

[CASE REPORT]

Oral Methotrexate-related Lymphoproliferative Disease Presenting with Severe Osteonecrosis of the Jaw: A Case Report and Literature Review

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Abstract:

Long-term methotrexate (MTX) treatment can cause MTX-related lymphoproliferative disorder (MTX-LPD). We experienced a case of MTX-LPD that was associated with severe osteonecrosis of the jaw mimicking medication-related osteonecrosis of the jaw. The patient was an 81-year-old woman with rheumatoid arthritis (RA) who was treated with MTX and bisphosphonate. After 7 years, she was referred to our department for the assessment of giant ulcer and exposure of the alveolar bone of the left maxilla. Histopathological and immunological analyses confirmed a diagnosis of MTX-LPD. At seven months after the cessation of MTX treatment, the ulcerative and necrotic lesions had markedly decreased in size. A 1-year follow-up examination showed no evidence of recurrence and good RA control.

Key words: methotrexate-related lymphoproliferative disorder, medication-related osteonecrosis of the jaw, rheumatoid arthritis, lymphoma, Epstein-Barr virus

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Introduction

Methotrexate (MTX) is the current first-line treatment for rheumatoid arthritis (RA) (1). However, many recent case studies have reported that long-term MTX treatment resulted in MTX-related lymphoproliferative disorder (MTX-LPD) in RA patients (2, 3). The recent World Health Organization classification of lymphoid neoplasms categorizes MTX-LPD as an “other iatrogenic immunodeficiency-associated LPD” (4). MTX-LPD may resolve several weeks after the withdrawal of MTX therapy; however, additional treatments, such as chemotherapy and radiotherapy, should be considered for patients with persistent LPD after MTX withdrawal (5-7). Regarding the mechanism underlying the onset of MTX-LPD, it is considered that immunosuppression by

MTX reduces the host immunosurveillance of Epstein-Barr virus (EBV)-infected B cells, because approximately 50% of patients with MTX-LPD are EBV-positive (8).

Bisphosphonates (BPs) are the primary treatment for osteoporosis, bone metastasis, hypercalcemia caused by malignancies, Paget disease of bone, and osteolytic lesions of multiple myeloma. Although BP treatment has many benefits for patients with skeletal complications, it is associated with a number of adverse effects, the most important of which is BP-related osteonecrosis of the jaw (BRONJ) (9, 10). Since BRONJ was first reported in 2003, many additional cases have been reported (11, 12). Because osteonecrosis of the jaw can also be caused by other drugs, the American Association of Oral and Maxillofacial Surgery updated their position paper on BRONJ in 2014. The term BRONJ was replaced with medication-related osteonecrosis

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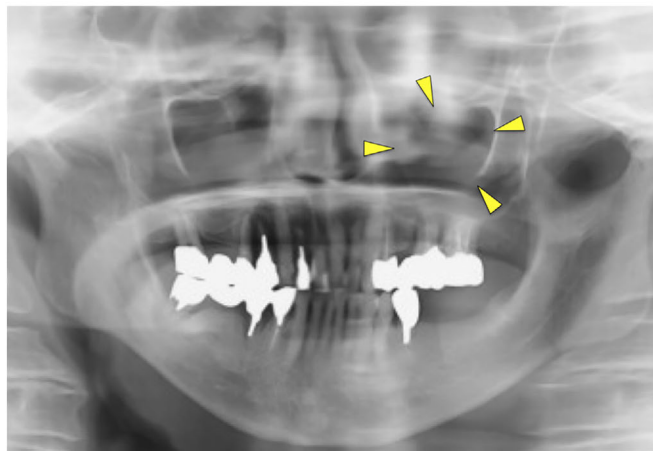
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Figure 1. A photograph and phoradiograph obtained at the first examination. (A) The exposure of the buccal and palate bone, and the buccal root of the molars were noted (mirror reflection). The upper-left first and second molars showed deflection. (B) The left sinus had a cloudy appearance (yellow arrowhead).

of the jaw (MRONJ) (13). The clinical manifestations of MRONJ include soft tissue swelling, fistula, abscess, pain, and bone exposure (14). There is currently no gold standard for the treatment of MRONJ or MTX-LPD. MTX-LPD generally develops at extra-nodal sites (8). To the best of our knowledge MTX-LPD of the oral cavity is rare, and no previous studies have reported the serial treatment of MTX-LPD with MRONJ.

