

Methotrexate-Induced Pancytopenia and Mucositis Caused by Medication Error

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SUMMARY

The use of methotrexate in routine clinical practice is becoming more common among specialties such as rheumatology, dermatology, oncology and obstetrics. General clinicians are increasingly encountering patients on this drug. Though it has a high safety profile, there is a recognised risk of acute toxicity or long-term complications associated with its use, which can be worsened by several factors such as advanced age, moderate to severe renal impairment, low folate level and/or inadequate folate supplementation, hypoalbuminaemia, polypharmacy causing drug-drug interactions and wrongful administration. We present a case of a 45-year old woman with rheumatoid arthritis who presented with acute pancytopenia and mucositis due to methotrexate toxicity. We highlight its peculiar dosing regimen to minimise prescribing errors.

Keywords: Methotrexate, pancytopenia, mucositis, side-effects, medication error

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INTRODUCTION

Methotrexate (MTX), either as monotherapy or combination therapy with other conventional disease modifying anti-rheumatic drugs (DMARDs) and biologic therapy is the cornerstone treatment for rheumatoid arthritis (RA). The dose used for RA (5mg to 25mg weekly, administered orally or subcutaneously) is considered to be very safe when prescribed in the right setting.^{1,2}

There is a recognised risk of acute toxicity or long-term complications associated with methotrexate which can be worsened by advanced age, moderate to severe renal impairment, low folate level and/or inadequate folate supplementation, hypoalbuminemia, polypharmacy causing drug-drug interactions and wrongful administration.^{3,4}

We present a female patient who was admitted acutely due to complications of methotrexate use. We identify a few early signs that herald MTX toxicity and highlight appropriate dosing as well as clinical and laboratory monitoring of patients to minimise poor outcomes.

CASE PRESENTATION

A 45-year-old woman presented to the rheumatology clinic with multiple joint pain and stiffness affecting some large joints and small joints of the hands and feet of four years duration.

The remaining history was unremarkable. Significant findings were mild synovitis of the wrists and tenderness in the left shoulder.

Diagnostic Assessment

Pre-treatment laboratory tests were as follows: haemoglobin (11.8 g/dL), white blood cell ($4.5 \times 10^9/L$), neutrophil count ($2.62 \times 10^9/L$), platelet ($224 \times 10^9/L$), urea (4.7mmol/L), serum creatinine (115umol/L) with an eGFR of 54 ml/min, aspartate aminotransferase (34IU/L), alanine aminotransferase (24IU/L) and albumin (45g/dL). Erythrocyte sedimentation rate (63mm/hr), hepatitis B and C and HIV were non-reactive. Immune serology showed positive ANA (1:640), anti-dsDNA -negative, raised anti-cyclic citrillunated peptide (73 U/ml, <7.0) and negative rheumatoid factor.

She was diagnosed with rheumatoid arthritis and methotrexate 10mg once weekly, folic acid 5mg once weekly (to be taken the day after methotrexate), prednisolone 20mg daily, hydroxychloroquine 400mg daily, omeprazole 20mg daily and celecoxib 200mg daily were prescribed. At clinical review two weeks later, the only complaint was pain in the right wrist. Medications were well tolerated.

Laboratory monitoring with full blood count, liver and kidney function tests were satisfactory. Subsequent reviews were arranged for 1 month and 3 months due to challenges the patient had attending more frequently. These were uneventful. Medications were restocked and follow-up booked per a 3-monthly schedule.

Follow up and outcome

She presented acutely to the emergency department with oral and peri-anal ulcerations. There was a history of fever and chills, headache, nausea, abdominal pain, diarrhoea, bleeding gums and increased urinary frequency. Positive findings on physical examination were the presence of ulcers in the mouth and vulval region. She was afebrile. Urinalysis and urine culture were normal as was blood culture and chest x-ray. Haemoglobin (10.4g/dL), platelets ($108 \times 10^9/L$), white blood cells (total count – $2.0 \times 10^9/L$; neutrophil count $1.0 \times 10^9/L$) were noted. As her prior laboratory investigations were normal, a diagnosis of methotrexate-induced mucositis and pancytopenia was made.

Upon review of methotrexate dose administration, she reported that the new pharmacist dispensing her drugs had insisted on daily administration, contrary to the weekly tablets she had been taking before. She did not feel empowered to challenge the pharmacist, hence had been taking methotrexate 10mg daily for two weeks prior to presentation.

Methotrexate was stopped immediately and folic acid (leucovorin) given first as a bolus intravenous dose followed by 15mg six hourly for 2 days. Oral lidocaine gel and iodine mouthwash were used for mouth care. There was no indication of concomitant infection, hence antibiotics were not given. Ten days after rescue therapy the full blood count parameters normalised [haemoglobin 11.8g/dL; WBC $8.4 \times 10^9/L$; neutrophil $5.28 \times 10^9/L$; platelet $179 \times 10^9/L$]. She received ten doses of Leucovorin in total. Subsequent treatment was with oral iron supplement and folic acid. Methotrexate was restarted (7.5mg weekly), with clear instructions on the treatment regime given to the patient.

