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## Case report

# Severe stomatitis caused by misuse of methotrexate in an elderly patient with chronic rheumatoid arthritis

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## ABSTRACT

Methotrexate (MTX) is an antifolate that has been used as a chemotherapeutic agent for the treatment of neoplasm, such as leukemia and osteosarcoma. Moreover, MTX is also commonly used for treatment of chronic rheumatoid arthritis (RA). Here, we report a case of severe stomatitis in a patient with RA, which was caused by misuse of MTX. An 83-year-old female patient visited our department with the chief complaint of oral mucosal pain, accompanied by extreme fatigue. Severe stomatitis lesions were observed throughout her oral mucosa. Moreover, blood examination revealed pancytopenia. The patient reported a history of RA, and had been prescribed MTX since 2004. Although 6 mg MTX should be used twice per week, the patient mistakenly used MTX every day following her last consultation, for a period of 1 month. These findings led to a diagnosis of severe stomatitis, pancytopenia, and sepsis, all induced by misuse of MTX. Ultimately, she was treated with blood transfusion, antibiotics, and intravenous hyperalimentation, as well as administration of granulocyte colony-stimulating factor.

MTX for the treatment of RA should be carefully managed to limit the risk of its misuse, especially in elderly patients, because of the severity and potential lethality of symptoms.

## 1. Introduction

Methotrexate (MTX), commonly used in treatment of various malignancies, is also used as a first-line therapy for treatment of rheumatoid arthritis (RA). In Japan, MTX is recommended for use in RA patients who no longer respond to normal amounts of other disease-modifying anti-rheumatic drugs (DMARDs). A dose of 5–35 mg MTX is typically administered once per week. The most common adverse effects of MTX treatment are gastrointestinal and bone marrow toxicities. Moreover, these adverse effects are dose-dependent and can be potentially fatal; therefore, when they develop, MTX treatment is reduced or stopped, and folic acid is administered. Although stomatitis is a common adverse effect of MTX therapy during treatment of malignant disease, it is uncommon in MTX therapy for treatment of RA [1,2]. Here, we report a case of an elderly patient who exhibited severe stomatitis accompanied by febrile neutropenia; this stomatitis was caused by misuse of MTX during treatment of RA. Elderly patients with chronic diseases are often treated with multiple medications; thus, they are at great risk for drug misuse, especially in cases of dementia. Therefore,

dental practitioners should be mindful of the potential risk for drug misuse, as oral manifestations may provide an initial sign of drug misuse symptoms.

## 2. Case report

An 83-year-old female patient was referred to our hospital in 2016 with a chief complaint of oral mucosal pain, accompanied with extreme fatigue. The patient had experienced those symptoms for approximately 1 week prior to her first visit to our department; she had been treated with vidarabine ointment, steroid ointment, rebamipide and acetaminophen, as directed by her primary physician. However, those symptoms had worsened, so she was referred to our department. On initial assessment, she was febrile (37.7 °C) and exhibited extreme fatigue. Extraoral examination revealed conjunctivitis in the left eye. Intraoral examination revealed multiple stomatitis lesions throughout her mouth, including on labial, buccal, palatal, and oral floor mucosa (Fig. 1A–C). These lesions were irregularly shaped and covered with a whitish pseudomembrane. Blood examination revealed pancytopenia