We herein describe a case of MTX-LPD with MRONJ. In addition, we performed a systematic literature review to identify all cases of MTX-LPD of the oral cavity, to investigate the characteristics of oral MTX-LPD.

Case Report

In July 2015, an 81-year-old Japanese woman was referred to the Department of Oral Surgery at Kyushu University Hospital for the evaluation of upper left mandible pain. In 2009, the patient was diagnosed with RA based on the findings of bone destruction and swelling at her wrists and a positive serum test for rheumatoid factor. She had been taking BP (Bonalon[®]; 35 mg/week) and prednisolone (Predni-

solon[®]; 5 mg/day) for 7 years and MTX (Metolate[®]; 8 mg/week) for 4 years. In April 2015, she fell while walking on stairs and noticed slight bleeding near her left first molar. Two weeks earlier she visited another dentist due to continuous pain of the left maxillary gingiva that had persisted for 2 months. The dentist suspected MRONJ based on the exposure of the maxillary bone.

Our initial examination revealed an ulcer with induration on the buccal gingiva, near the upper left molar, which was mobile (Fig. 1A). Radiography showed left sinusitis and the loss of vertical bone near the upper left molars (Fig. 1B). These findings suggested gingival carcinoma or lymphoma. A cytological analysis of the ulcerative gingiva revealed class III cytology accompanied by numerous atypical lymphocytes; however, these findings were not conclusive for malignancy. The results of serological tests were unremarkable; however, the patient's C-reactive protein concentration was slightly elevated (0.64 mg/dL). Coronal computed tomography revealed a lesion arising from the upper left second premolar to the left sinus and the destruction of the buccal cortical bone in the left posterior maxilla (Fig. 2A). ¹⁸Fluoro-2-deoxyglucose positron emission tomography

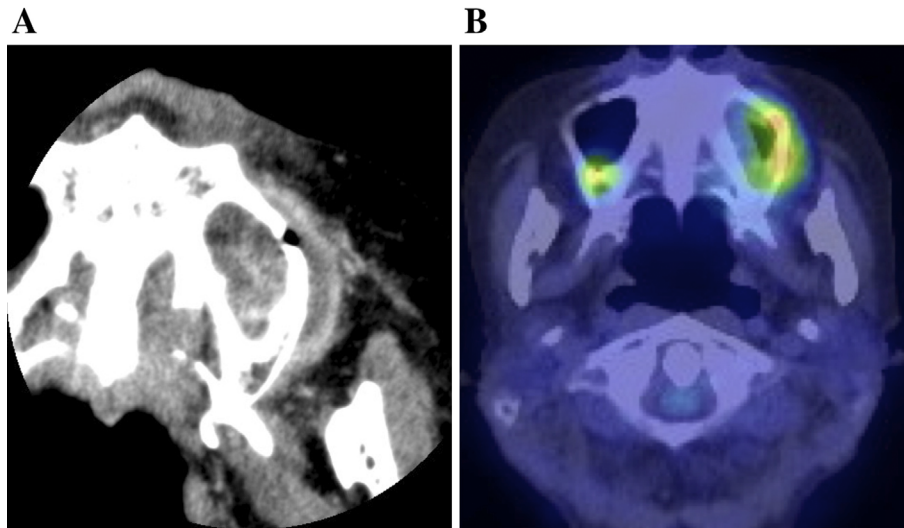


Figure 2. Computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET). (A) CT revealed a mass around the upper-left maxilla. (B) FDG-PET indicated abnormal accumulation in the upper-left gingiva.

