism is lost in osteonecrosis of the jaw (ONJ) which was recently recognized to occur with the use of the bone-modifying agents (BMA) such as the bisphosphonates (BPs) and a monoclonal receptor activator of NF-κB ligand (RANKL) antibody (*i.e.*, denosumab) [1]. Both BPs and denosumab are antiresorptive drugs that are beneficial for the treatment of osteoporosis, malignant progression of bone metastasis, and multiple myeloma by suppressing osteoclastic bone resorption [2]. Bisphosphonates are also indicated for the treatment of secondary osteoporosis, and they are linked to recent increased reports of bisphosphonate-related ONJ (BRONJ) in patients with rheumatoid arthritis (RA) [3-7]. The estimated incidence of ONJ in the general population is < 0.001% but greater at 0.001% to 0.01% in the osteoporosis patient population and 0.094% in patients with RA [8, 9]. It is possible that factors other than bisphosphonate use could cause ONJ in RA patients, but this has not been well studied. We present our clinical experience with two cases of intraoral ONJ that developed in RA patients in the absence of both BMA use and methotrexate-associated lymphoproliferative disorder (MTX-LPD) features.

Case Reports

Patient 1. The patient was a 76-year-old Japanese woman with marginal periodontitis. She had had RA for the prior 20 years, experienced a cardiogenic cerebral embolism 30 months ago, and had hypertension and insomnia. She was taking the following medications for these conditions: methotrexate (MTX) 8 mg/week,

Received June 9, 2022; accepted October 3, 2022.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

foliamin (folic acid) 5 mg/week, pravastatin sodium 10 mg/day, celecoxib 100 mg/day, Tramcet Combination Tablets (tramadol hydrochloride 37.5 mg and acetaminophen 325 mg) two tablets/day, rebamipide 100 mg/day, warfarin 1.5 mg/day, famotidine 20 mg/day, carvedilol, and brotizolam. Neither a bisphosphonate nor denosumab was being used. The patient had no history of radiation therapy to the craniofacial region. She had been taking MTX for approx. 7 years and had not complained of symptoms in the oral mucous membrane.

Although we had planned an extraction of the patient's upper right first and second molar teeth, we canceled the procedure due to our observation of gingival swelling with an accompanying ulcerative lesion and alveolar bone exposure (Fig. 1A). An intraoral examination revealed that the maxillary right first and second molars were severely affected by periodontitis, presenting obvious movement and deep gingival pockets. The gingival mucosa was swollen and a significant amount of dental plaque was observed, indicating poor oral hygiene control. There was no pus discharge, but dried brown-colored alveolar bone had been clearly exposed inside an ulcerative lesion (Fig. 1A). Radiography and computed tomographic scanning (CT) images revealed bone absorption and diffuse osteosclerosis around roots of the affected teeth (Fig. 1B, C). Magnetic resonance imaging (MRI) showed the lesion with low signal in T1-weighted images and high signal in T2-weighted images, suggesting alveolitis around the teeth (Fig. 1D).

We performed a cytodiagnosis to examine the ulcerative lesion in detail, observing a low-grade squamous intraepithelial lesion without cellular atypia where inflammatory cells and squamous epithelial cells were present. Consistently, neither CT nor MRI suggested malignancy, due to the absence of invasive bone destruction and tumor mass (Fig. 1C, D). Taking these findings together, we diagnosed this intraoral bone exposure as alveolitis causing an ONJ-like lesion although the patient had not been taking a bisphosphonate or denosumab.

We performed the treatment depicted in Fig. 2A. We first prescribed amoxicillin hydrate (750 mg/day) to control infection and inflammation for 1 month in parallel with local periodontal treatment including cleaning, scaling, pocket irrigation, and the application of Periofeel dental ointment 2% (minocycline hydrochloride) in the gingival pockets. The gingival inflammation, ulcerative lesion, and the patient's pain and discomfort were improved within 6 weeks (Fig. 2B).

Researchers in Japan have reported osteonecrosis of the jaw accompanied by oral ulceration and MTX-LPD [10-15]. Despite the cytodiagnosis in our present patient, her CT and MRI images did not agree with the possibility of LPD, and after a consultation with the patient's orthopedist to consider the potential side effects of MTX, the patient's medication for RA was changed from MTX to prednisolone (5 mg/day) (Fig. 2A). The intraoral bone exposure responded to these treatments and became smaller, detaching small pieces of bone. At

