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Case Report

Three Cases of Methotrexate-induced Oral Erosion and Ulcers without Conjunctivitis Mimicking Stevens-Johnson Syndrome

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Summary

We report three cases of methotrexate (MTX)-induced oral erosions and ulcers mimicking Stevens-Johnson syndrome (SJS) in older women with rheumatoid arthritis, although they did not had conjunctivitis. Furthermore, age, dehydration, and renal dysfunction could trigger adverse reactions of MTX, but one patient underwent dialysis, which is a contraindication for MTX. It is sometimes very difficult to differentiate the toxicity of MTX from SJS. Learning from the three cases, we propose that oral mucosal erosions without conjunctive mucosal inflammation, leukopenia, and thrombocytopenia differentiate MTX toxicity from SJS. Furthermore, our patients nearly recovered from myelosuppression within seven days and recovered from mucosal erosions characteristic of MTX toxicity within 14 days. These clinical courses could also be characteristic for MTX toxicity rather than SJS, although quick recovery does not happen in all cases. Therefore, physicians who prescribe MTX must accurately know MTX-induced adverse reactions to recognize them early. Furthermore, as seen in our patients, oral mucosal erosions occur often. Therefore, dermatologists or others who examine these symptoms should consider that mucosal erosions mimicking SJS could be an adverse reaction of MTX, regardless of whether or not SJS/toxic epidermal necrolysis is suspected.

Key Words: oral mucosal erosions, methotrexate, myelosuppression, Stevens-Johnson syndrome

Introduction

Methotrexate (MTX) is widely used to treat various diseases, especially rheumatoid arthritis (RA). However, before administering MTX, precautions must be taken, and contraindications must be considered to prevent potentially severe adverse reactions[1]. MTX-induced adverse reactions range from pneumonia (likely from MTX hypersensitivity)[2] to opportunistic infections and lymphoproliferative disorders (from immunosuppression), and myelosuppression and liver dysfunction (from MTX toxicity)[1,2]. Additionally, MTX targets highly replicative cells in a dose-dependent manner, causing MTX-induced epidermal necrosis (MEN)[3], gastrointestinal mucosal necrosis[4], and mucosal erosions and ulcers[5]. Pancytopenia is also possible and can be life-threatening, as can MEN and gastrointestinal mucosal necrosis.

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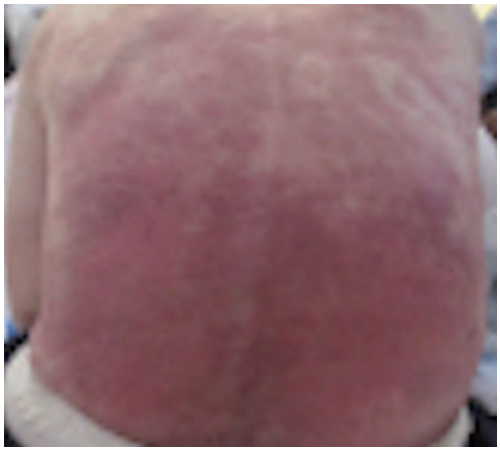

Figure 1 The patient in Case 1 presented with irregularly shaped, fresh red erythema and erythematous spots on the back.

Herein, we report three cases of methotrexate-induced oral erosions and ulcers mimicking Stevens-Johnson syndrome (SJS) in older women who did not have conjunctivitis. We also propose some critical points to differentiate MTX-induced adverse reactions from SJS.

Case Presentations

Case 1

A 78-year-old woman presented with cellulitis in the right lower leg for one week and a low-grade fever. Then she was suspected of SJS and was referred to our department because of newly developed oral pain and erythema on the trunk. The patient had taken 4 mg of prednisolone daily and MTX 12 mg/week without folic acid for RA for ten years. The physical examination found irregularly shaped, fresh red erythema distributed on the trunk and lower legs (Fig. 1), including erythematous spots with a target-like appearance and erosions. The oral cavity, but not the ocular mucosa, was reddish with erosions. The laboratory test results were: white blood cell (WBC) count: 1400/μL, red blood cell (RBC) count: 3.57×10^6/μL, platelet count: 6.7×10^4/μL, aspartate aminotransferase: 32 U/L, alanine aminotransferase: 34 U/L, lactate dehydrogenase: 328 U/L, blood urea nitrogen (BUN): 23 mg/dL, creatinine: 0.68 mg/dL, and C-reactive protein (CRP): 10.73 mg/dL. Oral MTX was discontinued, but the patient was admitted to our hospital the next day owing to decreased numbers of WBCs (1300/μL), neutrophils (127/μL), and platelets (1.3×10^4 μL). She had been given calcium folinate and fluid replacement for three days because it was judged to be a symptom due to the toxicity of MTX. The levels of BUN and creatinine decreased to 7 mg/dL and 0.53 mg/dL, respectively, suggesting she was in mild dehydration before administration. The WBC and platelet counts were normal six days after administering cefazolin sodium, platelets and filgrastim in addition to calcium folinate. The erythema, oral erosions and fever faded within one week and disappeared two weeks after the administration. We suspected that mild dehydration from cellulitis and the cellulitis medication (probably non-steroidal anti-inflammatory drugs) caused the increased blood levels of MTX, although the blood levels of MTX were analyzed on the day of admission and were under the detectable level.

