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Case Report

When weekly becomes daily: mucocutaneous ulceration and pancytopenia after a methotrexate dosing error

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ABSTRACT

The methotrexate is prescribed as a single dose per week for rheumatoid arthritis. It is dangerous if patient consumes the medication daily by mistake. We present a case of a 64-year-old female with diabetes with newly diagnosed rheumatoid arthritis who consumed 10 mg of methotrexate daily for five to six days instead of once weekly. In a few days the patient developed oral painful ulcers, difficulty in swallowing, bilateral leg ulcers with peeling of skin and fever. Blood tests showed pancytopenia, leucocytes were 1.75×10^3/µl, platelets were 50×10^3/µl. The methotrexate was stopped and gave 15 mg of intravenous folinic acid every sixth hourly for five days. Her platelets increased within four days. The oral and leg ulcers began to heal by the end of the first week. Skin ulcers are very uncommon manifestation of this toxicity - but clear instructions for weekly dosing can prevent this medication error.

Keywords: Folinic acid, Medication error, Methotrexate, Mucositis, Pancytopenia

INTRODUCTION

For patients with rheumatoid arthritis, methotrexate is commonly used as a disease-modifying antirheumatic drug, with treatment generally administered once weekly.[1,2] When the same tablet is taken every day, it can cause mouth ulcers and bone marrow suppression severe enough to cause hospitalisation.[3,4] The European Medicines Agency has reported deaths due to such errors.[5] Although oral mucositis is a recognised feature of methotrexate toxicity, ulcerative skin lesions are less frequently described. We present a case report of a female patient, who took MTX daily instead of weekly and developed oral and leg ulcers with pancytopenia.

CASE REPORT

A 64-year-old female patient came with complaints of painful oral ulcers and difficulty in swallowing for six to seven days. She was a known case of type 2 diabetes mellitus and hypertension on treatment. She was diagnosed with Rheumatoid arthritis approximately two and a half months ago and was started on MTX 5 mg once a week. The patient misunderstood and took MTX 10 mg every day for 5-6 days. After 2-3 days later the patient started complaining of oral ulcerations. The patient also developed ulcers over both legs with peeling of skin and discharge, fever upto 102°F was also documented. The patient was admitted to a nearby hospital initially, with suspected MTX toxicity and was started on oral folinic acid. Her blood counts continued to worsen on day 1 and day 2 (Table 1).

On general physical examination the patient was pale and had pedal oedema. Blood pressure was 120/80 mmHg, pulse 80/min and oxygen saturation 96% on room air. There were ulcers and erosions with whitish slough on the inner lips (Figure 1 a-c) and ulcers with peeling skin was

present on both legs. Tests after admission at the hospital showed pancytopenia on day 3 (Table 2). The blood smear showed small, pale red cells with tear-drop and target cells, few neutrophils and some large platelets. The reticulocyte count was 0.46%. Serum creatinine was 0.75 mg/dl. Liver tests were normal apart from alanine aminotransferase of 49 U/l. The international normalised ratio was 1.12 and the activated partial thromboplastin time 44.3 s (control 33.1 s). The serum MTX level was below 0.040 µmol/l. C-reactive protein was 52 mg/l and procalcitonin 0.11 ng/ml. Blood, urine and wound swab cultures were sterile, and cytomegalovirus polymerase chain reaction was negative. A transferrin saturation of 13% and reticulocyte hemoglobin of 19.3 pg.



Figure 1 (a-f): Ulcers and erosions with whitish slough on the inner lips.

Table 1: Blood counts and serum creatinine (at outside hospital).

Test	Reference range	Day 1	Day 3
Haemoglobin (g/dl)	12–15	9.9	8.0
Leucocytes (×10³/µl)	4–10	2.87	1.94
Neutrophils (/µl)	2000–7000	–	–
Platelets (×10³/µl)	150–410	104	63
Creatinine (mg/dl)	0.50–0.90	0.96	–

Table 2: Blood counts and serum creatinine (at our hospital).

Test	Reference range	Day 4	Day 5	Day 6	Day 8
Haemoglobin (g/dl)	12–15	8.6	8.9	8.7	9.8
Leucocytes (×10³/µl)	4–10	1.75	2.40	2.07	3.05
Neutrophils (/µl)	2000–7000	578	600	373	305
Platelets (×10³/µl)	150–410	50	71	140	351
Creatinine (mg/dl)	0.50–0.90	0.75	–	0.67	0.70

Patient was started on intravenous folinic acid 15 mg every sixth hourly for 5 days. The patient platelets improved from 50 to 351 × 10³/µl. The neutrophil count also showed improvement significantly. By 5th day of admission, the oral ulcers were healing and the leg ulcers had clean pink bases (Figure 1 d–f).

The Naranjo score was 8, which showed that the reaction was probably caused due to MTX.[6] The WHO-Uppsala Monitoring Centre assessment was also "probable".[7] The reaction was serious because it needed hospital admission.

DISCUSSION

An unintended change from weekly to daily methotrexate administration is a preventable medication error that may cause severe systemic toxicity.[3,5] The patient took the

medicine 5-6 times within 5 days and became ill within 2-3 days. MTX acts as an inhibitor of the enzyme dihydrofolate reductase.[8] This enzyme is used in rapidly dividing cells in the mouth, gastrointestinal tract, skin and bone marrow. This is the reason for her stomatitis, gastrointestinal bleeding, and low blood cell counts. Folinic acid antagonizes this effect, acting as an antidote.[9]

Oral mucosal injury may precede the development of haematological abnormalities, while cutaneous ulceration can accompany mucositis in severe MTX toxicity.[10] In one case series, three of five patients with toxicity from low-dose MTX, skin erosion occurred in addition to stomatitis.[11] The patient also had leg ulcers.

As her renal function was unimpaired, failure to clear MTX could not be the reason for her this manifestation. MTX serum level was undetectable, but it was measured about 2 weeks after her excessive intake of MTX and folinic acid was started before admission. Her fever and neutropenia raised concern about possible infection, but she had low procalcitonin levels and negative cultures, which ruled out the possibility of sepsis. Nowadays, the European Medicines Agency recommends a weekly reminder on the drug pack and a patient card.[5] In our consultation, writing the day of the week on the prescription and explaining the dose to both the patient and family members are simple steps to prevent this medication error.[12]

CONCLUSION

The administration of MTX at a low dose once daily compared to once weekly can lead to oral mucositis, ulcerations of the skin, and pancytopenia in just one week in the absence of any kidney dysfunction. Unusual findings of leg ulcers in our case need to raise suspicion regarding the usage of MTX and its frequency. The patient recovered following intravenous administration of folinic acid early in the course of this presentation. The inclusion of the day, of the week for every prescription is essential.

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