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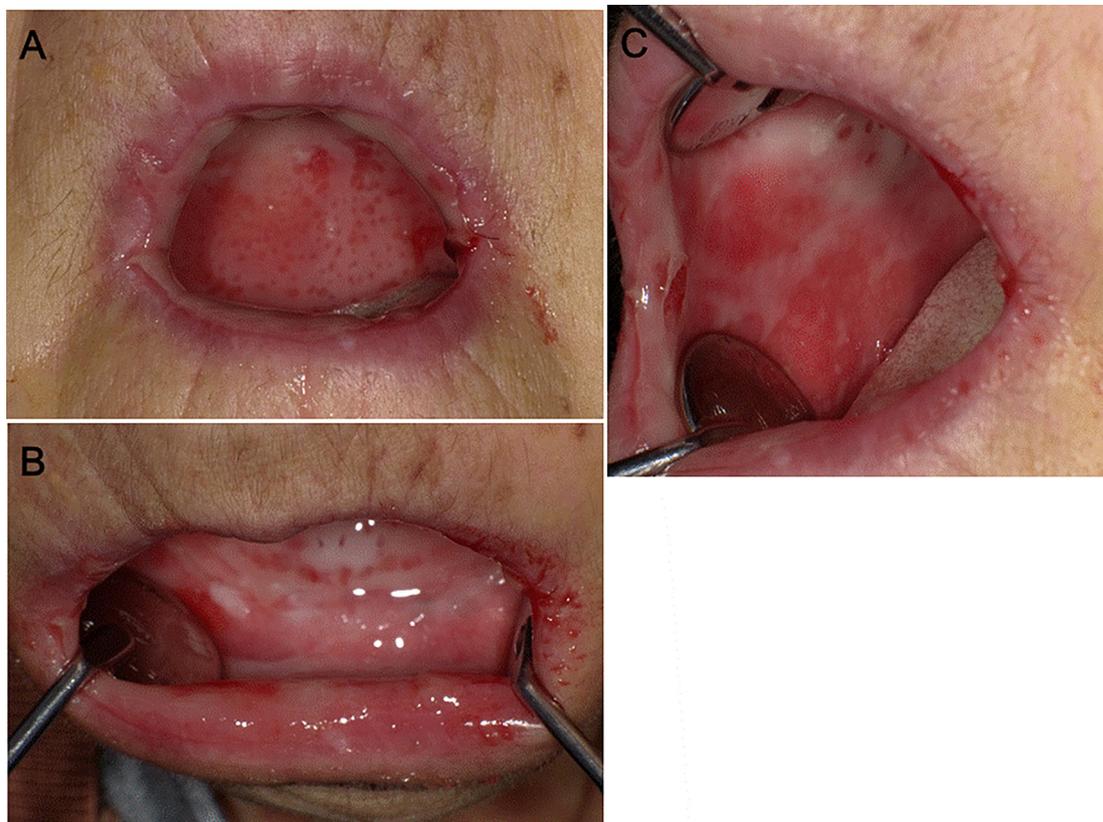


Fig. 1. An intraoral photograph revealing a severe stomatitis lesion in the (a) labial and palatal, (b) oral floor, (c) right buccal mucosa.

Table 1

Results of laboratory examination of the patient’s blood at time of admission. Laboratory examination of the blood revealed pancytopenia, high CRP, mild renal dysfunction, and liver dysfunction. TP, Total protein; Alb, Albumin; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; WBC, white blood cells; CRE, Creatinine; eGFR, estimated glomerular filtration rate; RBC, Red blood cells; CRP, C-reactive protein; Hb, Hemoglobin; PLT, Platelet. Anti- dsg 1 ab, Anti- desmoglein 1 antibody; Anti- dsg 3 ab, Anti- desmoglein 3 antibody; Anti- BP180 ab, Anti- BP180 antibody.

Test		Result	Normal value
TP	(g/dL)	6.2	6.7–8.3
Alb	(g/dL)	3.3	4.1–5.1
AST	(U/L)	87	12–31
ALT	(U/L)	91	8–40
CRE	(mg/dL)	0.78	0.40–0.80
eGFR		52.9	
WBC	( $\times 10^3/\mu\text{l}$ )	11.7	33–86
RBC	( $\times 10^4/\mu\text{l}$ )	254	386–492
CRP	(mg/dl)	7.75	0–0.14
Hb	(g/dL)	8.6	11.6–14.8
PLT	( $\times 10^3/\mu\text{l}$ )	2.3	15.8–34.8
Anti- dsg 1 ab	(U/mL)	< 3	< 20
Anti- dsg 1 ab	(U/mL)	< 3	< 20
Anti- BP180 ab	(U/mL)	< 3	< 9

