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*Case Report*

# Large Ulceration of the Oropharynx Induced by Methotrexate-Associated Lymphoproliferative Disorders

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**We present a case of a 67–year-old Japanese man with a serious oropharyngeal ulceration that at first seemed to be destructive malignant lymphoma or oropharyngeal carcinoma. We suspected methotrexate (MTX)-associated lymphoproliferative disorder (LPD) induced by MTX treatment for rheumatoid arthritis (RA). About 3 weeks after simple discontinuation of MTX, complete regression of the disease was observed, confirming our diagnosis.**

**Key words:** ulceration, methotrexate, oropharynx, lymphoproliferative disorders

Oral ulceration can occur as a side effect of methotrexate (MTX) therapy, which may often be due to a lack of folic acid supplementation or an overdosage of the drug [1]. Adverse effects, which are experienced by up to 80% of patients on long-term, low-dose MTX therapy, may develop at any stage of treatment, even after 30 years [2–4]. These effects are usually mild and well tolerated, and are relatively easily reversed by folate administration and either reduction or discontinuation of the drug [5]. Iatrogenic lymphoproliferative disorders (LPD) are atypical lymphoid proliferations or lymphomas that arise in patients treated with immunosuppressive drugs such as MTX [6]. Although some case reports have described the spontaneous regression and disappearance of lymphoproliferative lesions after simple discontinuation of MTX [7, 8], MTX-associated LPDs in rheumatoid arthritis (RA) patients could be crucial and sometimes need aggressive treatment, including chemotherapy and/or radiation therapy [7, 9]. Hence, it is important to determine whether or not MTX-associated adverse events are reversible. The present case report describes an RA patient with a seemingly critical oropharyngeal ulceration that was probably induced by MTX therapy and that indeed resolved immediately after MTX withdrawal.

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## Case Report

***Clinical history.*** A 67–year-old Japanese man was referred to our department for evaluation of a large and deep ulceration over the right oropharynx, which limited his ability to open his mouth (Fig. 1). The ulceration looked as if a right tonsillectomy had been performed. Although he had been experiencing pharyngeal pain for 6 months, the pain had recently worsened enough to cause difficulty in ingestion and a tendency toward dehydration. The rest of the physical examination of the head and neck region was unremarkable. There was no ulceration other than at the right oropharynx. Full-body computed tomography revealed only the ulceration over the right orophar-

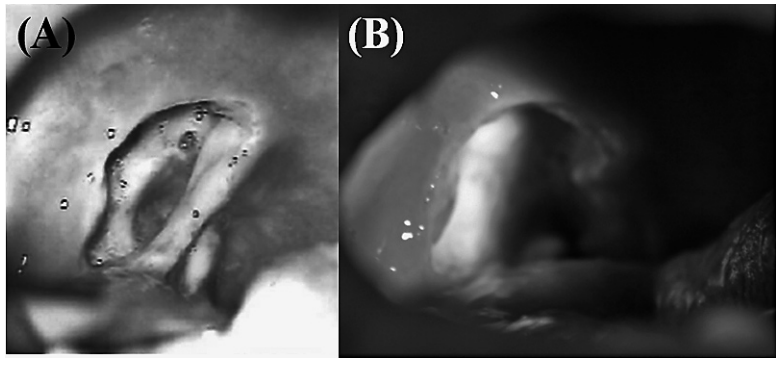


Fig. 1 A large and deep ulceration over the right oropharynx limited mouth opening.

ynx, and no other abnormalities such as lymphadenopathy.

The patient's medical history revealed that he had suffered from RA for 23 years and was currently being treated with MTX, prednisolone, sodium aurothiomalate, and diclofenac sodium. He had been treated for over 20 years with a 6 mg/week dose of MTX (oral administration) and 25 mg/2 weeks of sodium aurothiomalate (intravenous injection), and his disease had been controlled mainly by altering the dose of oral prednisolone (0–10 mg/day). The pain had been controlled by diclofenac sodium (oral administration) with a maximum dose of 75 mg/day. There was no other medication than these 4 kinds of drugs. Since his RA had progressively worsened, the dosage of MTX had been gradually increased to a once-weekly dose of 12 mg/2 weeks during the 10 months prior to his current history and presentation; administration of sodium aurothiomalate had been discontinued 10 months earlier. Our first clinical impression was destructive malignant lymphoma or carcinoma of the oropharynx. We also considered the possibility of MTX therapy as a causative even though we did not consider the dose of MTX to be very high.

