Case Report

Severe Myelosuppression Induced by Low-Dose Methotrexate: A Rare but Serious Adverse Effect

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ABSTRACT

Methotrexate (MTX) is a widely used disease-modifying antirheumatic drug (DMARD) primarily prescribed for rheumatoid arthritis, psoriasis, and various malignancies due to its immunosuppressive and antiproliferative properties. While generally safe at low doses, MTX therapy is associated with potentially serious adverse effects, including hepatotoxicity, nephrotoxicity, mucositis, and myelosuppression. Among these, myelosuppression—a condition characterized by the depletion of bone marrow cellular elements leading to pancytopenia—is a rare but life-threatening complication. The pathophysiology of MTX-induced myelosuppression involves the inhibition of Dihydrofolate Reductase (DHFR), impairing folate metabolism essential for DNA synthesis and cell replication. This effect disproportionately affects rapidly dividing hematopoietic progenitor cells, resulting in anaemia, leukopenia, and thrombocytopenia. Elderly patients, those with renal impairment, polypharmacy, or those lacking adequate monitoring are at heightened risk for MTX toxicity. Despite the known risks, MTX is sometimes prescribed in resource-limited or rural settings without adequate baseline investigations or follow-up, increasing the likelihood of severe adverse events. We report a rare case of a 70-year-old female with rheumatoid arthritis who developed severe pancytopenia and myelosuppression secondary to methotrexate therapy, initiated without prior investigations. The patient presented with systemic symptoms including fever, breathlessness, and Purpura, alongside laboratory findings indicative of pancytopenia and renal dysfunction. This case highlights the critical importance of regular haematological and renal monitoring during MTX therapy, early recognition of toxicity symptoms, and cautious use of MTX in vulnerable populations. Through this report, we emphasize the need for stringent prescribing practices and follow-up protocols to improve patient safety and outcomes in methotrexate therapy.

Keywords: Methotrexate (MTX), Myelosuppression, Drug-induced toxicity, Patient safety, Pancytopenia.

INTRODUCTION

Methotrexate (MTX), a folate antagonist, is widely used as a disease-modifying antirheumatic drug (DMARD) for rheumatoid arthritis, psoriasis, and certain malignancies due to its anti-inflammatory and immunosuppressive effects. However, MTX is associated with several adverse effects, the most serious being haematological toxicity such as myelosuppression and pancytopenia, which can be life-threatening[1]. Myelosuppression results from suppression of bone marrow activity, leading to decreased production of red blood cells, white blood cells, and platelets[2].

The pathophysiology of MTX-induced myelosuppression involves inhibition of Dihydrofolate reductase, impairing DNA synthesis in rapidly dividing cells, including hematopoietic progenitors[3]. Risk factors for toxicity include advanced age, renal impairment, hypoalbuminemia, drug interactions (e.g., with NSAIDs or proton pump inhibitors), and improper dosing[4]. Elderly patients are particularly vulnerable due to decreased renal clearance causing drug accumulation[5]. This risk is amplified in rural or resource-limited settings where baseline and follow-up investigations may be inadequate before prescribing MTX.

Several case reports have documented severe myelosuppression after low-dose or inappropriate MTX therapy. For example, a septuagenarian developed pancytopenia after standard MTX dosing for rheumatoid arthritis, highlighting the necessity of regular monitoring even with low doses[2]. Another report described bone marrow aplasia induced by MTX in a patient with rheumatoid arthritis, emphasizing the cumulative risk of chronic therapy[3]. Additionally, mucocutaneous ulcerations and systemic toxicity often present as early signs of MTX overdose or sensitivity[9].

Despite its relatively low incidence, MTX-induced pancytopenia is under-recognized and often diagnosed late when clinical manifestations such as mucositis, petechiae, infections, or anaemia appear[7]. Early detection through routine laboratory monitoring—including complete blood counts and renal function tests—is critical to prevent severe outcomes[6]. Furthermore, patient education about correct weekly dosing schedules and awareness of toxicity symptoms are essential to reduce risks[8].

Our case of a 70-year-old rural female with rheumatoid arthritis and hypertension who developed pancytopenia and Purpura secondary to MTX-induced myelosuppression, exacerbated by unmonitored MTX therapy prescribed without prior investigations, underscores the importance of vigilant monitoring and appropriate prescribing practices, particularly in underserved areas.

CASE REPORT

A 70-year-old married female with a medical history of hypertension for 2 years and rheumatoid arthritis for 3 years was admitted to the High Dependency Unit (HDU) with complaints of bilateral lower limb pain with ulceration for the past 15 days, accompanied by fever for 2 days and breathlessness since the morning of admission. The patient reported a tingling sensation in both lower limbs and appeared disoriented upon examination. Notably, she had a social history of chronic tobacco chewing for 8 years and occasional alcohol use.

