

Methotrexate-related other iatrogenic immunodeficiency-associated lymphoproliferative disorder in the CNS and medication-related osteonecrosis of the jaw occurring simultaneously: A case report

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Abstract. Methotrexate-related other iatrogenic immunodeficiency-associated lymphoproliferative disorder (MTX-OIIA-LPD) is prone to extranodal involvement but rarely involves the central nervous system (CNS). The present study reports a case of MTX-OIIA-LPD of the CNS discovered during medication-related osteonecrosis of the jaw (MRONJ) treatment in a 76-year-old woman with rheumatoid arthritis (RA). The chief complaint of the patient was bone exposure and pain in the right mandibular molar. The patient had been receiving MTX for RA and alendronate sodium hydrate for osteoporosis, followed by denosumab. Treatment was initiated based on a diagnosis of MRONJ. However, the patient experienced lightheadedness and floating dizziness afterwards. Examinations revealed scattered neoplastic lesions in the brain. The histopathological diagnosis was diffuse large B-cell lymphoma. A systemic search also revealed adrenal involvement. Since the patient was taking MTX, a diagnosis of MTX-OIIA-LPD was made and MTX was discontinued. Chemotherapeutic agents were administered since the central lesions became symptomatic. The MTX-OIIA-LPD lesions in

the brain and adrenal glands completely resolved 8 months after onset. The physical condition of the patient improved, and the bone-exposed areas became epithelialized. Reports on MTX-LPD in the oral and maxillofacial region are few, which may delay its diagnosis. Therefore, biopsy of oral lesions in patients with MRONJ who are taking MTX and collaboration with related diagnostic departments, such as rheumatology and hematology, must be done to initiate the diagnosis and treatment of extraoral MTX-LPD.

Introduction

Methotrexate (MTX) is widely used to treat rheumatoid arthritis (RA) (1). However, it has been linked with MTX-associated lymphoproliferative disorder (MTX-LPD), a malignant lymphoma (2). According to the World Health Organization's (WHO) histological classification (Revision 4), MTX-LPD is currently classified as other iatrogenic immunodeficiency-associated LPD (OIIA-LPD), a subgroup of immunodeficiency-associated LPDs (IA-LPDs). Harigai (2) characterized MTX-LPD to be prevalent at an age of 60-70 years, associated with more than 10 years of MTX use, predominant in patients having B-cell non-Hodgkin's lymphoma, and in those having a positive laboratory test for Epstein-Barr virus (EBV). Spontaneous remission with the discontinuation of MTX alone is another feature (3,4), and this tendency is particularly strong in EBV-positive cases (5). MTX-OIIA-LPD is characterized by extranodal involvement at various sites, including the skin, lungs, muscles, and gastrointestinal tract (5). However, reports of MTX-OIIA-LPD involvement in the central nervous system (CNS) are rare, with only 15 cases reported in the literature (3,4,6-16), and none in the field of oral surgery. In the present study, we report the case of a patient with RA who developed lightheadedness and floating dizziness during treatment for medication-related osteonecrosis of the jaw (MRONJ). Furthermore, close examination revealed neoplastic lesions in the left cerebellum and the right frontal lobe, which proved to be

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Abbreviations: MTX, methotrexate; RA, rheumatoid arthritis; MTX-OIIA-LPD, MTX-related other iatrogenic immunodeficiency-associated lymphoproliferative disorder; CNS, central nervous system; DLBCL, diffuse B-cell lymphoma

Key words: methotrexate, methotrexate-related iatrogenic immunodeficiency-associated lymphoproliferative disorder, central nervous system, medication-related osteonecrosis of the jaw, rheumatoid arthritis

diffuse B-cell lymphoma (DLBCL). Thus, a diagnosis of MTX-OIIA-LPD of the CNS was made. Also, we review the literature relevant to this case.

Case report

The patient was a 76-year-old woman, who presented to the referring dentist with a chief complaint of bone exposure and pain in the right mandibular molar. The patient was then referred to our department for further examination and treatment. Her medical history included MTX, iguratimod, and tocilizumab use, which were initiated in 2016 to treat RA. Alendronate sodium hydrate was also used in 2016 for the treatment of osteoporosis. However, a switch to denosumab was made in 2019 to control the progression of bone destruction caused by osteoporosis and RA. The patient had a stroke in 2000 but was independent in her activities of daily living. In 2021, the patient underwent endoscopic submucosal dissection for colorectal cancer at another hospital, and the pathological diagnosis was adenocarcinoma pT1b. No metastasis or recurrence was noted before her initial visit to our department.