DISCUSSION

Methotrexate is one of the safest DMARDs available. Clinicians and pharmacists, however, need to remain vigilant over its use due to potential complications. Commonly, gastrointestinal disturbances such as nausea, vomiting, diarrhoea and deranged hepatic transaminases may occur in about 60% of patients. Lung complications including acute methotrexate-induced pneumonitis and fibrosis are rare.⁴

Myelosuppression is a rare but a life-threatening complication which can arise suddenly and without warning signs. The prevalence of haematological toxicity is estimated to be around 3%.⁵ Patients may present with leukopenia, thrombocytopenia, megaloblastic anaemia and pancytopenia. Pancytopenia is associated with significant mortality ranging from 17-44%.^{6,7}

When there is pancytopenia within the first few weeks of starting therapy, it suggests an idiosyncratic reaction which is difficult to predict. Reduced cell lines occurring later on in treatment is more suggestive of a cumulative effect.⁵ Regular monitoring of laboratory tests is prudent to be able to detect any abnormalities early on.

Many of the international rheumatological societies have devised monitoring guidelines for patients on DMARDs. General recommendations are: full blood count, liver transaminases and serum creatinine performed at baseline before starting MTX; repeat 2- to 4-weekly for the first 3 months followed by 8- to 12- weekly for the next 3 months and then 12-weekly thereafter.^{8,9} Our patient was able to do the first set of monitoring tests at two weeks, however this became less frequent due to financial constraints; a regular challenge faced by clinicians managing patients in a resource-poor environment.

Methotrexate is classified as an antimetabolite due to its antagonistic effect on folic acid metabolism through the selective inhibition of dihydrofolate reductase, reducing the production of thymidylate and DNA synthesis.¹⁰ As it competes structurally with folic acid, it can also lead to folate deficiency which worsens methotrexate side effects. Tissues undergoing rapid cellular turnovers, such as oral mucosa, gastrointestinal tract and bone marrow cells are the most susceptible to its cytotoxic effects. As a result, early clinical manifestations of oral ulcerations, abdominal pain and diarrhoea can occur, which may herald signs of marrow toxicity as was seen in the case presented.¹¹ Folate supplementation should be prescribed to mitigate the mucosal and gastrointestinal side effects as well as derangement of liver function tests for patients on methotrexate.^{12,13}

Patients should be screened well for renal and hepatic abnormalities as these increase the risk of pancytopenia. Myelotoxicity may arise from toxic serum levels of methotrexate due to delayed elimination of drug in even mild to moderate renal dysfunction or where there is active inflammation and consumption of albumin in inflammation sites or chronic liver disease causing hypoalbuminaemia as it binds to albumin.⁵

Though the patient had mild renal impairment (eGFR 54ml/min) at baseline, this improved to 74ml/min during follow-up. Albumin was within normal range. Despite the slight anomalies, cytopaenia did not occur when methotrexate was being administered properly.

Incorrect dose administration, including dosage frequency errors, and drug interactions are significant yet avoidable causes of toxicity and mortality. As clearly demonstrated, normal monitoring values were observed when methotrexate was taken correctly, ie once weekly for several months, but side-effects ensued with daily administration. The toxic effect of MTX on normal tissue is a function of the duration of exposure to suprathreshold concentrations of the drug rather than the peak level achieved.¹⁴

Certain drugs can cause displacement of methotrexate at binding sites or impact on renal clearance thus increasing the risk of cytopenia. These include high-dose aspirin, trimethoprim-sulfamethoxazole (cotrimoxazole) and penicillins.¹⁵⁻¹⁷ Other associations are doxycycline, ciprofloxacin, phenytoin, omeprazole and non-steroidal anti-inflammatory drugs, but the significance of these interactions have not been substantiated by extensive clinical observations.^{18,19} In cases of presumed toxicity, serum drug levels of methotrexate can be monitored. For patients receiving antibiotics for concurrent infections, it is advised that methotrexate should be withheld for the duration of treatment.⁹

Methotrexate has become common place in our clinical practice. Methotrexate-induced pancytopenia is more common than expected and probably under-reported. As such, specialists and pharmacists alike need to become familiar with its peculiar dosing to minimise prescribing errors. In the case of toxicity, vigilance and prompt identification are paramount. Stomatitis, fever and diarrhoea can precede or accompany pancytopenia and should alert the clinician. Neutropaenia with mucositis also increases the relative risk of septicaemia by four fold compared to patients without mucositis leading to poorer outcomes.¹⁰ Treatment is generally with leucovorin rescue therapy, and if total white cell count is below $1.0 \times 10^9/L$ or values consistently decrease, granulocyte colony stimulating factors (G-CSF) and broad-spectrum antibiotics should be added as indicated, to prevent the adverse outcome. In cases of recent oral overdose, activated charcoal is beneficial in the treatment of methotrexate toxicity as it binds the drug and facilitates urinary excretion.

CONCLUSION

Dosage per tablet and total dose, route and day of administration for methotrexate and folic acid must be clearly

explained to patients. Patients should be informed to watch out for any complications of therapy. This enables the patient to review any directives given to them which may be different from the norm. It is also important to involve carers of patients during consultations. They can be taught the correct dosage and frequency of drug administration to minimise errors. Periodic blood test monitoring should be made available and patients must be encouraged to keep up with the schedule.

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Case Report

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