

A Case of Acute Methotrexate Toxicity

Dear Editor,

Methotrexate (MTX) is an anti-metabolite frequently used in the treatment of psoriasis, rheumatoid arthritis and cancer. Long-term use of methotrexate is associated with hepatic and pulmonary toxicity. Acute methotrexate toxicity may present with extensive cutaneous ulceration, myelosuppression and gastrointestinal symptoms. It is important to recognise this as the drug must be discontinued immediately and rescue measures instituted. We report a patient who was recently commenced on methotrexate for psoriasis presenting with acute methotrexate toxicity following inadvertent overdose of the drug. This case report also highlights the importance of early follow-up and regular laboratory investigations of patients on methotrexate.

Case Report

A 62-year-old Chinese female with a 3-year history of seropositive rheumatoid arthritis was diagnosed with plaque psoriasis affecting the limbs and scalp. She had been on long-term prednisolone, tacrolimus and minocycline prescribed by her rheumatologist. Following the diagnosis of psoriasis, she was commenced on 7.5 mg of oral methotrexate once a week. She was given a 4-month supply of the medication before her next review. However, she presented to the emergency department 2 weeks later with nausea, vomiting and extremely painful and malodorous skin erosions over the trunk, especially over the 'V' of the neck (Fig. 1) and the

intertriginous areas. This included areas both affected and unaffected by psoriasis. She also developed acute, painful lip erosions and oral ulcers which caused difficulty with oral intake and swallowing. She was dehydrated and unwell.

Laboratory investigations on admission showed pancytopenia (haemoglobin 7.5 g/dL, white cell count $1.1 \times 10^3/\mu\text{L}$, platelet $124 \times 10^3/\mu\text{L}$) with neutropenia (absolute neutrophil count $0.8 \times 10^3/\mu\text{L}$, normal range 2 to $7.5 \times 10^3/\mu\text{L}$) as well as acute renal failure, likely from dehydration due to poor oral intake (urea 15.1 mmol/L, creatinine 124 $\mu\text{mol/L}$, bicarbonate 15 mmol/L). Direct questioning revealed the patient had mistakenly ingested the methotrexate on a daily basis for the past 2 weeks, instead of once a week as instructed. A clinical diagnosis of acute methotrexate toxicity was made and the drug was discontinued immediately. Skin biopsy showed apoptotic keratinocytes and focal spongiosis (Fig. 2).

Methotrexate drug level was found to be elevated at 0.02 $\mu\text{mol/L}$. The patient was isolated and nursed in a reverse barrier room in the intensive care unit. Intravenous folinic acid 50 mg was given 6 hourly. Subcutaneous granulocyte-colony stimulating factor (G-CSF) was also given. The patient was covered with broad spectrum empiric antibiotics and hydrated aggressively and sodium bicarbonate was added to aid with alkalinisation of the urine. The cutaneous lesions healed after 2 weeks of treatment with improvement of the blood counts and renal function.



Fig. 1. Painful erosions over the neck.

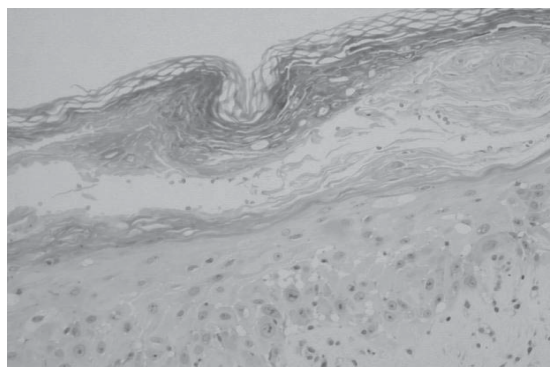


Fig. 2. Skin biopsy showing intra-epidermal split, apoptotic keratinocytes and focal severe spongiosis.