To make a definitive diagnosis, a biopsy of the ulcer was performed. The biopsy samples demonstrated an ulcer with granulation tissue, and severe inflammatory cell infiltration was found in the submucosa (Fig. 2A). A high-power view revealed polymorphic features in the lesion, namely, numerous large atypical lymphoid cell proliferations with small lymphocytes (Fig. 2B). On immunohistochemical study, the large atypical lymphoid cells were positive for CD20, CD79a, and CD30, and negative for CD3 (Fig. 2C). These cells were also positive for Epstein-Barr virus-encoded small RNA oligonucleotides (Fig. 2D). Thus, a diagnosis of MTX-associated LPD was made.

In laboratory findings, the white blood cell count was 8,310/$\mu$l; C-reactive protein, 5.64 mg/dl (reference range, $<$ 0.30 mg/dl); lactate dehydrogenase, 215 IU/l (120–240 IU/l); and soluble interleukin-2 receptor, 666 U/ml (122–496 U/ml).

The patient was admitted to our hospital to receive intravenous nourishment. He was advised not to take any more MTX, and was started on the intravenous administration of 10 mg prednisolone/day. Cessation of MTX gave him immediate relief from the pharyngeal pain. Surprisingly, a review after 3 weeks demonstrated almost complete resolution of the ulcer and abatement of his symptoms (Fig. 3). Our histological diagnosis of MTX-associated LPD was thus confirmed by the clinical outcome. The patient is now treated with prednisolone and tacrolimus hydrate, and his RA remains well controlled.

## Discussion

Since MTX mostly affects cells undergoing rapid turnover, including mucosal and bone marrow cells, myelosuppression and mucositis are among the more commonly reported adverse reactions to MTX [10]. Oral ulceration is experienced by 14% of patients on long-term, low-dose MTX therapy, and established lesions are exacerbated by further administration of the drug but heal within about 3 weeks after MTX discontinuation [11]. This side effect of MTX is generally dose-dependent and often occurs due to an

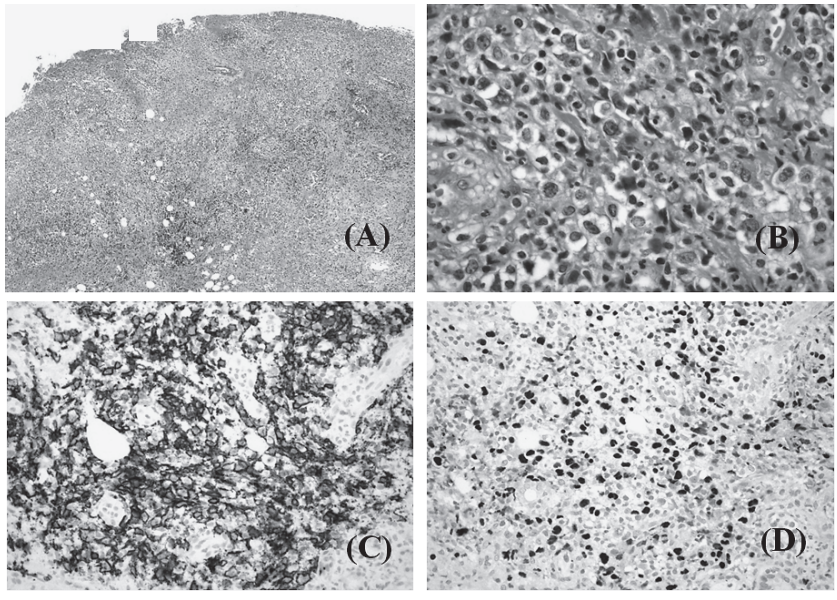


Fig. 2 The biopsy samples demonstrated an ulcer with granulation tissue, and severe inflammatory cell infiltration was seen in the submucosa (**A**) (Hematoxylin and eosin staining). A high-power view revealed polymorphic features of the lesion, namely, the proliferation of numerous large atypical lymphoid cells with small lymphocytes (**B**) (Hematoxylin and eosin staining). On immunohistochemistry, large atypical lymphoid cells were positive for CD20 (**C**), CD79a, and CD30, and were negative for CD3. Moreover, large atypical lymphoid cells were positive for Epstein-Barr virus-encoded small RNA oligonucleotides (**D**).

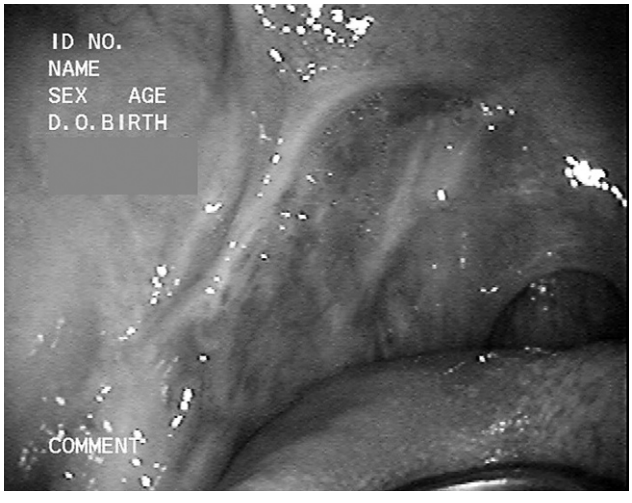


Fig. 3 Three weeks after the cessation of MTX, almost complete resolution of the ulcer was observed. Now the patient can open his mouth fully.