Case 2

An 85-year-old woman presented with a high-grade fever and stomatitis for ten days. She was suspected of SJS and was referred to our department. The patient had taken MTX with folic acid for two years for RA. A physical examination identified erosions on the lower lip and oral cavity (Fig. 2, 3). The laboratory test results were: WBC count: 600/μL, RBC: 190×10^4 μL, platelet count: 6.5×10^4/μL, CRP: 12.35 mg/dL, BUN: 41 mg/dL, and creatinine: 1.4 mg/dL. Oral MTX was discontinued, then the patient received meropenem hydrate, filgrastim and a blood transfusion. The WBC and platelet counts were normal six days later, and the erythema and oral cavity erosions disappeared two weeks later. The MTX dosage had been increased from 6 mg/week to 8 mg/week two months earlier, which may have contributed to the increased blood levels of MTX; age and renal dysfunction may have also been involved, while the blood levels of MTX were analyzed on the day of admission and were under the detectable level.

Case 3

A 65-year-old woman, who had been on dialysis for four years due to kidney failure caused by chronic nephritis, presented with pancytopenia ten days after starting MTX 6 mg/week without folic acid for RA. Furthermore, the patient developed a high-grade fever

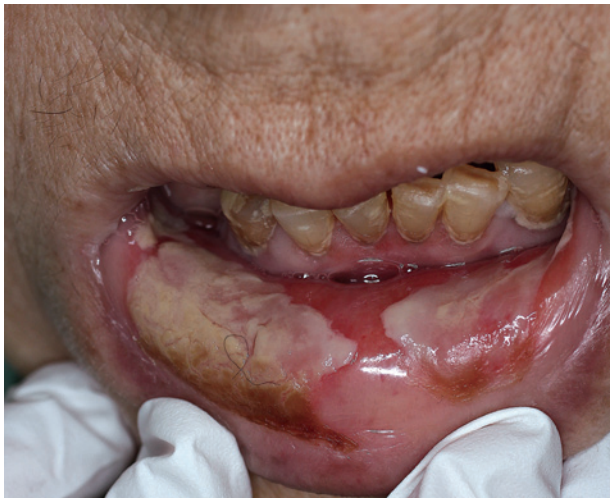

Figure 2 The patient in Case 2 presented with erosions and ulcers with white belag in the lower lip.

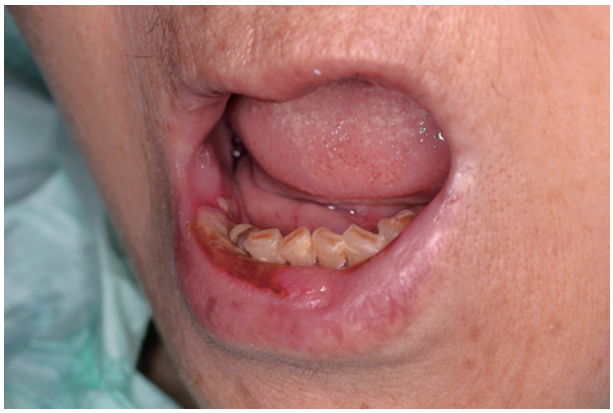

Figure 3 Lower lip erosions (Case 2).

and erythema on the buttocks one day after taking MTX. She was suspected of SJS and was intravenously given forty milligrams of prednisolone sodium succinate for the fever and the rash for three days one week after starting MTX. However, the patient was referred and admitted to our hospital for pancytopenia and lower lip and oral mucosal erosions (Fig. 4). The laboratory test results were: WBC count: 400/μL, RBC count: 2.68 × 10^6/μL, platelet count: 0.9 × 10^4/μL, and CRP: 5.92 mg/dL. She had been given calcium folinate for three days, although the blood levels of MTX were analyzed on the day of admission and were under the detectable level. Since prednisolone sodium succinate resolved the fever, 40 mg per day of oral prednisolone was administered and then tapered off after four weeks. The patient also received filgrastim and several blood and platelet transfusions. Six days after admission, the number of WBCs returned to normal. The number of platelets also increased, but it took one month to return to the pre-onset level. The lip and oral cavity erosions disappeared within two weeks. In this case, dialysis was a contraindication for MTX administration in Japan.