Discussion

Methotrexate is a folate analogue with anti-inflammatory, anti-proliferative and anti-neoplastic properties widely used in the treatment of rheumatoid arthritis, psoriasis and cancers. It inhibits folic acid synthesis by blocking the function of dihydrofolic acid reductase. It has 100,000 times greater affinity than folic acid for dihydrofolic acid reductase. MTX interferes with DNA synthesis, DNA repair, and cellular replication.

MTX has good gastrointestinal absorption and is 50% to 70% bound to albumin in the serum.¹ MTX may thus be displaced by other drugs that bind to albumin (e.g. salicylates, phenytoin, sulfonamides, phenylbutazone). It is excreted mainly by the kidneys, with only a small proportion undergoing hepatic metabolism.

Early recognition is the key to management of MTX toxicity. Cutaneous manifestations, along with evidence of myelosuppression and gastrointestinal symptoms should alert the clinician to the possibility of acute MTX toxicity.

Means of Reducing Inadvertent MTX Overdose

Drug dose schedules should be reinforced to the patient or the carer by a nurse practitioner or pharmacist using an education leaflet. The exact number of MTX tablets that the patient requires should be prescribed to help the patient be accustomed to the dose schedule. Upon commencing MTX, the patient should be given folic acid supplementation. A complete blood count should also be done 7 days after starting MTX as well as after any dose increase. Thereafter, the blood counts can be monitored every 2 to 4 weeks for the first few months.²

Factors Influencing MTX Toxicity

Factors that increase the risk of MTX toxicity include renal impairment, change in MTX dose, drug interactions and infection. Implicated drugs include: penicillin, aspirin, probenecid, phenylbutazone (by acting as competitive inhibitors of tubular secretion); non-steroidal anti-inflammatory drugs, sulfonamides, salicylates (by competing with MTX for binding sites on plasma protein, hence displacing MTX and increasing free MTX levels); trimethoprim-sulfamethoxazole, triamterene, pyrimethamine (as these are also dihydrofolate reductase inhibitors).³ In our patient, none of her other medications appeared to play a significant role in affecting the MTX levels.

Long-term use of MTX has been associated with hepatic and pulmonary toxicity. Guidelines have suggested regular liver chemistry tests and liver biopsy to monitor for hepatic toxicity, while some authorities have suggested monitoring

levels of amino-terminal peptide of procollagen III (PIIINP) in place of liver biopsies.⁴ Acute MTX toxicity, however, presents differently. Our patient with psoriasis initially complained of nausea, vomiting and poor appetite, followed by painful mouth ulcers and skin erosions on the trunk. Lawrence CM et al⁵ described 2 patterns of skin ulceration in patients on MTX for psoriasis – in Type 1 ulceration, the psoriatic plaques became painful and eroded shortly after starting MTX (median 10 days), while in Type 2, the ulcers occurred in clinically uninvolved skin. The former may be confused with an exacerbation of psoriasis, and the MTX dose may be mistakenly increased rather than reduced.

Management of MTX Toxicity

It is of paramount importance that MTX is immediately discontinued. Supportive measures include leucovorin (folinic acid) rescue, alkalinisation of urine, intravenous hydration, G-CSF and blood products. A multidisciplinary approach is crucial to the management of the patient.

Leucovorin replenishes intracellular stores of reduced folate required for the production of thymidylate and purines. It supplies the active form of folic acid by bypassing the blocked enzyme. It is administered parenterally at a dose equal to or higher than the dose of MTX within 12 to 24 hours of the last dose of MTX.⁶ The effectiveness decreases with increasing time intervals. When there is renal impairment, leucovorin should be repeated every 6 hours until the level of MTX falls below 0.1 $\mu\text{mol/L}$.¹ Alkalinisation of urine helps in the excretion of MTX as MTX and its metabolites are poorly soluble in acidic pH. An increase in the pH of urine from 6.0 to 7.0 increases the solubility of MTX and its metabolites by 5 to 8 times. Aggressive hydration also helps with the renal excretion of MTX and its metabolites.

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