accidental overdosage of MTX [12]. MTX is usually given in a once-weekly dose of up to 25 mg [13]. Hence, it was not likely that the side effect seen in our patient was due to overdosage of MTX, because the maximum dosage in the present case was only 12 mg/week. Oral side effects are of significance to the patient not only because of the pain but also as a factor affecting diet, exacerbating folate deficiency, causing weight loss, and leading to a general deterioration of health [14]. It has been reported that folic acid supplementation can result in a 79% reduction in mucosal and gastrointestinal side effects of MTX [15]. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce MTX excretion by their effect on renal tubules. Hence, the British national formulary advises that the MTX dose should be carefully monitored in patients concurrently receiving aspirin or other NSAIDs [12]. When RA and oral ulceration worsen, patients may be inclined to increase their NSAID dosage, which might result in a vicious cycle that includes worsening of the oral ulceration. Our patient was also treated with diclofenac sodium, but the maximum dose was 75 mg/day. Although sodium aurothiomalate may also induce oral ulcers [16], administration of this drug in the present case was stopped at least 4 months prior before the symptom of pharyngeal pain first occurred.

Adverse events with MTX are usually mild and well tolerated [5]. To our knowledge, the ulceration of

the oropharynx in the present case seems to be the most advanced one associated with MTX therapy that has ever been reported. Thus, we considered that this ulceration was the LPD lesion itself, not the advanced stage of oral ulceration or LPD combined with oral ulceration, although it may be difficult to show evidence to back up this assertion. The frequency of extranodal occurrence of MTX-induced LPD is about 40% [17]. Since RA disease activity correlates with higher rates of malignant lymphoma and LPD [18], the possibility of iatrogenic LPD or malignant lymphoma was suspected in the present case. In MTX-associated LPD patients, the mean duration of MTX treatment was 5.2 years (range, 1.4–13 years) with a mean cumulative dose of 2,200 mg (range 500–5,200 mg) [19]. In the present case, the duration of treatment was about 20 years and the total dose of MTX was about 3,800 mg. Although it has been reported that there was no relationship between the total dose of MTX or the duration of MTX treatment and the occurrence of LPD in RA patients [17, 20, 21], the extremely long period of MTX treatment in the present case might be related to such a severe LPD lesion. In the present study, histological examination and clinical outcome revealed a diagnosis of MTX-associated LPD, which is a form of immunosuppression-related LPD. As in the present case, about 40% of LPD in RA patients treated with MTX are EBV-positive [6, 11]. Latent EBV infection may be involved in the development of EBV-associated B-cell LPDs, like those occurring in immunosuppressed patients [21]. It is hypothesized that the withdrawal of MTX results in partial recovery of the immune system, with subsequent elimination of the malignant clone due to enhanced oncogenic surveillance [22]. Although EBV-positive LPDs or lymphomas have a special tendency to undergo spontaneous remission after MTX is withdrawn [6, 7], it was striking that even such an extensive and destructive lesion, as in the present case, completely regressed within 3 weeks after MTX was simply withdrawn. Steroidal or nonsteroidal anti-inflammatory drug use is unlikely to have been responsible for the disease remission seen in our patient [23]. On the other hand, EBV-associated lymphoma can sometimes be lethal [24]. Hence, pathological examination was deemed to be important in the present case. If no remission was seen within 3 weeks of MTX withdrawal, the therapeutic plan was to immediately treat the condition as a diffuse large B-cell lymphoma (DLBCL); most cases of these are non-Hodgkin's B-cell lymphomas of the large cell or diffuse mixed type [25], although he did not perfectly fulfill the pathological criteria for DLBCL.

Physicians should be aware of the adverse effects of MTX therapy and the possible value of MTX cessation with subsequent close monitoring for regression prior to considering radiotherapy or chemotherapy in patients receiving MTX therapy, even if the lesions look like destructive lymphomas. Further, since some patients with initial regression of LPD after cessation of MTX experience a recurrence of LPD at a later date [26], patients with MTX-associated LPD should continue to be monitored for a while, even after complete recovery from the disease.

In conclusion, patients in whom MTX-associated lymphomas or LPDs are suspected should be initially managed by withdrawal of MTX. If no regression is seen within 3 weeks after MTX cessation, chemotherapy and/or radiation therapy should be considered as soon as possible in order to avoid disease progression. Histological diagnosis and close monitoring for regression after MTX cessation are important in these patients.

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