The patient had been taking methotrexate 7.5 mg once weekly, diclofenac sodium 50 mg twice daily, and Telmisartan 40 mg once daily for the past 3 years. Methotrexate was prescribed in a rural healthcare setting for bilateral knee pain, presumed to be due to rheumatoid arthritis, without appropriate baseline investigations such as CBC, renal or liver function tests. Over time, the patient developed features of progressive toxicity, likely unnoticed due to the lack of regular monitoring and follow-up.

On admission, clinical examination revealed she was febrile, hypotensive (BP 90/70 mmHg), tachypneic (RR 30 bpm), and had an SpO_2 of 90%. Systemic examination showed bilateral air entry with no added sounds, a soft and non-tender abdomen, and she was conscious but disoriented. Laboratory tests revealed significant pancytopenia: haemoglobin 6.5 g/dL, WBC 3.2 $\times 10^9$/L, and platelet count 32,000/cumm. Neutrophils were reduced (18%), while lymphocytes were elevated (71%). Inflammatory markers were elevated (CRP 58.1 mg/L, ESR 150 mm/hr), and metabolic parameters revealed hyperglycaemia (RBS 373 mg/dL), newly diagnosed diabetes mellitus, elevated BUN (45 mg/dL), and serum creatinine (3.3 mg/dL), indicating chronic kidney injury. Liver function tests showed mildly elevated SGOT and SGPT, and low serum protein (5.5 g/dL).

A peripheral blood smear confirmed pancytopenia with normocytic, normochromic anemia, leukopenia, and severe thrombocytopenia. Autoimmune markers including Anti-CCP were negative and RA Factor was 9.27 IU/mL, ruling out active rheumatoid flare. Imaging (Chest X-ray, USG abdomen) did not reveal any acute pathology. These findings, combined with her clinical picture and medication history, led to a diagnosis of methotrexate-induced myelosuppression.

Methotrexate was immediately discontinued. The patient was started on supportive management including IV fluids, broad-spectrum antibiotics (Piperacillin-Tazobactam and Clindamycin), insulin therapy for glycemic control, folic acid supplementation, multivitamins, and topical hydrocortisone for purpura secondary to thrombocytopenia. She was closely monitored in the HDU and gradually stabilized over the following days.

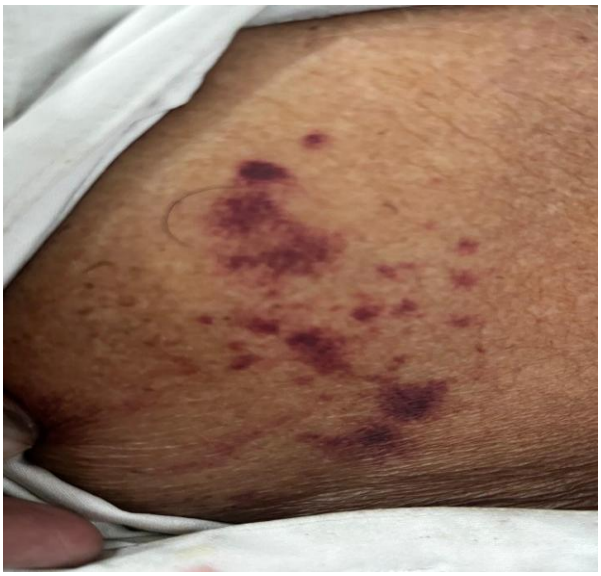

Figure 1: Purpura rash on the patient's thigh due to thrombocytopenia secondary to methotrexate-induced myelosuppression.

This case highlights a critical issue: the unmonitored use of methotrexate in rural healthcare settings without baseline or routine investigations can lead to severe, potentially fatal complications like myelosuppression. Methotrexate, although effective, requires strict monitoring of complete blood counts, liver and renal function, especially in elderly patients and those with co-morbidities. Increased awareness, education, and regular follow-up are essential to prevent such adverse drug reactions in vulnerable populations.

DISCUSSION

Methotrexate (MTX) is a cornerstone disease-modifying antirheumatic drug (DMARD) widely used in the management of rheumatoid arthritis and other autoimmune diseases. Despite its efficacy, MTX can cause severe toxicities, including myelosuppression, which is potentially fatal if not promptly recognized and managed. The primary mechanism underlying MTX-induced myelosuppression involves its inhibition of the enzyme dihydrofolate reductase (DHFR), which leads to depletion of tetrahydrofolate, a critical cofactor in the synthesis of purines and thymidylate. This disruption impairs DNA synthesis and repair, predominantly affecting rapidly dividing cells such as hematopoietic progenitors in the bone marrow, leading to pancytopenia [3,5,10].