At the initial examination, the patient experienced pain in the mandibular right molar and 65 (indicates right side mandibular) mobility, 6 mild swelling in the distal buccal gingiva, but no inflammation in the 6 proximal buccal and lingual gingiva and 54 buccal and lingual gingiva. Furthermore, 6 of the proximal to 5 buccal gingiva and 5 of the distal to 6 lingual gingiva showed bone exposure and retraction (Fig. 1). Panoramic radiography and computed tomography (CT) showed no obvious bone resorption or osteosclerosis in the 654 area (Figs. 2 and 3), and magnetic resonance imaging (MRI) showed high signal in the T2 short τ inversion recovery image (Fig. 4). Based on these clinical and imaging findings, the patient was diagnosed with MRONJ on the right side of the mandible. Amoxicillin was administered for anti-inflammatory purposes, and the patient's pain improved. At the follow-up visit, the patient was found to have severe lightheadedness and floating dizziness. Therefore, a CT scan was performed, which suggested a cerebellar infarction (Fig. 5). Subsequent MRI showed scattered neoplastic lesions in the left cerebellum and the right frontal lobe on gadolinium contrast T1-weighted volumetric interpolated breath-hold examination (Fig. 6). Neurosurgery was performed to remove the tumor from the cerebellum because of severe dizziness and nausea and anticipated tumor compression into the brainstem. As a metastatic brain tumor was suspected as the brain lesion, 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) was performed postoperatively for the purpose of a systemic search. No obvious lymphadenopathy or other lesions suggestive of malignancy were found, except for a strong accumulation of FDG in the right adrenal gland (Fig. 7). The pathological results showed DLBCL with CD20, CD30, and EBV positivity (Fig. 8). Peripheral blood EBV-PCR testing was performed within our hospital and results were detected at 70 copies/ μg DNA but was not high; thus, retesting was deemed clinically unnecessary and was not performed during or after treatment. Because the patient had a history of MTX therapy and the central lesion was identified as DLBCL, the patient was diagnosed with MTX-OIIA-LPD. MTX treatment was immediately discontinued. Due to the patient's age



Figure 1. Images of the intraoral findings of the patient at the initial visit. Bone exposure was noted in the molars. The gingiva was slightly swollen on the buccal and lingual sides.



Figure 2. Panoramic image. No osteosclerotic lesions were noted in the right molar region of the mandible.

and poor performance status, high-dose MTX was deemed difficult to tolerate. Whole-brain irradiation would have been an option if only central lesions were present; however, because of adrenal involvement, R-CHASE (cyclophosphamide, cytarabine, etoposide, dexamethasone, rituximab) was administered as systemic chemotherapy, including cytarabine, which has central transferring activity. During chemotherapy, oral care was performed regularly to prevent acute inflammation of the MRONJ in the mandibular right molar and keep the exposed bone area clean. However, the extent of bone exposure expanded to 7654. During the outpatient follow-up after chemotherapy, 654 had spontaneously fallen off; therefore, we sculpted the bone exposure area while waiting for the patient's physical condition to recover. The multiple brain lesions and MTX-OIIA-LPD lesions in the right adrenal gland completely disappeared eight months after onset. Subsequently, the patient's physical condition improved without recurrence, and the bone-exposed area became epithelialized.

Discussion

MTX-LPD is a lymphoproliferative disorder that occurs in patients receiving MTX and was first reported by Ellman *et al* (17) in 1991. Since then, similar reports have been published, and the term MTX-LPD has been proposed. In 2001, the WHO histological classification of hematopoietic and lymphoid tissue tumors (3rd edition) included the classification of MTX-LPD (1). However, in 2008, because LPD occurred with biological agents, such as anti-tumor necrosis factor- α agents and tacrolimus, in addition to MTX, the WHO Tissue Classification (4th edition) classified it as OIIA-LPD, a subgroup of IA-LPDs (18). According to WHO,



Figure 3. Computed tomographic image (axial sections). No obvious osteosclerotic lesions were noted in the right mandible.

