

# Early-Onset Methotrexate-Induced Hepatotoxicity in Rheumatoid Arthritis Despite Normal Baseline Liver Function: A Case Report

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder primarily characterized by symmetric polyarthritis. However, atypical clinical presentations and drug-related complications can pose diagnostic and therapeutic challenges in routine clinical practice.

**Case Summary:** We report the case of a 52-year-old female who presented with migratory joint pain involving small and large joints, associated with morning stiffness and fatigue. Initial clinical evaluation suggested a non-specific inflammatory arthritis, leading to a delay in definitive diagnosis. Laboratory investigations revealed elevated erythrocyte sedimentation rate and C-reactive protein levels, along with positive rheumatoid factor and anti-cyclic citrullinated peptide antibodies. The patient was initiated on methotrexate-based therapy; however, subsequent monitoring demonstrated elevated liver enzymes suggestive of drug-induced hepatotoxicity.

**Intervention and Outcome:** Methotrexate was withheld, and supportive management was initiated, resulting in gradual normalization of liver function tests. The patient was subsequently managed with alternative disease-modifying therapy,

leading to clinical improvement and stabilization of disease activity.

**Conclusion:** This case highlights the dual challenge of atypical presentation and potential drug-induced adverse effects in RA management. Early recognition, to careful monitoring, and timely therapeutic modification are essential to optimize patient outcomes and prevent complications.

**Keywords:** Rheumatoid Arthritis; Methotrexate; Hepatotoxicity; Adverse Drug Reaction; Liver Function Tests; DMARD

## INTRODUCTION

Rheumatoid arthritis is a long-term autoimmune condition characterized by persistent systemic inflammation, primarily affecting synovial joints and resulting in progressive structural damage. While the classical presentation involves symmetrical polyarthritis, atypical manifestations such as migratory joint involvement may obscure early diagnosis.

Methotrexate is widely recognized as the cornerstone therapy for rheumatoid arthritis due to its ability to suppress disease activity and slow joint destruction. However, its use is associated with several adverse effects, with hepatic toxicity being one of the most clinically relevant. Although liver injury is

often associated with prolonged therapy or predisposing factors such as alcohol consumption or metabolic disease, hepatotoxicity can occasionally appear early in treatment, even in patients with normal baseline investigations. This case highlights such an early adverse reaction and underscores the importance of vigilant monitoring.

### CASE PRESENTATION

A 52-year-old female presented with complaints of migratory joint pain involving multiple joints for 3 months, associated with morning stiffness lasting more than one hour. The symptoms initially involved the wrists and gradually progressed to involve the knees and ankles. On examination, tenderness and mild swelling were noted in the affected joints. Laboratory investigations revealed an erythrocyte sedimentation rate of 65 mm/hr and elevated C-reactive protein (28 mg/L). Rheumatoid factor and anti-cyclic

citrullinated peptide antibodies were positive. Baseline liver function tests were within normal limits. Based on clinical and laboratory findings, a diagnosis of rheumatoid arthritis was made. The patient was initiated on oral methotrexate 15 mg weekly along with folic acid supplementation (5 mg/week). After 6 weeks of therapy, the patient developed elevated liver enzymes (AST: 120 IU/L, ALT: 135 IU/L), suggestive of hepatotoxicity. Viral hepatitis markers were negative, and there was no history of alcohol consumption or other hepatotoxic drug use. Methotrexate was discontinued, and the patient was managed conservatively. Causality assessment using the WHO-UMC scale indicated a probable association between methotrexate and hepatotoxicity. Follow-up investigations showed normalization of liver function tests within 3 weeks, and the patient was subsequently initiated on leflunomide.

Table 1: Liver function Test parameters during Treatment and follow-up

Parameter	Baseline (Before MTX)	6 Weeks (On MTX)	After Withdrawal (3 Weeks)	Reference Range
AST (IU/L)	32	120	30	10-14
ALT (IU/L)	30	135	40	7-56
ALP (IU/L)	90	140	95	44-147
Total Bilirubin mg/dl	0.8	1.2	0.9	0.3-1.2

### DISCUSSION

Methotrexate remains the first-line disease-modifying antirheumatic drug for the management of Rheumatoid Arthritis due to its proven efficacy and cost-effectiveness. However, hepatotoxicity is one of the most clinically significant adverse effects associated with its use. Elevated hepatic transaminases are commonly linked with prolonged therapy, cumulative dose exposure, alcohol consumption, obesity, diabetes mellitus, and pre-existing liver disease.