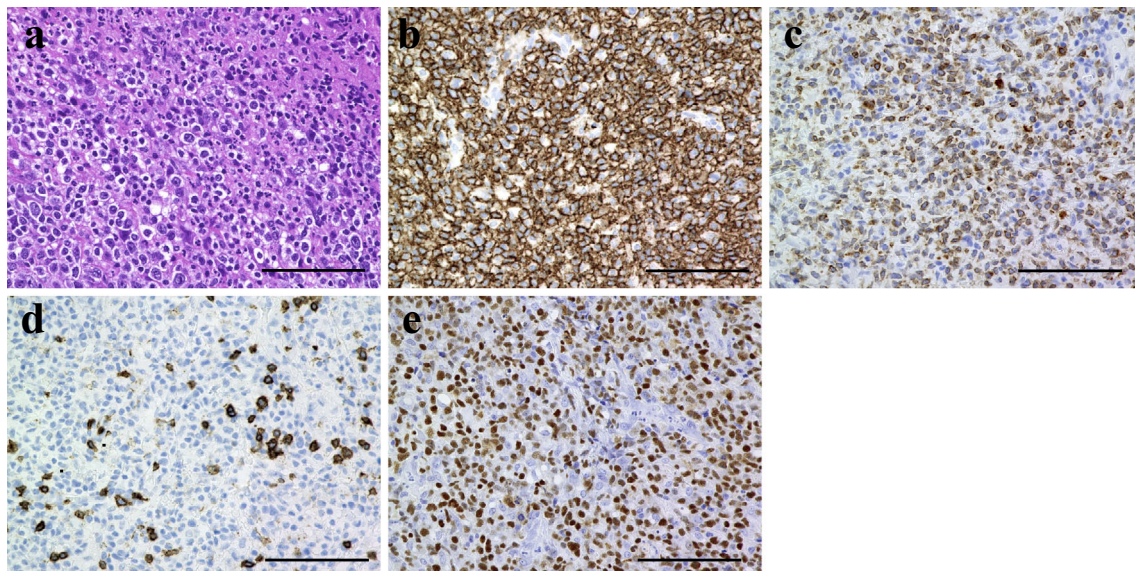


Figure 3. The histological and immunohistochemical findings of the upper-left gingiva. Hematoxylin and Eosin staining (a). Immunohistochemical staining for CD20 (b), CD79a (c), CD3 (d), and Epstein-Barr encoding region (EBER) (e). Scale bars: 100 μ m.

(FDG-PET) was performed to evaluate the extent of the primary lesion, the status of the regional lymph nodes, and the possibility of distant metastasis. The images showed the abnormal accumulation of FDG in the left upper maxilla and sinus (maximum standardized uptake value, 4.94) and no accumulation in several systemic lymph nodes or other lesions (Fig. 2B). These findings indicated that the lesion was malignant or another type of tumor. She was immediately referred to the hematology department of our hospital and an incisional biopsy of the upper left region was performed. Immunophenotyping of the upper left gingiva gated by CD45+ cells yielded the following findings: CD3+ CD20-, 48.3%; CD3- CD20+, 14.6%; natural killer cells, 30.5%;

CD19+, 17.7%; κ chain, 4.25%; and λ chain, 3.72%. These findings were not conclusive for a diagnosis of any type of malignant lymphoma. A pathological analysis showed the infiltration of numerous lymphocytes and the diffuse proliferation of medium- to large-sized atypical lymphoid cells with large nuclei and clumped chromatin. Moreover, an immunohistochemical analysis revealed extensive lymphocytic infiltration. The cells were mostly B cells (positive for CD20 and CD79a); however a few T cells were found to be CD3-positive. The additional performance of *in situ* hybridization to detect EBV-encoded RNA (15) showed the strong infiltration of EBV-positive atypical lymphoid cells (Fig. 3). In sum, these findings confirmed a diagnosis of EBV-

