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Case report

Methotrexate-related osteonecrosis of the jaw: Report of two cases☆

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ABSTRACT

Although methotrexate (MTX) is widely used to treat malignancies and autoimmune diseases, it is associated with a range of adverse effects. We report the cases of two men aged 88 and 73 years who were treated with MTX for rheumatoid arthritis and who both presented with exposed bone in the jaw, characteristic of osteonecrosis. We saw no change in symptoms in the first patient while MTX was being administered, while expansion of the jaw and bone exposure stopped immediately after cessation of MTX in the second case. We therefore suspected that both cases were MTX-related osteonecrosis of the jaw. Osteonecrosis has been reported with drugs that are not among those recognized as causing medication-related osteonecrosis of the jaw. Dentists and oral surgeons must carefully examine the oral cavity of patients on MTX therapy as part of regular practice.

1. Introduction

Methotrexate (MTX) is used to treat malignancies, including leukemia, and autoimmune diseases such as rheumatoid arthritis (RA), and is frequently used as first-line therapy for RA worldwide [1]. MTX has been associated with a range of adverse effects, including myelopathy, interstitial pneumonia (MTX pneumonia), and MTX-associated lymphoproliferative disorder (MTX-LPD). However, we are unaware of any report of MTX-related osteonecrosis of the jaw with bone exposure. Here, we report two cases of MTX-related osteonecrosis of the jaw.

2. Case report

2.1. Case 1

An 88-year-old man underwent extraction of the upper right second premolar at a dental clinic in January 2013. In July 2013 he visited our department due to ongoing drainage from the extraction site.

His medical history included RA, bladder cancer, and prostate cancer. He had no evidence of bone metastases from either malignancy. His RA had been treated with MTX 4 mg once weekly since 2013. Physical examination revealed exposed bone at the extraction site (Fig. 1A). CT revealed a sequestrum in the right maxillary sinus floor surrounded by soft tissue (Fig. 1B and C), while bone scintigraphy showed the accumulation of radiotracer in the right upper molar region and right maxilla (Fig. 1D–F). Blood tests revealed a mild increase in inflammatory markers. Based on these clinical findings, the lesion was diagnosed as osteonecrosis of the maxilla with a sequestrum and maxillary sinusitis.

Administration of antibiotics and regular irrigation with saline via a syringe commenced in July 2013 on an outpatient basis. Although the drainage stopped, the exposed bone at the extraction site remained. The patient developed primary rectal cancer and underwent surgery. He died in October 2014.

2.2. Case 2

A 73-year-old man became aware of left lower occlusal pain in July 2013 and developed paresthesias in the left mental region in December. His past medical history included RA, abdominal aortic aneurysm, and angina pectoris. The RA has been treated with MTX 6 mg once weekly and prednisolone 7.5 mg once daily since 2011. Physical examination revealed bone exposure in the left upper first molar and left lower second molar gingiva (Fig. 2A and B). CT showed bone resorption around the left lower second molar apex without associated osteosclerosis (Fig. 2C and D) and bone scintigraphy revealed increased uptake in the involved regions (Fig. 2E–G). Blood test values revealed reference values. Based on these clinical findings, the lesion was diagnosed as osteonecrosis of the left maxilla and mandible.

☆ AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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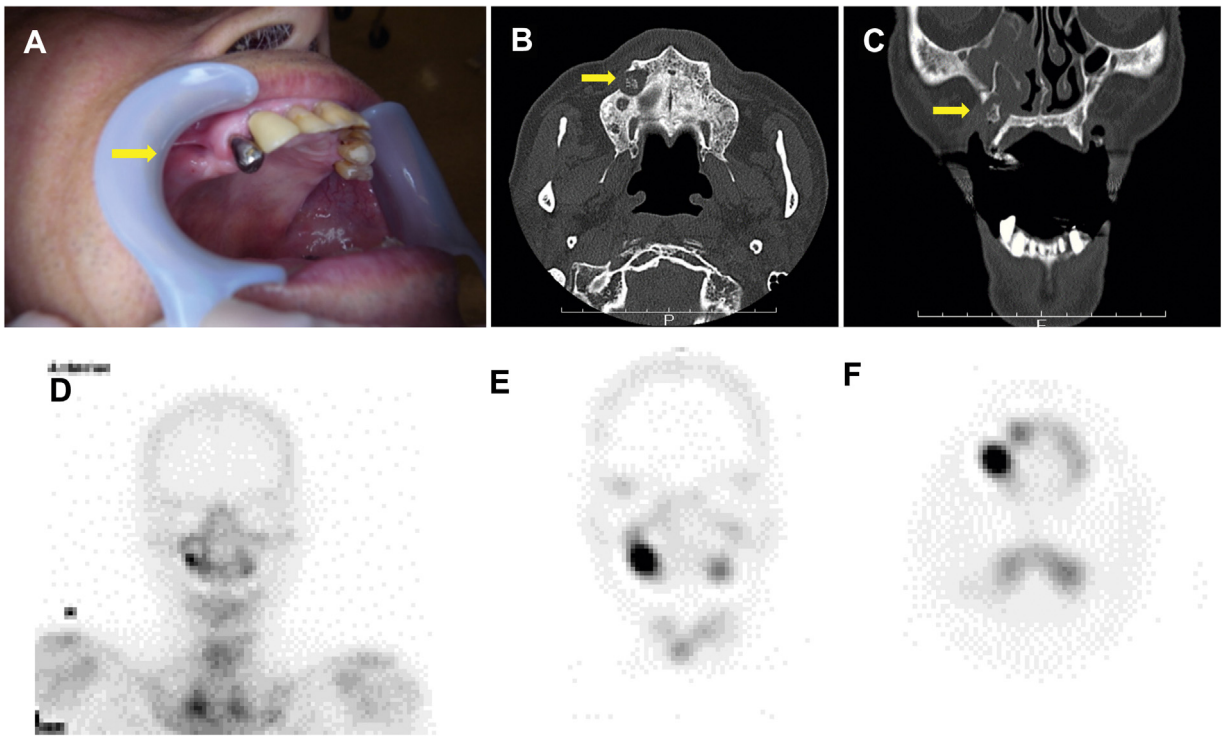