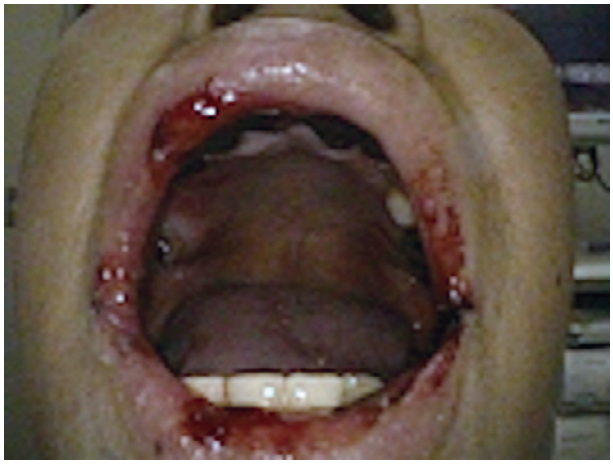

Figure 4 The patient in Case 3 presented with erosions and ulcers with crust on the upper and lower lips.

Discussion

We experienced three cases of adverse reactions due to MTX toxicity, presenting as leukopenia, thrombocytopenia, and lip and oral mucosal erosions. However, each patient was referred to our department for suspected SJS. At first, drug or infection-induced SJS was considered in addition to adverse reactions to MTX because of the clinical similarities, such as lip and oral mucosal erosions and fever. Especially SJS due to mycoplasma pneumonia needs to be checked which frequently shows mucosal lesions without rash or with minimal skin lesions[6], which were not found in all three cases. Finally, we diagnosed all cases as adverse reactions to MTX because they had similar clinical courses including oral or lip mucosal erosion without conjunctive inflammation, decreased number of blood cells, and quick recoveries from the symptoms.

Oral mucosal erosions are one of the most frequent adverse reactions from MTX toxicity[5]. They have sometimes been accompanied by MEN, appearing as widespread and extensive erythema and skin detachment[3]. SJS and toxic epidermal necrolysis (TEN) are clinically similar but differentially classified based on

the proportion of lesions. SJS/TEN mimic oral mucosal erosions due to toxicity of MTX with or without MEN and are the most important initial differential diagnosis. MEN and SJS/TEN do differ despite sometimes having similar findings, but it is very difficult in cases. For example, MEN does not have target lesions, which frequently appear in SJS/TEN. However, MEN has small and round erythema in cases, which mimics target lesions in SJS/TEN. An atrophic epidermis, and enlarged reactive epidermal nuclei or nuclear atypia are characteristic for MEN, although degeneration of epidermal cells, which mimics the findings of MEN, is found in SJS/TEN[3]. Furthermore, unlike SJS/TEN, MEN does not have up-regulated inflammatory mediators[3]. However, our cases had increased CRP levels, but this was likely due to febrile leukopenia in Case 1 and 2 because we could not find any signs for organ specific infection and treatment with antibiotics was effective. On the other hand, CRP levels was also increased in Case 3, while we did not use antibiotics because she had no fever when she was hospitalized. This indicates toxicity due to MTX could induce inflammation. Thus, these clinical characteristics make distinguishing between MEN and SJS/TEN difficult. Moreover, differentiating MTX-induced oral erosions from SJS-induced oral erosions is not possible.

Based on these cases, we propose critical points for differentiating MTX-induced adverse reactions from SJS/TEN. MTX toxicity results in oral mucosal erosion without conjunctive mucosal inflammation, leukopenia, and thrombocytopenia. Also, patients with adverse reactions due to toxicity of MTX nearly recover from myelosuppression within seven days and mucosal erosions within 14 days. However, rapid recovery does not occur in all cases, and bone marrow suppression or infection may be lethal in the most severe cases. Our hypothesis is based on a few clinical cases; thus, its accuracy is limited. However, we hope this guidance may help others differentiate SJS/TEN from mucocutaneous MTX toxicity.

These three cases strongly emphasize that physicians who prescribe MTX must have accurate knowledge regarding its adverse reactions to recognize them in the early stages. For example, the patient in Case 3 was a dialysis patient, and MTX was prescribed despite its contraindication. Also notable are the risk factors for adverse reactions to MTX, including older age, a high initial MTX dose without folic acid supplementation, and chronic kidney disease. In addition, severe renal disease and leukopenia are associated with poor MEN prognosis. These risk factors are also related to other adverse reactions due to MTX toxicity, such as myelosuppression and gastrointestinal mucosal necrosis. For example, the patient in Case 1 was older (78 years old), and mild dehydration due to cellulitis in combination with use of nonsteroidal anti-inflammatory drugs may have triggered the adverse reaction. The patient in Case 2 was also older (85 years old) and had chronic renal dysfunction. Thus, increasing the MTX dose two months prior may have caused the adverse reaction. Moreover, we have to know that administration of glucocorticoids is not effective on the adverse reactions due to MTX toxicity but might induce additional infections or conceal MTX-related pneumonia, although glucocorticoid was used in Case 3 because it relieved fever in the beginning.

Oral mucosal erosions, as observed in our cases, occur often, and dermatologists or others who examine these symptoms should consider that mucosal erosions mimicking SJS are an adverse reaction of MTX, regardless of whether or not SJS/TEN is suspected.

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