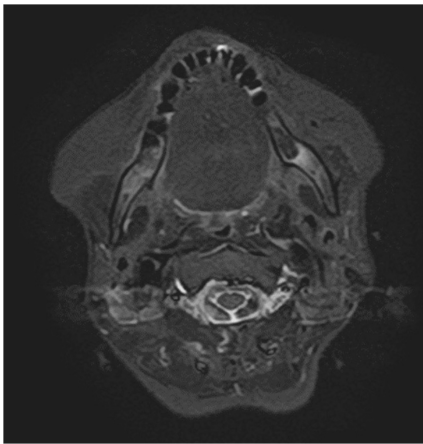


Figure 4. Magnetic resonance imaging (axial sections). High signals were noted in the bilateral mandibular molars.

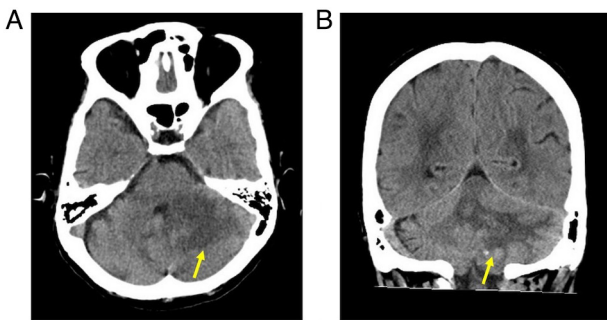


Figure 5. Head computed tomographic image: (A) Axial and (B) coronal. The left cerebellar hemisphere showed a hypointense area, suggesting a subacute infarction (arrow).

the characteristics of MTX-OIIA-LPD are: (1) presence of RA (85% of patients with MTX-OIIA-LPD have RA), (2) similarity to lymphomas occurring in non-immunocompromised individuals, (3) EBV involvement (occurs in approximately half of the cases), and (4) most common type of lymphoma

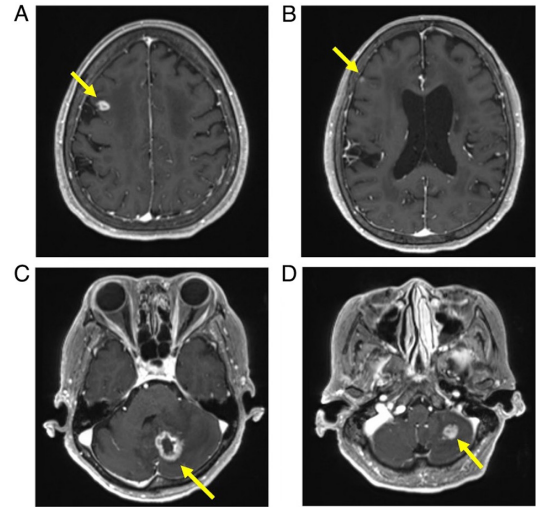


Figure 6. Contrast-enhanced magnetic resonance imaging of the T1-enhanced volumetric interpolated breath-hold examination image (axial sections). (A) Ring-shaped contrast effects were observed in the right frontal lobe (arrow). (B) One contrast effect was observed in the right frontal cortex (arrow). (C) Ring-shaped contrast effects were observed in the left cerebellar hemisphere (arrow). (D) Slight ring-shaped contrast effects were observed in the left cerebellar hemisphere (arrow)

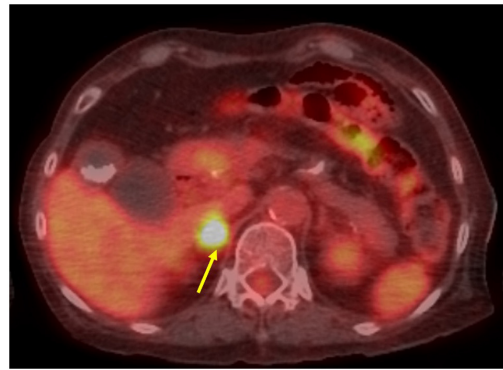


Figure 7. 2-[¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography showed strong accumulation in the right adrenal node (arrow).