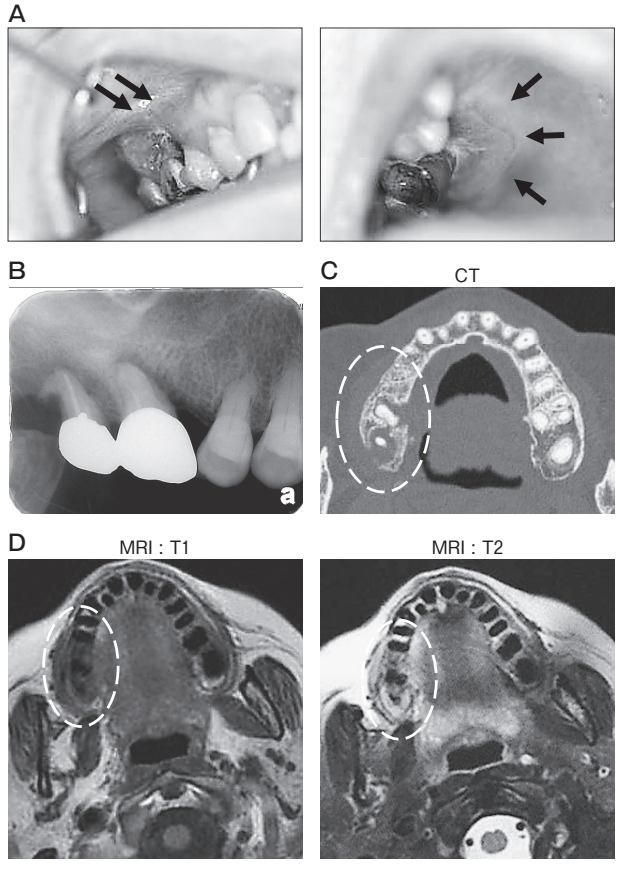

Fig. 1 Intraoral findings and diagnostic imaging of ONJ in Patient 1. **A**, Dried exposed bone with a brown color was observed around the right maxillary first molar, accompanied by ulceration (*black arrows*); **B–D**, Diagnostic imaging by dental radiography (**B**), CT (**C**), and MRI (**D**) before the treatment. The radiography and CT images showed periodontal bone absorption and diffuse osteosclerosis around the root of the right upper first and second molars (*A white dotted circle*). The MRI showed the lesion with low signal in T1-weighted images and high signal in T2-weighted images, suggesting alveolitis around the teeth (*white dotted circles*).

3 months after the first visit, a large and hard mass of dead bone with no observable cellular components freely separated from the lesion (Fig. 2C, D). The area of bone exposure continued to shrink and was finally covered with gingival mucosa at 5 months after the first visit (Fig. 2E). The patient restarted MTX medication with her orthopedist's approval, and we did not observe RA deterioration during the MTX interruption based on the data of C-reactive protein (CRP), rheumatoid factor (RF), and the Disease Activity Score 28 (DAS28) scale (Fig. 2A).

Patient 2. The patient was a 71-year-old Japanese man who was introduced to our department due to the lack of wound healing after tooth extraction (Fig. 3A). His medical history included RA for the prior 15 years, RA-related interstitial pneumonia, diabetes mellitus (DM), hypertension, angina pectoris treated with stenting, and cataracts. He was taking the following medications for these conditions: MTX 6 mg/week, bucillamine 200 mg/day, mecobalamin 1,500 μg/day, rebamipide 300 mg/day, and loxoprofen 180 mg/day for the control of his RA; prednisolone 4 mg/day to control his RA-related interstitial pneumonia; insulin aspart (genetic recombination) 31 units/day, miglitol 150 mg/day, pioglitazone hydrochloride 15 mg/day, and sitagliptin phosphate hydrate 50 mg/day for the control of his DM; and aspirin 100 mg/day, bisoprolol fumarate 5 mg/day, rosuvastatin calcium 5 mg/day, olmesartan medoxomil 40 mg/day, nifedipine 40 mg/day, and lansoprazole 15 mg/day to control his cardiovascular disease. Bisphosphonates, denosumab, and radiation therapy to the craniofacial area had never been used. The patients' DM was under control, as his hemoglobin A1c (NGSP) value was 6.8-7.0%. He had not complained of symptoms in oral mucous membrane.

An intraoral examination showed that dried brown-colored bone was clearly exposed in the socket although the patient's right maxillary first molar was extracted 6 months before his first visit (Fig. 3A). We performed the cytodiagnosis and diagnostic imaging with CT. The lesion had resulted in inflammation resembling osteomyelitis in the right maxillary area, excluding a possible malignancy (Fig. 3B).

Because the patient preferred to receive conservative therapy, we performed repetitive irrigation and provided medication (clarithromycin 400 mg/day) along with an intra-oral splint to protect the lesion. Sequestration subsequently occurred, producing some dead bone after 1 month (Fig. 3C), and the lesion was fully healed after 3 months (Fig. 3D). No recurrence was observed at a 7-month follow-up.

