

Case Series

When cure becomes a threat: A case series on methotrexate-induced liver injury in a tertiary care setting

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ABSTRACT

Methotrexate, a cornerstone of modern therapeutics, is widely used as an immunosuppressant and anticancer agent. The occurrence of methotrexate-associated hepatotoxicity has been well documented. This case series highlights the spectrum of methotrexate-induced liver injury and emphasises the need for regular liver function monitoring to facilitate early detection and prevention of hepatotoxicity in patients receiving methotrexate therapy. This case series details have been collected from the outpatient department between the years 2019 and 2023 at a tertiary care teaching hospital. Causality assessment was performed using the World Health Organisation-Uppsala Monitoring Centre criteria. Methotrexate was prescribed for a duration ranging from 3 weeks to 4 years on a dose ranging from 2.5 mg to 25 mg once weekly. Among them, five were female and two were male, aged 19 years–70 years. Three patients already had renal involvement, and two more had diabetes. This case series reaffirms the principle that prevention is better than cure. It majorly emphasises the importance of routine liver monitoring in methotrexate patients to early detection and prevention of hepatotoxic effects.

Keywords: Drug-induced liver injury, Hepatotoxicity, Immunosuppressant, Methotrexate, Pharmacovigilance programme of India

INTRODUCTION

Methotrexate is frequently used as an immunosuppressant and anticancer drug.^[1] It is a folate antagonist that primarily penetrates cells through the reduced folate carrier. Inside the cell, methotrexate undergoes polyglutamation, a process catalysed by folylpolyglutamate synthetase, which enhances its intracellular retention and inhibitory potential. Methotrexate polyglutamates inhibit several key enzymes involved in purine and pyrimidine nucleotide synthesis. One of the primary targets is dihydrofolate reductase, which blocks the conversion of dihydrofolate into tetrahydrofolate, thereby disrupting the synthesis of thymidylate and purines. Thymidylate synthase facilitates the synthesis of thymidine monophosphate, essential for DNA replication. Inhibiting aminoimidazole carboxamide ribonucleotide transformylase (AICART) causes aminoimidazole carboxamide ribonucleotide accumulation, leading to elevated adenosine levels, thereby exerting anti-inflammatory effects. Overall, methotrexate hampers cellular replication by interfering with the synthesis of DNA, RNA and proteins through enzyme inhibition.^[2,3]

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Methotrexate treats cancers such as leukaemia and lymphoma, as well as rheumatoid arthritis (RA) and psoriasis. The adverse effects include bone marrow suppression, nausea, abdominal pain, diarrhoea, hepatotoxicity, stomatitis, exanthems and mouth ulcers. According to the World Health Organisation (WHO) Vigibase pharmacovigilance data, approximately 3% of global adverse drug reaction (ADR) reports linked to methotrexate are related to liver toxicity. The pathophysiology in the induction of hepatotoxicity with methotrexate involves several mechanisms such as oxidative stress, mitochondrial dysfunction, folate depletion and inflammatory cytokine release and induction of hepatic stellate cell activation and fibrogenesis through adenosine accumulation.^[4]

Aim

The aim of this study was to facilitate the early detection of methotrexate-induced hepatotoxicity through regular monitoring and to improve patient safety and better outcomes.

MATERIALS AND METHODS

This case series details have been collected from the outpatient department (OPD) between the years 2019 and 2024 at a tertiary care teaching hospital. Causality assessment was performed using the WHO-UMC criteria, which were based on data from the Believers Church Medical Colleges ADR monitoring centre. Only instances with appropriate and credible evidence of methotrexate-induced hepatotoxicity were considered for the final analysis. Therefore, seven cases met the inclusion requirements and were chosen for this case series. All participating patients provided written informed consent in a language that they understood, assuring both ethical compliance and patient understanding.

CASE SERIES

Case 1: Methotrexate-induced transaminitis

A 70-year-old female with seropositive RA, type 2 diabetes mellitus with diabetic nephropathy, systemic hypertension, dyslipidaemia and lumbar spondylosis was admitted on 24th May 2024 for her 10th dose of IV infliximab (200 mg). She had been on methotrexate 10 mg once weekly since March 2023, along with hydroxychloroquine (HCQ), glimepiride, dapagliflozin, folic acid, vildagliptin, losartan and rosuvastatin with ezetimibe. During admission, routine investigations revealed elevated liver enzymes, alanine aminotransferase range 81 U/L and aspartate aminotransferase 49 U/L, indicating transaminitis. Based on rheumatology and general medicine consultations, methotrexate was discontinued. At 1-month follow-up,

liver function tests (LFTs) had normalised, suggesting methotrexate-induced hepatotoxicity. Further clinical details are summarised in Table 1.