Fig. 1. Case 1.
Bone exposure was probed in the upper right extraction site (yellow arrow indicates bone exposure) (A). Separation of a sequestrum was noted in the right maxillary sinus floor on computed tomography images (yellow arrows indicate separation of a sequestrum) (B) and (C). Radiotracer accumulation was detected in the right upper molar region on bone scintigraphy (D: anterior), (E: coronal), (F: axial). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Outpatient hyperbaric oxygen therapy (HBO) and administration of antibiotics were initiated, but the lesions enlarged (Fig. 2H and I). A sequestration developed, small sections of which were removed at several sessions of debridement. On biopsy of the exposed bone (left upper second premolar and left upper second molar lingual alveolar bone) and surrounding gingiva (left upper second molar and left lower second premolar lingual gingiva), histopathology showed gingival inflammation and necrotic bone, with a sequestrum in the exposed bone (left upper second premolar and left upper second molar lingual alveolar bone). No tumor cells, atypical cells, or atypical lymphocytes found in MTX-LPD were identified (Fig. 2J and K).

Despite ongoing inpatient treatment with HBO and antibiotics, expansion of the areas of bone exposure occurred, with no epithelialization or separation of the sequestration. After consultation with our rheumatologist, therapy was changed to tacrolimus 14 mg once weekly, which resulted in improvement, with shrinkage of the exposed areas and partial epithelialization. Additional debridement and extraction of the left lower first molar and second premolar pontic was performed, with further improvement (Fig. 2L and M).

3. Discussion

MTX is an antifolate which exhibits various cell growth-inhibitory effects by suppressing DNA synthesis through the inhibition of dihydrofolate reductase. It mainly inhibits the growth of lymphocyte system cells, exhibiting strong immunosuppressive and anti-inflammatory actions. However, MTX induces a range of adverse reactions, including myelopathy, interstitial pneumonia (MTX pneumonia), infection, liver disorders, and MTX-LPD. Ellman et al. first reported LPD in MTX-treated RA patients in 1991 [2], and since that time the number of cases has continued to increase. However, the mechanism of MTX-LPD remains to be determined. Suggested hypotheses include infection with EBV in an MTX-induced immunosuppressed state, reactivation-induced growth of immortalized B cells, and the involvement of RA in the immunopathogenesis [3]. Our patients were both diagnosed with osteonecrosis of the jaw. Histopathologically, we did not recognize the variety of atypical lymphocytes typically present in MTX-LPD or abnormal lymphocytes present in hematopoietic tumor in the specimen from Case 2.

Several cases of MTX-LPD accompanied by osteonecrosis of the jaw have been reported [4]. Bone necrosis in MTX-LPD may occur as a result of an opportunistic infection and malignant invasion of bone. In our cases, bone exposure was considered not due to MTX-LPD and malignant cells were not detected on histopathological examination.

For case 2, prednisolone had been administered at 7.5 mg once daily since 2011, and osteonecrosis due to glucocorticoid side effects was considered. Zizic et al. reported that the mean daily dose of prednisone exceeded 40 mg/day for ≥1 month in 93% of patients and 20 mg/day in 100% of patients who developed osteonecrosis. For this case, we considered that the relationship of osteonecrosis of the jaw with prednisolone was negative because the dose was low [5].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper on Medication-related Osteonecrosis of the Jaw (MRONJ) has reported a growing incidence of osteonecrosis cases involving the maxilla and mandible associated with bisphosphonates, anti-receptor activator nuclear factor kappa β ligand (anti-RANKL) (denosumab) and antiangiogenic therapies [6].

The MRONJ case definition is current or previous treatment with antiresorptive or antiangiogenic agents, exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks, and

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