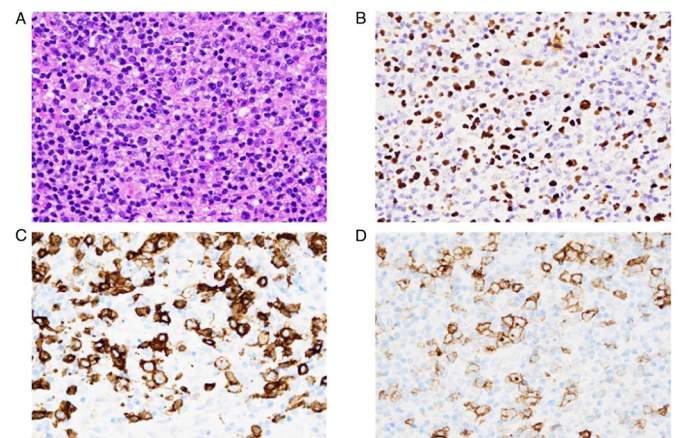


Figure 8. Histopathological examination findings. (A) Hematoxylin and eosin staining showed dispersed Hodgkin-like large cells with small lymphocytes (magnification, x400). (B) *In situ* hybridization of Epstein-Barr virus-encoded small RNAs was positive (magnification, x400). (C) Atypical lymphoid cells were positive for CD20 (magnification, x400). (D) Atypical lymphoid cells were positive for CD30 (magnification, x400).

Table I. MTX-LPD cases in the central nervous system.

No.	Author	Years	Age, years	Sex	Primary illness	Central nervous system symptom	LPD site	MTX duration, years	Pathology	EBER	Regression after cessation of MTX	Additional treatment	(Refs.)
1	Kleinschmidt-DeMasters <i>et al</i>	2008	78	F	RA	Neurological symptoms	Cerebrum	≥10	P/L LPD	+	+	-	(3)
2	Fukushima <i>et al</i>	2013	64	F	RA	Impairment of cognitive function	Cerebrum	4	PTCL-NOS	+	+	High-dose MTX with leucovorin rescue	(4)
3	Migita <i>et al</i>	2013	53	F	RA	Vertigo, vomiting, and double vision	Medulla	1	DLBCL	+	+	Resection of mass	(6)
4	Liu <i>et al</i>	2015	58	M	RA	Depressive disorder, dizziness, vomiting	Cerebrum	2	DLBCL	-	NA	Radiotherapy	(7)
5	Shimada <i>et al</i>	2015	60 ^s	F	RA	Convulsion, impaired consciousness	Cerebrum	7	NA	+	+	-	(8)
6	Kikuchi <i>et al</i>	2016	50	F	RA	-	Hypertrophy of frontal dura mater	3	Intravascular large B cell lymphoma	-	-	R-CHOP + intrathecal chemotherapy (prednisolone+ MTX + cytarabine)	(9)
7	Matsuda <i>et al</i>	2018	76	F	RA	Staggering gait	Cerebrum	2	DLBCL	+	+	-	(10)
8	Miyaza <i>et al</i>	2019	68	F	RA	Hemiparesis	Cerebrum	5	DLBCL	+	+	-	(11)
9	Kawazoe <i>et al</i>	2020	75	M	RA	Gait ataxia	Cerebrum pons	9	DLBCL	Brain- + Stomach	Brain- + Stomach	High-dose MTX rituximab	(12)
10	Uneda <i>et al</i>	2020	68	F	RA	Motor aphasia, right hemiparesis	Cerebrum	≥10	DLBCL	+	+	-	(13)
11	Kawano <i>et al</i>	2021	75	F	RA	Unsteady gait, nausea and vomiting	Cerebellum, cerebrum	3	T-cell lymphoma	-	+	-	(14)
12	Ueno <i>et al</i>	2022	64	M	RA	Ataxia	Cerebellum, cerebrum	3	DLBCL	-	+	-	(15)
			86	F	RA	Weakness	Cerebrum, thalamus	3	NA	+	+	-	
13	Mizushima <i>et al</i>	2022	66	F	RA	Gait disturbance	Cerebrum	13	NA	+	+	-	(16)
			59	F	RA	Staggering gait, memory deficit	Cerebrum	9	DLBCL	-	-	R-MPV Radiotherapy	

Table I. Continued.

No.	Author	Years	Age, years	Sex	Primary illness	Central nervous system symptom	LPD site	MTX duration, years	Pathology	EBER	Regression after cessation of MTX	Additional treatment	(Refs.)
14	Kato <i>et al</i>	2023	75	F	RA	Dizziness	Cerebellum, cerebrum	6	DLBCL	+	+	R-CHASE	Present case

*Detailed ages were not given in the text. P/L LPD, polymorphic/lymphoplasmacytic lymphoproliferative disorder; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; DLBCL, diffuse large B-cell lymphoma; IVLBCL, intravascular large B cell lymphoma; NA, not available; MTX, methotrexate; R-MPV, rituximab, methotrexate, procarbazine, vincristine.

(35%) being DLBCL. On average, the disease occurs ~3 years (0.5-5.5 years) after MTX administration. Furthermore, 60% of patients achieve at least partial remission after discontinuation of MTX (1). In our case, all the characteristics were met.