Case 2: Methotrexate-induced fatty liver and transaminitis

A 49-year-old female with psoriatic arthritis (diagnosed in 2022) and a history of uveitis presented on 21st June 2024 with joint pain and stiffness. She had been on methotrexate 5 mg once weekly, tofacitinib and rosuvastatin. Routine laboratories revealed elevated liver enzymes (serum glutamic-oxaloacetic transaminase [SGOT]: 68 U/L, serum glutamic-pyruvic transaminase [SGPT]: 91 U/L), and ultrasound (USG) showed Grade I fatty liver changes. Methotrexate was discontinued due to suspected hepatotoxicity, and she was started on apremilast 20 mg and udiliv 300 mg twice daily. On follow-up after 2 weeks, liver enzymes had normalised, indicating methotrexate-induced liver injury. Further clinical details are summarised in Table 1.

Case 3: Methotrexate-induced hyperbilirubinemia

A 19-year-old female patient came for review in the dermatology department with complaints of new lesions over the forearms on 24 May 2023. She had a previous history of childhood nephrotic syndrome and psoriasis from the age of 10. On general examination, there are numerous well-defined erythematous plaques with silvery white scales covering the scalp, trunk and upper and lower limbs. She had been started on methotrexate 5 mg once weekly on 3 May 2023. After 4 weeks, the direct bilirubin was recorded at 0.3 mg/dL, indirect at 1.2 mg/dL, resulting in a total bilirubin of about 1.5 mg/dL, prompting discontinuation of methotrexate. On follow-up after 4 weeks, bilirubin levels improved to 1.04 mg/dL, suggesting methotrexate-induced liver dysfunction. Further clinical details are summarised in Table 1.

Case 4: Methotrexate-induced transaminitis

A 56-year-old male patient with psoriasis came for a follow-up visit with scaly lesions on the trunk and limbs. On general examination, it was noted with scaly plaques in the trunk, presence of limb follicular papules and onycholysis. The patient was prescribed to take T. Methotrexate 15 mg P/O once weekly for psoriasis from 2019. On routine, mild abnormalities were noted in the LFT: Total bilirubin was 1.53 mg/dL, indirect bilirubin 1.30 mg/dL, with SGOT and SGPT measured at 60 U/L and 52 U/L, respectively. Methotrexate was discontinued on 8 September 2023 due to transaminitis. Follow-up after 2 weeks showed normalisation of liver function, indicating methotrexate-induced liver dysfunction. Further clinical details are summarised in Table 1.

Table 1: An overview of patient demographics, clinical diagnosis, methotrexate dosing, laboratory values, hepatic adverse drug reactions, co-medications, causality assessment, interventions and outcomes.

Case no.	Case no.1	Case no.2	Case no.3	Case no.4	Case no.5	Case no.6	Case no.7
Age	70-year	49-year	19-year	56-year	64-year	57-year	58-year
Gender	Female	Female	Female	Male	Male	Female	Female
Underlying disease	Rheumatoid arthritis	Psoriatic arthritis	Psoriasis	Psoriasis	Rheumatoid arthritis	Rheumatoid arthritis +CKD	Rheumatoid arthritis
Methotrexate Start date and Stop date	March 2023 and 24 May 2024	2022 and 21 June 2024	03-May-23 and 24 May 2023	2019 and 8 September 2023	2019 and 22 September 22	2018 and 1 March 2023	12 March 20 and 14 December 2022
Dosage	10 mg weekly	5 mg weekly	5 mg weekly	15 mg weekly	10 mg weekly	2.5 mg weekly	25 mg weekly
Hepatic ADR	Transaminitis	Fatty liver and transaminitis	Hyperbilirubinemia	Transaminitis	Hepatic injury	Early CLD	Hepatic injury
Co-medications	Hydroxychloroquine, glimepiride, dapagliflozin, folic acid, vildagliptin, losartan and rosuvastatin with ezetimibe	Tofacitinib, rosuvastatin	Apremilast, topical steroids	None reported	HCQ, anti-diabetics	Statins, Erythropoietin, nebivolol, cilnidipine	HCQ, statins, dapagliflozin, metformin
WHO-UMC scale	Probable	Probable	Probable	Probable	Probable	Probable	Probable
Action taken	Withdrawn	Withdrawn	Withdrawn	Withdrawn	Withdrawn	Withdrawn	Withdrawn
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered
Test	Before dose withheld		After dose withheld		Normal range		
SGOT	49 U/L		32 U/L		10–40 U/L		
SGPT	81 U/L		35 U/L		10–40 U/L		
SGOT	68 U/L		23 U/L		10–40 U/L		
SGPT	91 U/L		35 U/L		10–40 U/L		
Total bilirubin	1.45 mg/dL		1.04 mg/dL		0.20–1.00 mg/dL		
Direct bilirubin	0.3 mg/dL		0.19 mg/dL		0.00–0.2 mg/dL		
Indirect bilirubin	1.15mg/dL		0.85 mg/dL		0.20–1.00 mg/dL		
Total bilirubin	1.53 mg/dL		0.98 mg/dL		0.20–1.00mg/dL		
Direct bilirubin	0.23 mg/dL		0.19 mg/dL		0.00–0.2mg/dL		
Indirect bilirubin	1.30 mg/dL		0.79 mg/dL		0.20–1.00 mg/dL		
SGOT	45 U/L		33 U/L		10–40 U/L		
SGPT	52 U/L		37 U/L		10–40 U/L		
SGOT	102 U/L		37 U/L		10–40 U/L		
SGPT	96 U/L		37 U/L		10–40 U/L		
USG Abdomen+pelvis showed chronic parenchymal liver disease, bilateral increased renal cortical echogenicity and liver enzymes found to be normal							
SGOT	133 U/L		19 U/L		10–40 U/L		
SGPT	200 U/L		26 U/L		10–40 U/L		
WHO: World health organization, CKD: Chronic kidney disease, CLD: Chronic liver disease, HCQ: Hydroxychloroquine, ADR: Adverse drug reaction, USG: Ultrasound, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, WHO-UMC: World health organization-Uppsala monitoring centre scale							