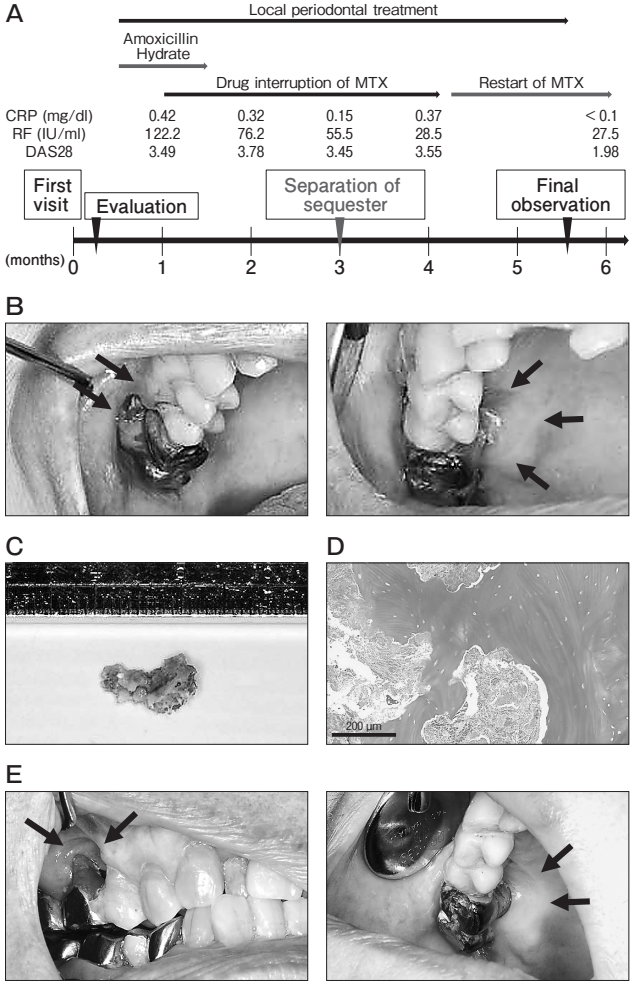

Fig. 2 The clinical course and treatment of Patient 1. **A**, The clinical course and results of blood exams. The Disease Activity Score 28 (DAS28) calculated based on clinical findings for defined 28 articular regions, the C-reactive protein (CRP) values, and the visual analogue scale (VAS) results. Disease activity of RA was not markedly changed during the treatment period. RF, rheumatoid factor; **B**, The ulceration and inflammation were improved by the treatment, and sequestration started (*black arrows*). **C**, **D**, A photo and histological image of the sequestration. No cellular component could be seen in the dead bone; Bar in (**D**), 200 μm; **E**, Post-treatment intra-oral findings (*black arrows*).

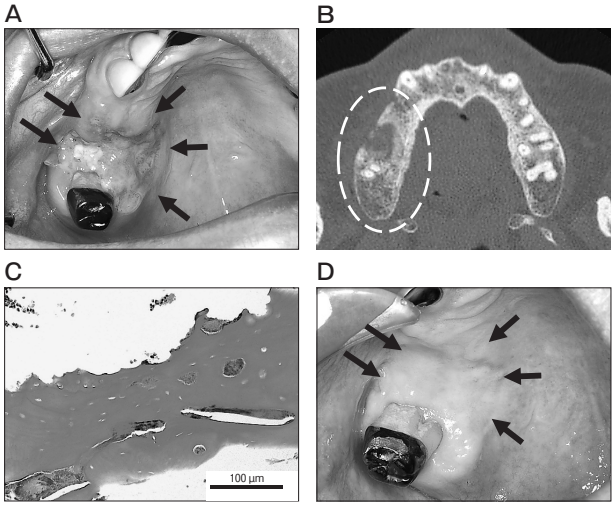

Fig. 3 The ONJ observed in Patient 2 after extraction of the right maxillary first molar. **A**, An intraoral photo showing the poor wound healing and bone exposure (*black arrows*); **B**, The CT image of the lesion remaining in the extraction socket even after 6 months (*A white dotted circle*); **C**, Histology image of the sequestration with a lack of cellular component; Bar, 100 μm; **D**, A good prognosis was obtained due to the treatment (*black arrows*).