Although MTX-OIIA-LPD is prone to extranodal involvement (19), there are few reports of MTX-OIIA-LPD in the CNS. We have identified 15 such reported cases in the literature (3,4,6-16) (Table I). The mean age of the patients in these cases was 67.7 years (range: 50-86 years, except for the patient in one case where the details were unknown), the primary disease was RA, and the mean duration of MTX use was 5.6 years (range: 2-13 years; reports stating more than 10 years were considered as 10 years). The histopathologic diagnoses were DLBCL in eight patients, T-cell lymphoma in two, pleomorphic/lymphoplasmacytic lymphoproliferative disease in one, and intravascular large B-cell lymphoma in one; in three cases, the primary disease was not described (20). Reportedly, EBV-DNA in the peripheral blood was positive in patients with MTX-OIIA-LPD who did not require chemotherapy after discontinuation of MTX and went into remission, whereas EBV-DNA was negative in patients who required chemotherapy.

Among the 15 cases of MTX-OIIA-LPD that developed in the CNS, 11 involved patients were EBV-positive. Among them, in 10 cases, the lesions resolved with interruption of MTX, whereas in one case, the tumor shrank after MTX withdrawal, but chemotherapy was administered because the tumor worsened. Considering that it takes ~4 weeks from MTX discontinuation to remission (19) and that remission is not achieved in all cases after MTX withdrawal, we decided that we could not wait for disease shrinkage by MTX discontinuation and decided to administer chemotherapy.

Several patients with RA also have osteoporosis (2), and a number of patients are likely to have been administered with MTX and bone resorption inhibitors concomitantly. However, There are few reports of cases with MRONJ and MTX-OIIA-LPD (21). Furthermore, to the best of our knowledge, there are no reports of concomitant MRONJ and CNS MTX-OIIA-LPD in the literature, as in our own case. Unless there is evidence of metastatic lesions to the jawbone in MRONJ, surgical biopsy is generally not recommended because of the possibility of exposing new fresh bone surfaces (22,23); thus, the diagnosis of MRONJ is made based on clinical symptoms (24) without biopsy. Furukawa *et al* (21) reported a case of MRONJ and MTX-OIIA-LPD in a patient who had been taking bisphosphonates (BP) and MTX. They reported that clinicians should keep in mind that intraoral MTX-OIIA-LPD is sometimes complicated by MRONJ, and that pathological examination is necessary for a final diagnosis.

There have been few reports of MTX-OIIA-LPD in the oral and maxillofacial region (21), and dentists are thought to be less aware of MTX-OIIA-LPD than MRONJ. We were able to identify only one case of MTX-OIIA-LPD and MRONJ occurring simultaneously in the oral and maxillofacial region (21). Moreover, our case is the first to report extraoral MTX-OIIA-LPD and MRONJ. Although simultaneous occurrence of MTX-OIIA-LPD and MRONJ is rare, when a patient with MRONJ is taking MTX, biopsy of the oral lesions should be performed considering oral and extraoral MTX-OIIA-LPD. In addition, systemic search should

be performed in collaboration with related departments, such as rheumatology and hematology, to promptly diagnose MTX-OIIA-LPD and initiate prompt treatment. One of the side effects of MTX is dizziness. In our case, the patient already had CNS and progressive symptoms at the disease onset, different from MTX side effects, and imaging tests were performed, leading to the discovery of a neoplastic lesion in the brain. Neurosurgery was performed to remove the tumor from the cerebellum immediately because of severe dizziness and nausea and anticipated tumor compression into the brainstem and a pathological diagnosis was done. Thus, although MTX-OIIA-LPD of the CNS is rare, we were able to diagnose it early.

In conclusion, oral and maxillofacial surgeons should perform biopsies of oral lesions in patients with RA who are taking BP and MTX and have MRONJ. Further, collaboration with related diagnostic departments, such as rheumatology and hematology, is essential to enable early diagnosis and treatment of extraoral MTX-LPD. Moreover, although central MTX-LPD is rare, as in our case, it is also necessary to collaborate with neurosurgery and other related departments depending on the symptoms.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TK acquired the patient's clinical data, performed the literature review and edited the manuscript. TK, FI, TW, SY and SF contributed substantially to the conception and design of the study. CM and KN acquired data, provided clinical advice and revised the manuscript. TK played a major role in writing the manuscript. TK and CM confirm the authenticity of all the raw data. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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

Competing interests

The authors declare that they have no competing interests.

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