Case 5: Methotrexate-induced hepatic injury

A 64-year-old male with type 2 diabetes mellitus and RA, on methotrexate 10 mg once weekly since 2019, presented with joint stiffness and nocturnal paresthesia and was on T. Methotrexate 10 mg once a week from 2019, T. Ziten, T. Glyciphage SR, T. Remogliflozin and T. Diamicron, HCQ.

The patient was advised to do LFT and USG, then review back in the OPD. Initial LFT on 15th February 2022 showed mildly elevated SGPT/SGOT (46/41 U/L), which worsened to 96/102 U/L by 22nd September 2022. USG revealed Grade 1 fatty liver with subtle surface nodularity. Consequently, the T. Methotrexate was discontinued on 22 September 2022 as there were noticeable hepatic changes. Follow-up after 2 months showed normalised liver function. Further clinical details are summarised in Table 1.

Case 6: Methotrexate-induced early chronic liver disease

A 57-year-old female with chronic kidney disease (CKD) stage IV, hypertension, sero-positive RA and secondary Sjogren's syndrome had been on Methotrexate 2.5 mg once a week from 2018, T. Ferrisome, T. Folic acid, C. Calcitriol, T. Nebivolol, T. Cilnidipine, T. Neurobion forte and T. Rosuvastatin. The USG Abdomen + Pelvis done on 1 March 2023 showed Chronic parenchymal liver disease, bilateral increased renal cortical echogenicity and liver enzyme SGOT/PT was found to be normal (31 and 35 U/L). Methotrexate was discontinued on 1 March 2023 based on imaging findings. Further clinical details are summarised in Table 1.

Case 7: Methotrexate-induced hepatic injury

A 58-year-old female came for review in the rheumatology OPD with a history of seropositive RA, type 2 diabetes mellitus and dyslipidaemia. The patient was on the following medications such as HCQ 200 mg 1-0-1, T. Methotrexate 25 mg weekly since March 2020, T. Glyciphage SR 500 mg 1-0-1, T. Dapagliflozin 10 mg 1-0-0 and T. Atorvastatin 10 mg 0-0-1. On 14 December 2022, liver enzymes were markedly elevated (SGPT 200 U/L, SGOT 130 U/L). To prevent further hepatic complications, T. Methotrexate 25 mg once weekly was ceased on 14 December 2022. On follow-up after 1 month, LFT normalised. Further clinical details are summarised in Table 1.

DISCUSSION

Our findings are supported by previous studies. Sotoudehmanesh *et al.* reported transaminitis in 23.7% of RA patients on methotrexate doses ≥ 7.5 mg/week.^[5] Tilling *et al.* reported methotrexate-induced hepatotoxicity in 12% of patients overall, underscoring its potential to cause

liver injury irrespective of the underlying autoimmune condition.^[6] Conway and Carey demonstrated a 2.63-fold increase in the risk of transaminase elevation with methotrexate.^[7] Zhi directly implicated methotrexate as a causative agent of hepatotoxicity, particularly in patients with metabolic dysfunction-associated fatty liver disease and type 2 diabetes, both common in our cohort.^[8] Similarly, Bilal *et al.* identified increasing age as a key risk factor for methotrexate-induced liver injury, with no significant difference between genders.^[9] Despite the presence of comorbidities such as diabetes and CKD, hepatotoxicity resolved in all cases after stopping methotrexate, confirming its central role.^[10]

CONCLUSION

Methotrexate, a commonly used drug for immunosuppression and cancer therapy, demands cautious administration and vigilant monitoring. Routine LFT is crucial for early identification of liver complications, allowing prompt management and recovery, as demonstrated in all seven cases in this series. Implementing preventive measures, especially regular biochemical surveillance, is vital, particularly in patients with underlying kidney disease or diabetes reduce the risk of serious hepatic damage.

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