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Case Report

# Low-Dose Methotrexate Toxicity in a Hemodialysis Patient: A Case Report

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## ABSTRACT

Methotrexate (MTX) is an effective drug used to treat various diseases, especially rheumatological diseases. However, myelosuppression is a severe side effect, the frequency of which increases in patients with renal insufficiency. Here, we presented a chronic hemodialysis patient who developed pancytopenia and mucositis after using low-dose MTX to treat psoriasis.

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## Introduction

Methotrexate (MTX) is widely used to treat various malignancies and chronic inflammatory diseases. This antimetabolite agent impairs DNA synthesis by competitively inhibiting the dihydrofolate reductase enzyme. MTX may cause side effects such as nausea, stomatitis, myelosuppression, hepatic, renal and pulmonary toxicity due to usage in its high doses, decreased elimination and polypharmacy. Since the primary excretion site is the kidneys (90%), MTX may accumulate in cases with impaired renal function. Herein, we presented a subject in the hemodialysis (HD) program and developed pancytopenia and mucositis due to using low-dose MTX to treat psoriasis.

## Case Report

A 30-year-old female patient with psoriasis and hypertension was treated with intermittent HD for end-stage renal disease secondary to membranoproliferative glomerulonephritis. The patient was using ramipril, amlodipine, carvedilol, doxazosin and moxonidine. Two weeks ago, a dermatologist started subcutaneous 7.5 mg/week MTX treatment for psoriasis. Four days after the first dose, the patient developed diarrhoea and increased after the second MTX administration. Two days later, severe widespread abdominal pain developed. There were plaques on the oral mucosa, crusty ulcerations on the lips, widespread erythematous plaques in the body, widespread abdominal tenderness, voluntary defence, and rebound in his

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physical examination. Other system examinations were normal. Abdominal CT angiography performed with the preliminary diagnosis of the acute abdomen revealed diffuse edematous wall thickening, increased mucosal staining, and marked valarectasis in the colon loops, ascending colon, and cecum. In the laboratory examination, leukocyte 1.910/mm³, neutrophil 1360/mm³, hemoglobin 8.7 g/dL, platelet 76,000/mm³, CRP 207 mg/L, vitamin B12 level 125 ng/L in peripheral blood. His blood MTX level was 0.03 mcmol/L. Blood CMV-DNA PCR was negative. There were no parasites in the stool.

A bone marrow biopsy was performed because atypical cells were seen in the peripheral smear. The bone marrow imprint material revealed an increase and paused in early myeloid elements. Although the serum MTX level was low due to the 6-8 hour serum half-life of MTX, we considered MTX toxicity due to pancytopenia and mucositis after the last MTX treatment, and she was hospitalized. We started folinic acid 3x50 mg, granulocyte colony-stimulating factor 5 mcg/kg/day, vitamin B12 replacement and total parenteral nutrition for oral intake insufficiency due to mucositis. Upon the deepening of pancytopenia, we replaced erythrocyte and thrombocyte suspensions. She recovered from neutropenia on the 8th day of his hospitalization. The patient continued the routine HD program. She received ciprofloxacin and metronidazole treatment for ten days. After 15 days of hospitalization, the patient's clinical condition improved, and she was discharged.

## Discussion

Methotrexate is a folic acid analogue, and it binds to dihydrofolate reductase, reducing thymidylate, purine synthesis and cell proliferation. And also, methotrexate is a disease-modifying, anti-rheumatic drug used in treatment schemes of different diseases; however, long-term use may cause side effects in 61% of patients and may lead to discontinuation of the drug in 20% of patients.[1] High-dose MTX is defined as a dose greater than 500 mg/m$^2$ given intravenously and is mainly used to treat diverse malignancies.[2] Low-dose treatment (5 mg to 25 mg once weekly) has been widely and safely used to treat rheumatoid arthritis and psoriasis, and many other rheumatologic diseases.

The kidneys excrete more than 90% of MTX and its metabolites through both glomerular filtration and tubular secretion; therefore, renal failure is a limiting risk factor for side effects that may occur for MTX treatment. Myelosuppression is one of the most feared side effects.[3,4] In our case, oral mucositis and gastrointestinal mucositis developed as side effects besides pancytopenia. According to an analysis of 11 clinical studies of 496 patients, patients using MTX to treat rheumatoid arthritis were found to have a fourfold increased probability of excessive toxicity in patients with reduced kidney function compared to those with average creatinine clearance.[5] As in our case, cases of pancytopenia associated with the use of low-dose MTX have been reported in HD patients.[6-8] Deaths have been reported as a result of the use of 2.5 mg MTX in HD patients.[9,10]

On the other hand, Mori et al.[11] retrospectively analyzed 40 cases of low-dose MTX induced myelosuppression. They stated that serum albumin levels and folic acid supplementation were the most critical risk factors affecting the severity of pancytopenia. In our case, the serum albumin level was not very low and timely, and the appropriate dosage of folic acid replacement perhaps caused pancytopenia to last shorter than expected.

Boey et al.[12] strongly recommended that MTX toxicity be carefully monitored in patients with stage 3 or stage 4 kidney disease, and MTX should not be used in patients with stage 5 kidney disease. Diskin et al. [13] reported that the amounts of MTX in the dialysate were completely equal in the first hour of both HD and peritoneal dialysis, but not after the first hour. Indeed, HD is superior because of the constantly renewed dialysate. But neither method could prevent the patient's death.[13] Alzate et al.[14] prevented MTX-related toxicity in peritoneal dialysis patients by switching to multiple exchange peritoneal dialysis without transferring the patient to HD. In another study, researchers reported that acute intermittent HD with a high-flux dialyzer was effective in MTX clearance in 6 patients.[15]

In 2012, the US FDA approved glucarpidase, a recombinant form of carboxypeptidase G2, a bacterial enzyme that splits MTX into two catabolites for intravenous use in MTX toxicity in renal failure. Currently, data on the use of glucarpidase in low-dose MTX toxicity are lacking.[16] In conclusion, management of MTX toxicity is directed towards increasing MTX elimination in conjunction with folinic acid rescue therapy.

## Conclusion

One of the reasons why MTX is not sufficiently removed by dialysis is the tight binding to plasma proteins and accumulation of metabolites in the cell. Under normal conditions, MTX treatment is not recommended in HD patients. However, it can be applied by reducing the dose, especially in malignant diseases with no alternative option. In this case, MTX was prescribed because there was no response to secukinumab in the treatment of psoriasis. It should be kept in mind that toxicity may develop even with low-dose MTX use in HD patients, and the patients should be followed closely.

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***Conflict of interest***

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

***Authors' Contribution***

Study Conception: TY; Study Design: MS; Supervision: KA; Materials: FA; Data Collection and/or Processing: TY, MRG; Statistical Analysis and/or Data Interpretation: TY, MRG; Literature Review: MS; Manuscript Preparation: MS, AE; Critical Review: AE.

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