Discussion

We have described the cases of two patients with RA in whom ONJ-like intraoral bone exposure developed in the absence of bisphosphonate use. Medication-related ONJ has been defined by the following criteria: (1) current or previous treatment with anti-resorptive or anti-angiogenic agents, (2) exposed bone in the maxillofacial region that has persisted for >8 weeks, and (3) no history of radiation therapy or obvious metastatic disease to the jaws [8]. The current incidence of ONJ in the osteoporosis patient population appears to be very low, and only slightly higher than the frequency seen in the general population. The incidence of ONJ is much higher in the oncology patient population because of use of high-dose intravenous bisphosphonates [8].

Treatment recommendations for ONJ are conservative or surgical management based on the stage of ONJ deterioration. For stage 0 ONJ (non-specific oral symptoms in the absence of bone exposure) and stage I ONJ (asymptomatic bone exposure without regional inflammation and/or infection), conservative treatment is recommended; this includes oral hygiene control, the elimination of active dental and periodontal disease, the use of an antibiotic mouth rinse, and systemic antibiotic therapy. For stage II ONJ (exposed bone with inflammation and/or secondary infection) and stage III ONJ (worsening ONJ accompanied by pathological fracture(s), an extraoral fistula, or extension to the inferior border of the mandible or the floor of the maxillary sinus), surgical procedures such as debridement and the resection of affected bones are recommended [16,17]. Both of the present patients had stage II ONJ, and conservative therapy was carried out in each case, resulting in good prognoses.

Rheumatoid arthritis is an inflammatory autoimmune disease that occurs most frequently in middle-aged females, and it causes articular inflammation and destruction. Methotrexate, a folic acid inhibitor, has often been used to treat RA through immunosuppression [18,19]. However, MTX has some potential adverse effects: myelosuppression, pneumonitis, hepatotoxicity, acute kidney injury, gastrointestinal and oral ulceration, and MTX-LPD [20]. Because RA patients are likely to be affected by secondary osteoporosis with or without treatment with a steroid, they are often treated with a BMA, and BRONJ has been observed in association with RA [3-7].

The present two cases of ONJ were in RA patients who were free of BMA use. The pathophysiology of this ONJ is not fully understood, and it merits discussion. There are several reports from Japan that describe ONJ occurring without bisphosphonate use concomitant with MTX-related oral ulceration or MTX-LPD [10-15]. Although our patients showed no LPD features such as a tumor mass, a side effect of MTX in the oral mucosa or gingiva might be a trigger of ONJ [21]. In addition, since MTX suppresses the immune system, it might negatively influence monocyte-macrophage precursor cell differentiation to osteoclast precursors [22]. This could locally influence osteoclast differentiation and bone metabolism in jaw bone. Moreover, other general factors such as steroid use, the age of the patient, and several general diseases and medications might be involved in cases of ONJ that are not associated with bisphosphonate treatment.

Glucocorticoid therapy is reported to be a risk factor for BRONJ [8], but it is not known whether MTX and steroid use have additive or synergistic effects to cause ONJ in bisphosphonate-naïve patients. Other local factors such as oral hygiene and the preoperative condition of the affected teeth also cannot be ignored when interpreting such cases. Since MTX has immunosuppressive

effects, the bacterial infection in the present patients' affected teeth might have been advanced. Collectively, the past and present findings indicate that several factors can directly or indirectly cause intraoral ONJ in RA patients in the absence of BMA use, and further attention should be paid to the diagnosis and treatment of these patients.

The discontinuation of MTX is assumed to be a way to improve ONJ and prevent its recurrence. Indeed, MTX treatment was discontinued in Patient 1 but not in Patient 2. Despite the difference, a good prognosis was obtained in both cases. Similarly, a recent review described that the lesions eventually healed even in patients who did not discontinue MTX, and the recurrence of the ONJ was not observed for ≥ 2 years after the lesions were healed [23]. Based on the present and past reports, we suggest that the discontinuation of MTX treatment is not indispensable and can be optional. Bisphosphonates have a high affinity to bone tissue and remain in the tissue for a long term, whereas MTX and 7-hydroxymethotrexate (7-OH-MTX) have short half-lives in blood and disappear with 8-15 hr [24].

Most cases of ONJ reported in patients treated with MTX occurred simultaneously with MTX-LPD [10-15]. To the best of our knowledge, there have been only four previous reports describing six patients with RA who were diagnosed with ONJ in the absence of MTX-LPD features and bisphosphonate use [25-28]. The cases of the present two patients could thus be categorized as showing an unusual and rare type of ONJ. Their cases also provide a novel finding, *i.e.*, that conservative therapy can be applied to such cases of ONJ and work well. Their clinical courses also illustrate the diagnoses of ONJ that occurred both with and without extraction.

Acknowledgments. K. Amano was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (JSPS KAKENHI, no. 19K10286).

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