(WBC: 1170/ $\mu\text{L}$ , Hb: 8.6 g/dL, PLT:  $2.3 \times 10^4/\mu\text{L}$ ), elevated CRP (7.75 mg/dL), mild renal dysfunction (eGFR: 52.9) and liver dysfunction (AST: 87 U/L, ALT: 91 U/L) (Table 1). Initially, systemic illnesses were suspected, such as autoimmune diseases, herpesvirus infection, or pemphigus. However, the patient reported a medical history of RA, and had been prescribed with the following medications since 2004: MTX (6 mg/week), prednisolone (4 mg/day), celecoxib (400 mg/day), alfacalcidol (1  $\mu\text{g}/\text{day}$ ), rebamipide (200 mg/day), misoprostol (600  $\mu\text{g}/\text{day}$ ) and folic acid (5 mg/day). During verbal interview, it was revealed that she had mistakenly used MTX every day for one month, rather than

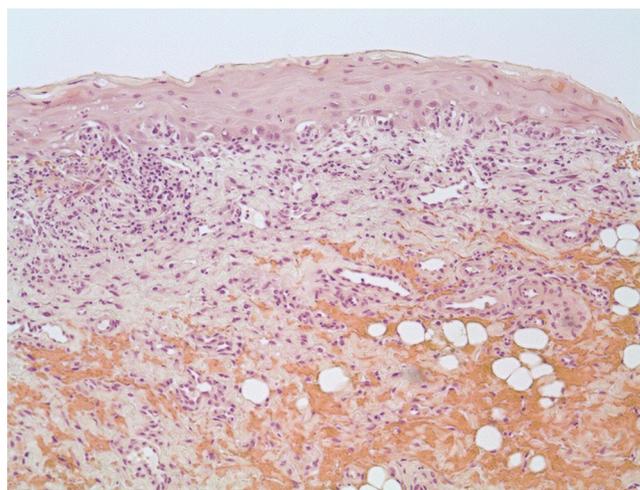


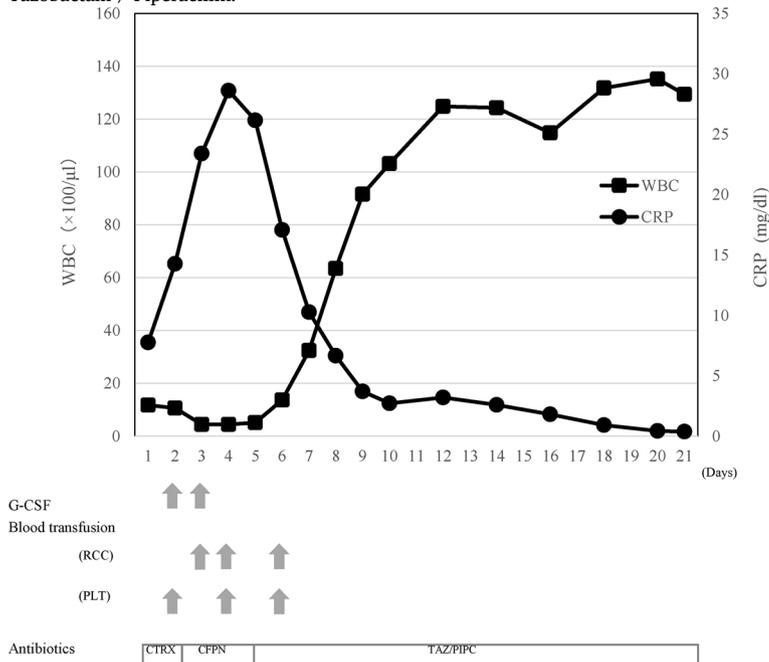
Fig. 2. Histopathological findings of the biopsy specimen. Microscopic examination showed a thinning of squamous epithelia due to loss of basal and parabasal cells. The inflammatory cells including lymphocytes and neutrophils infiltrated in the submucosal tissue. The lesion was diagnosed as severe mucositis.