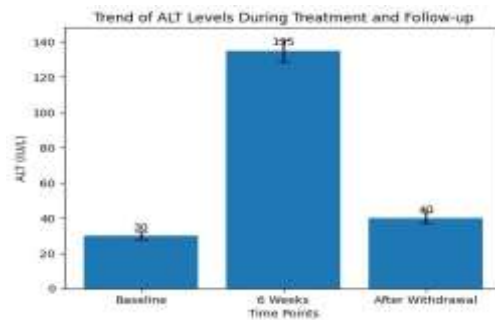
In the present case, hepatic enzyme elevation occurred within 6 weeks of therapy despite normal baseline liver function tests and absence of conventional risk factors. The temporal relationship between methotrexate

administration and subsequent normalization following drug withdrawal strongly supports methotrexate-induced hepatotoxicity. Furthermore, WHO-UMC causality assessment categorized the adverse reaction as probable.

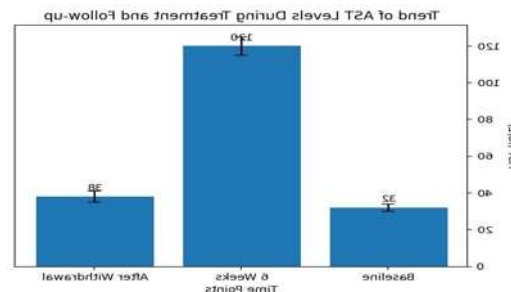
Previous studies have reported that methotrexate-induced liver injury may occasionally occur early during therapy, even at low weekly doses. This emphasizes the importance of regular biochemical monitoring from the initiation of treatment. Early identification and prompt discontinuation of methotrexate are essential to prevent progression to severe hepatic injury, fibrosis, or cirrhosis.

The successful transition to leflunomide in this patient further highlights the importance

of individualized therapeutic strategies in patients who develop methotrexate intolerance or toxicity.



**Figure 1: Trend of aspartate aminotransferase (AST) Levels during methotrexate therapy and after Drug withdrawal. Error bars represent standard deviation.**



**Figure 2: Trend of alanine aminotransferase (ALT) levels during methotrexate therapy and after drug withdrawal. Error bars represent standard deviation.**

## CONCLUSION

Methotrexate remains a cornerstone in the management of rheumatoid arthritis; however, its potential to cause hepatotoxicity necessitates careful clinical monitoring. This case demonstrates that hepatotoxicity may develop within a short duration of therapy despite normal baseline investigations and absence of traditional risk factors. The temporal association between drug exposure and liver enzyme elevation, along with improvement following withdrawal, supports a probable causal relationship. The patient was advised regular follow-up and serial monitoring of liver function tests. Early identification and intervention are crucial to prevent progression to severe hepatic injury. Clinicians should ensure regular biochemical monitoring and consider alternative therapeutic options when adverse effects are identified, thereby optimizing patient safety and treatment outcomes. This case emphasizes the critical role of early detection, regular monitoring, and timely

intervention in preventing serious drug-related complications in routine clinical practice.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given their consent for clinical information and images to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Key Clinical Message

Methotrexate-induced hepatotoxicity can occur even in patients with normal baseline liver function tests and at an early stage of therapy. Regular monitoring of liver enzymes is essential from the initiation of treatment, as early detection and dose modification or withdrawal of methotrexate can prevent progression to severe liver injury. Clinicians

should maintain a high index of suspicion even in asymptomatic patients.

**Declaration by Authors**

**Ethical Approval:** Approved

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**Conflict of Interest:** The authors declare that there is no conflict of interest regarding the publication of this case report. The authors alone are responsible for the content and writing of the manuscript.

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