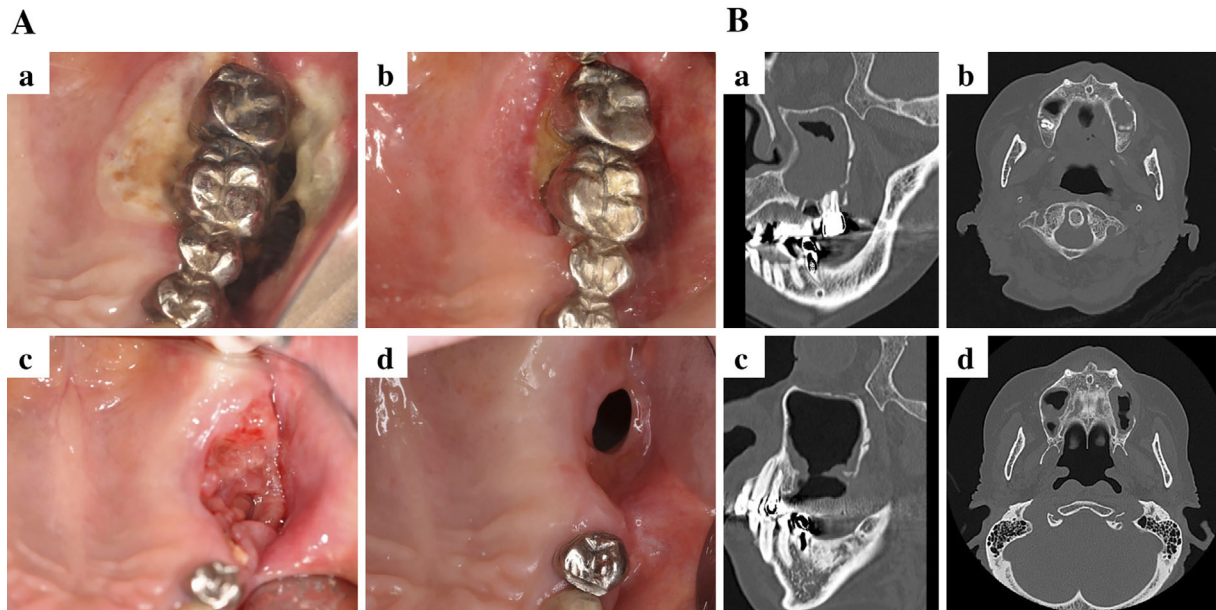


Figure 4. Photographs and photoradiographs obtained after the withdrawal of methotrexate (MTX). (A) Photographs of the upper-left maxilla at 0 days (a), 2 weeks (b), 4 months (c), and 7 months (d). All of the photographs show mirror reflections. (B) CT images obtained after the withdrawal of MTX for 4 months (a, b) and 7 months (c, d).

positive diffuse large B-cell lymphoma (DLBCL). Based on the pathological and clinical findings, the patient was diagnosed with MTX-LPD, and MTX therapy was immediately stopped (Fig. 4A-a). To control RA, the patient was treated with prednisolone (3 mg/day). We continued to monitor the patient carefully during the initial 2-week cessation of MTX. The exposed bone was rinsed three times a week with 0.05% glucuronic acid chlorhexidine solution, and the necrotic gingiva and induration gradually disappeared (Fig. 4A-b). At four months after the withdrawal of MTX and rinsing with glucuronic acid chlorhexidine solution, the upper left molars were easily extracted, along with the surrounding floating bone (Fig. 4A-c). The necrotic and indurated tissue had disappeared, and no other adverse events were noted (Fig. 4A-d). CT images obtained at 4 and 7 months after the withdrawal of MTX showed the improvement of the left sinusitis and the absence of inflammation or floating bone in the maxilla (Fig. 4B). No inflammation was observed near the upper left gingiva during this period, and the patient did not require antibiotic treatment. There was no recurrence of MTX-LPD or extra-nodal lymphoma, and her RA remained well controlled at 1 year after the discontinuation of MTX treatment.

Discussion

Evidence from numerous reports indicates that the risk of LPD in RA (RA-LPD) patients is 2.0-5.5 times that of the general population (16). The underlying mechanism is unclear; however, patients with RA have persistent immunological abnormalities that may lead to clonal selection, which can result in the malignant transformation of B cells,

the decreased apoptosis of infected B cells, reduced natural killer cell activity, the proliferation of latent EBV infection, and direct oncogenic action. All of these conditions may be potentiated by immunomodulation therapies. The number of reported LPD cases has been increasing among patients with RA receiving MTX, a condition referred to as MTX-LPD (8). The characteristics of MTX-LPD are as follows: (1) the most frequent subtype of MTX-LPD is DLBCL rather than Hodgkin lymphoma or Hodgkin disease-like lymphoma, (2) the frequency of EBV-positive case is higher in MTX-LPD than in RA-LPD or age-related LPD, (3) the possibility of improvement is high (20-60%), but only when MTX is withdrawn for several weeks, (4) the frequency of extra-nodal lymphoma is higher in MTX-LPD cases than in RA-LPD or age-related LPD cases, and (5) the duration to the outcome is shorter in patients with MTX-LPD than in those with RA-LPD (17, 18). In approximately 40-50% of cases, MTX-LPD develops at extra-nodal sites, such as the skin, lung, liver, gastrointestinal tract, and kidney (8).