twice per week as prescribed. Ultimately, she was diagnosed with severe stomatitis, pancytopenia, and sepsis, all of which were strongly suggested to be induced by misuse of MTX. A biopsy specimen was taken from labial mucosa. Histopathologically, the surface epithelium was thinned and the rete ridges were disappeared. Lack of the basal and parabasal cells was noted. The inflammatory cells including lymphocytes and neutrophils diffusely infiltrated in the submucosal tissue. The lesion was diagnosed as severe mucositis (Fig. 2).

The patient was admitted to our hospital and received intensive treatment, including blood transfusion and intravenous

**Table 2**

Therapeutic course resulted in changes in WBC and CRP values. G-CSF, granulocyte-colony stimulating factor; CTRX, Ceftriaxone; CFPN, Cefepime; TAZ/PIPC, Tazobactam / Piperacillin.



hyperalimantation, as well as administration of both granulocyte colony-stimulating factor therapy and prophylactic parenteral antibiotics for her pancytopenia (Table 1).

For oral management during intensive treatment, she was instructed to gargle with sodium azulene sulfonate; she also underwent application of dimethyl isopropylazulene or Vaseline. There were gradual improvements in her general condition, pancytopenia, and oral mucositis after MTX interruption, and she was referred to another hospital for recuperation and physical rehabilitation on day 22 of admission.

**3. Discussion**

The estimated prevalence of RA has been estimated at 1.0% of the Japanese population; a large portion (27%) of these RA patients are treated with MTX [3].

MTX inhibit the nucleic acid synthesis by inhibiting activation of folic acid, and is therefore effective for treatment of RA [4]; for this purpose, MTX is usually administered once per week, and the typical worldwide dose range is 7.5–25 mg/week [5].

Toxicity of MTX is reported to be dose-dependent; thus, it is more frequently observed when high-dose MTX is used for treatment of malignant disease [1]. The most common adverse effects of MTX are gastrointestinal and bone marrow toxicities [2], especially when MTX is used at high doses [5,6,7]. However, stomatitis is more frequently observed than other adverse effects when MTX is used at low doses for treatment of RA [2]. MTX accelerates active oxygen production, thereby increasing free radicals in oral mucosa, which directly injure cells and gap junctions, facilitating mucosal damage [8,9]. Moreover, the stomatitis may occur as an early sign of systemic failure [10].

Drug adherence is a critical health issue in elderly patients. Non-compliance, over-compliance or under-compliance has been reported in > 28% of people who are > 65 years old [11]. Several factors can affect medication adherence in elderly patients, including advanced age, low education level, physical and mental status, and health literacy [12]. Medication factors can also affect adherence in elderly patients; these factors include complexity of the medication regimen, as well as poor labeling instructions, and high medication costs [13]. MTX is commonly administered once per week for treatment of RA, a regimen

that decreases the risk of adverse effects. However, MTX treatment facilitates the development of confusion, thereby increasing the risk of drug misuse [5]. In fact, the patient in this report had been correctly prescribed with MTX 6 mg/week; however, she mistakenly used 28 mg/week for the preceding 1 month prior to presenting in our department. The patient self-managed her medication regimen because she lived alone at that time. Hence, living situations may be an important factor affecting medication adherence in elderly people (Table 2).

Oral manifestation may be an initial sign of adverse reaction to prescription drug misuse; therefore, dental practitioners should be aware of stomatitis, especially in elderly patients who are prescribed with many medications for multiple chronic diseases. As we have shown in this report, stomatitis can be caused by medication misuse, and these elderly patients are at great risk for medication misuse.

**Conflict of interests**

The authors declare that they have no conflict of interests.

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**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

**Ethics approval and consent to participate**

Because this report involves no experiment, ethics approval is waived.

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