In our reported case, a 70-year-old female on long-term low-dose MTX therapy developed severe pancytopenia, complicated by purpura and sepsis. This presentation aligns with findings from Kanderi et al., who documented a septuagenarian with rheumatoid arthritis who similarly developed pancytopenia after low-dose MTX administration. In their case, renal impairment and advanced age contributed to reduced MTX clearance and accumulation, precipitating myelosuppression [2]. This is consistent with our patient's chronic kidney injury, which likely impaired MTX excretion, increasing toxicity risk.

Sáenz et al. also reported a case of severe secondary bone marrow aplasia due to MTX in a rheumatoid arthritis patient, highlighting the cumulative toxicity of prolonged MTX use without proper monitoring. Their patient exhibited similar haematological abnormalities and systemic symptoms, necessitating cessation of MTX and supportive care [3]. Both cases emphasize the risk posed by unmonitored MTX therapy, especially when prescribed without baseline or follow-up investigations, as seen in our patient where MTX was initiated for bilateral knee pain in a rural setting without prior screening.

Additional factors such as drug-drug interactions can exacerbate MTX toxicity. Trivedi et al. described MTX-induced myelosuppression resulting from interactions with other medications that impair its renal clearance or potentiate its effects [4]. Our patient was also on diclofenac, which can reduce renal perfusion, potentially increasing MTX levels. The inflammatory state from infection or sepsis further complicates metabolism and clearance.

Clinically, MTX-induced myelosuppression manifests as pancytopenia—anaemia, neutropenia, and thrombocytopenia—which increase the risk of infections, bleeding, and fatigue. Our patient's laboratory investigations showed marked pancytopenia with elevated inflammatory markers such as CRP and ESR, reflecting systemic inflammation and sepsis secondary to bone marrow suppression. Peripheral blood smear confirmed normocytic normochromic anaemia with severe thrombocytopenia and leukopenia, consistent with MTX toxicity [1,7,8].

The management of MTX-induced myelosuppression involves immediate discontinuation of MTX, administration of folinic acid (leucovorin) to bypass DHFR inhibition, and supportive care including antibiotics for infections and transfusions if necessary. Early detection through regular monitoring of blood counts and renal function tests is critical to preventing severe outcomes [5,6,9].

Naranjo Adverse Drug Reaction Probability Scale:

Questions	Yes	No	Do Not Know	Score
1. Are there previous CONCLUSIVE reports on this reaction?	+ 1	0	0	+1
2. Did the adverse reaction appear after the suspected drug was administered?	+ 2	– 1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist given?	+ 1	0	0	0
4. Did the adverse reaction reappear when the drug was re-administered?	+ 2	– 1	0	+2
5. Are there alternative causes (other than the suspect drug) that could have caused the reaction?	– 1	+ 2	0	+2
6. Did the reaction reappear when a placebo was given?	– 1	+ 1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+ 1	0	0	0
8. Was the reaction more severe when dose was increased or less severe when dose was decreased?	+ 1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+ 1	0	0	0
10. Was the adverse reaction confirmed by any objective evidence?	+ 1	0	0	+1
	Total Score		08	

According to the Naranjo Scale, a score of 5–8 indicates a "Probable" ADR. Therefore, MTX-induced myelosuppression in this case is probably related to methotrexate.

CONCLUSION

Methotrexate-induced myelosuppression is a rare but serious adverse drug reaction that can result in life-threatening complications such as pancytopenia, sepsis, and multi-organ dysfunction. This case highlights the critical importance of vigilant patient selection, thorough baseline assessment, and continuous monitoring throughout methotrexate therapy. In particular, elderly patients with comorbid conditions like renal impairment, diabetes, and hypertension are at higher risk and require closer supervision.

Clinical pharmacists have a vital role in preventing such adverse outcomes by acting as medication experts within the healthcare team. They can contribute significantly through several key interventions: conducting comprehensive medication reviews to identify potential drug interactions or contraindications; ensuring appropriate dosing adjustments based on renal function; educating healthcare providers and patients about the importance of

adherence to monitoring guidelines, including regular complete blood counts and renal function tests; and recognizing early signs of toxicity for prompt intervention.

Moreover, clinical pharmacists can advocate for and implement standardized protocols and checklists to guide prescribers in initiating and managing methotrexate therapy safely. Their active involvement in patient counselling empowers patients to promptly report symptoms suggestive of toxicity, such as unexplained bruising, bleeding, or infections. Ultimately, integrating clinical pharmacists into multidisciplinary care teams enhances patient safety, reduces the incidence of preventable adverse drug reactions, and improves overall therapeutic outcomes in methotrexate-treated patients.

Therefore, strengthening the role of clinical pharmacists in routine clinical practice is essential to minimize the risk of methotrexate-induced myelosuppression and ensure optimal management of patients requiring this potentially toxic but highly effective medication.

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