A review of the literature revealed only 19 cases of oral MTX-LPD, including our 3 cases (Table 1) (7, 19-30). At the time of the diagnosis of MTX-LPD, the mean age of the patients was 71.1 years (range, 44-87 years) and the male-to-female ratio was 4:15 (the male-to-female ratio in RA was 1:4). The mean duration of MTX treatment was 6.6 years (range, 0.1-20 years). The frequency of bone exposure and DLBCL was 56.2% (9/16), the frequency of EBV positivity was 100.0% (13/13), and MTX-LPD resolved in 80.0% (12/15) of patients after the discontinuation of MTX. The data on the mean age, sex ratio, and the duration of MTX treatment were similar to those of previous reports on oral MTX-LPD. In contrast, the frequency of DLBCL and

Table 1. Clinicopathological Findings of 19 Cases with Oral Methotrexate-related Lymphoproliferative Disorders (MTX-LPD).

No.	Age	Sex	Lesion	Complaining	MTX intake (y)	Histology	EBV	BP intake (y)	Bone Exposure	MTX withdrawal	Recurrence	Chemotherapy	Reference
1.	72	F	gingiva	ulcer	NA	poly-B cell lymphoma	+	NA	+	+	-	-	(19)
2.	69	F	gingiva	ulcer	NA	Wegener's lymphoma	NA	NA	+	+	-	-	(19)
3.	73	F	oral cavity	NA	2	peripheral T cell lymphoma	NA	-	-	+	-	-	(21)
4.	73	F	oral cavity	NA	2	DLBCL	LMP-1	-	+	+	-	-	(20)
5.	70	F	palate	ulcer	6	DLBCL	EBNA2	-	-	+	-	-	(7)
6.	69	F	gingiva	NA	NA	Hodgkin	LMP-1	-	NA	+	NA	NA	(22)
7.	80	M	tongue	ulcer	NA	NA	NA	NA	-	NA	NA	NA	(30)
8.	76	F	gingiva	ulcer, bleeding	10	DLBCL	EBER	-	-	+	+	R-THP-COP	(24)
9.	67	F	palate	ulcer	9	DLBCL	EBER	9	+	+	-	-	(25)
10.	75	F	gingiva	swelling	5	DLBCL	EBER	NA	+	+	+	R-CHOP	(26)
11.	60	M	gingiva	swelling	20	DLBCL	EBER	-	+	+	-	-	(27)
12.	71	F	buccal mucosa	ulcer	0.1	NA	NA	+	-	+	-	-	(28)
13.	87	F	buccal mucosa	ulcer	2	NA	NA	+	-	+	-	-	(28)
14.	66	F	gingiva	ulcer	3	DLBCL	NA	8M	+	+	-	-	(29)
15.	76	F	gingiva	NA	NA	Hodgkin	LMP-1	NA	NA	+	NA	NA	(23)
16.	67	M	palate	NA	NA	NA	LMP-1	NA	NA	+	NA	NA	(23)
17.	81	F	gingiva	ulcer	4	DLBCL	EBER	7	+	+	-	-	This case
18.	71	F	gingiva	ulcer	NA	BL	EBER	+	+	+	-	-	our cases
19.	77	F	gingiva	ulcer	12	DLBCL	EBER	+	+	+	+	R-CHOP	our cases

MTX: methotrexate, EBV: Epstein-Barr Virus, DLBCL: diffuse large B-cell lymphoma, LMP: latent infection membrane protein, EBNA: EBV nuclear antigen, EBER: Epstein-Barr encoding region, R-THP-COP: rituximab, pinorubin, oncovin, endoxan, and prednisolone, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, +: positive, -: negative, NA: not available

Table 2. Comparison of Clinicopathological Findings between Oral and Non-oral MTX-LPD.

	Oral MTX (n=17)	Non-oral MTX (n=52)
Mean age (years)	71.1	63.0-69.0
Sex (male : female)	4:13	20:32
Affected regions	gingiva, palate, buccal mucosa, tongue	lymph node, spleen, lung, skin, liver, pleura, kidney, small bowel, breast, neck, thymus, stomach, heart
Duration of MTX treatment (years)	6.6	3.1-5.8
DLBCL (%)	56.2	30.8-55.3
EBV-positive (%)	100	50.0-62.8
Reference	Table 1	(7), (21), (32)

MTX-LPD: methotrexate-related lymphoproliferative disorder, DLBCL: diffuse large B-cell lymphoma, EBV: Epstein-Barr virus

EBV-positivity in the patients with oral MTX-LPD were higher in comparison to previous reports on non-oral MTX-LPD, as summarized in Table 2 (6, 21, 24, 31). Some reports have suggested that spontaneous remission occurs due to the withdrawal of MTX and noted an association between EBV positivity and the spontaneous remission of MTX-LPD (32). The initial symptoms of oral MTX-LPD included ulcer (80.0%, 12/15) and swelling (20.0%, 3/15), and the main sites affected included the gingiva (66.7%, 12/18), the hard palate (11.1%, 2/18) and the buccal mucosa (11.1%, 2/18). Other regions of the oral cavity, including the tongue, soft palate, sinus, and lip, can also be target organs because EBV in the head and neck region, including the pharynx and the salivary glands, generally remains dormant. Dentists and clinicians should bear in mind that MTX-LPD can be observed in any lesion.

Our patient had been treated with BPs for 9 years and MTX for 4 years. A diminished CTL function caused by the immunosuppressive effect of MTX permits the reactivation of EBV and the monoclonal proliferation of EBV-infected B cells in the buccal gingiva. Since the gingiva has a unique environment, characterized by its direct contact with the alveolar bone through the periodontal pocket, patients with LPD affecting the cervical gingiva are prone to develop bone exposure, and those who are treated with BPs may subsequently develop necrosis of the alveolar bone.

Recently, EBV-positive mucocutaneous ulcer (EBV-MCU) was proposed as a novel clinical entity that presents as mucocutaneous ulcers of the oropharynx, gastrointestinal tract, or skin, which are caused by latent EBV infection. Iatrogenic immunosuppression for autoimmune disease and age-related immunosenescence have been implicated as risk factors (30). The clinical conditions of this case might be close to those of EBV-MCU.

The presence of ulcer and adjacent bone exposure in the gingiva complicated the initial diagnosis because the common manifestations of MRONJ include ulcer, swelling, fistula, abscess, and bone exposure. However, our patient also exhibited the progression of ulceration and induration. We therefore performed an incisional biopsy as soon as we suspected malignancy or another tumor. After the diagnosis was confirmed, MRONJ was treated by daily cleaning around the

site of bone necrosis with glucuronic acid chlorhexidine solution. After this, the floating necrotic bone and molars gradually resolved. The gingival ulceration and induration resolved in association with bone removal. No guidelines have been established for the treatment of MTX-LPD; however, pathological and immunological examinations are necessary in the selection of treatment.

We described a case of MTX-LPD with severe MRONJ and the effects of treatment after MTX withdrawal. Many previous case reports have described gingival ulcers or swelling near the sites of osteonecrosis; however, no previous reports have described the treatment of MRONJ or differentiation between MRONJ and MTX-LPD with MRONJ. The present case and the associated review of the literature on oral MTX-LPD suggest that oral MTX-LPD will continue to be a concern because RA patients are increasingly treated with MTX and BPs. Despite the risk of severe adverse effects, MTX is the treatment of choice for RA. Clinicians should bear in mind that oral MTX-LPD is occasionally complicated by MRONJ, and that a pathological examination (e.g., an incisional biopsy and immunohistological examination) is required for the final diagnosis. Additionally, close collaboration with internists or hematologists should be considered when developing a treatment plan.

Written informed consent was obtained from the patient for publication of this report and the use of any accompanying images.

The authors state that they have no Conflict of Interest (COI).

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