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Methotrexate-Induced Hepatotoxicity in a Patient with a History of Alcohol Abuse: Case Report

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***Abstract*—Methotrexate (MTX) is a widely used treatment for conditions such as rheumatoid arthritis and psoriasis. Although its potential for hepatotoxicity is known, there is limited research on how to prevent this adverse effect, and despite this risk, MTX continues to be frequently prescribed. We present the case of a 56-year-old male with a history of alcohol abuse who developed acute jaundice, malaise, and a positive Murphy's sign after starting MTX therapy for inflammatory rheumatoid arthritis. The patient was advised to abstain from alcohol due to the shared hepatic first-pass metabolism of both alcohol and MTX, and although he successfully stopped heavy drinking, he continued to consume alcohol occasionally in small amounts. After one month of treatment, the patient developed symptomatic grade 2 hepatic steatosis, requiring emergent plasmapheresis. This case highlights the lack of data on the effects of MTX in patients with prior alcohol abuse and demonstrates how a brief period of MTX use can result in the progression of hepatotoxicity in patients with pre-existing liver damage.**

***Index Terms*—Alcohol-Related Disorders; Arthritis, Drug-Induced Liver Injury; Liver Failure; Methotrexate; Rheumatoid.**

I. INTRODUCTION

Methotrexate (MTX) is a widely prescribed immunosuppressive drug used to manage various conditions, including rheumatoid arthritis (RA) and psoriasis [1]. Despite its therapeutic benefits, MTX carries a well-documented risk of hepatotoxicity, primarily through the accumulation of intracellular MTX-polyglutamate (MTX-PG) which induces oxidative stress, inflammation, steatosis, fibrosis, and apoptosis in hepatocytes [2]. This risk is particularly pronounced in patients with existing liver conditions or risk factors, such as a history of alcohol abuse, due to the liver's role in metabolizing both alcohol and MTX via the same hepatic pathway.

Several studies have examined the influence of concomitant alcohol consumption on MTX-related hepatotoxicity. In one study of 71 psoriatic patients who underwent liver biopsy during MTX monitoring, all patients who consumed more than 30 grams of alcohol daily developed hepatic fibrosis, compared with 66% of those without excessive alcohol intake [3]. Similarly, another study involving 66 patients and 121 liver biopsies found that excessive alcohol consumption of 40 units per week (≈ 320 g/week ≈ 46 g/day) was associated with advanced hepatic fibrosis [4]. By contrast, a Canadian retrospective study of 104 psoriatic patients, in which most adhered to advice to avoid alcohol, found no significant correlation between alcohol consumption and MTX-related hepatotoxicity; this was likely due to the generally low levels of alcohol intake in that cohort [5]. However, studies on alcohol consumption in RA patients treated with MTX are more limited.

MTX is considered a low-grade hepatotoxin, often associated with mild hepatic fibrosis, even in the absence of overt liver disease [2]. MTX is more likely to cause liver enzyme elevation in early periods of treatment in patients with preexisting conditions such as obesity, untreated high cholesterol, pre-methotrexate LFT elevations, biologic agent use, and lack of folic acid supplementation [6].

While the American College of Rheumatology has issued guidelines for liver function monitoring—initially every 2–4 weeks for a couple of months, then every 8–12 weeks—variability remains due to the lack of evidence-based methodology in creating those guidelines [6]. There is limited literature exploring the precise effects of MTX in patients with a prior history of alcohol abuse and how therapy should be adjusted. We describe a patient who developed grade 2 hepatic steatosis within one month of MTX initiation, culminating in acute liver injury requiring plasmapheresis. This case emphasizes the need for cautious risk stratification before initiating MTX in high-risk individuals.

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II. CASE PRESENTATION

A 56-year-old male, with a significant history of alcohol abuse, presented to the internal medicine outpatient clinic with complaints of abdominal pain, fatigue, and malaise. The patient reported jaundice, generalized muscle weakness, and right upper quadrant pain on palpation, with a positive Murphy's sign noted during physical examination. The patient had been recently diagnosed with RA and had commenced MTX treatment one month prior at a dose of 10 mg weekly. He had been advised to abstain from alcohol during his treatment but admitted to occasional drinking since starting MTX.

On admission, the patient's vital signs were stable, with a normal heart rate, blood pressure, and body temperature. The patient's blood work is illustrated in Table 1. A hepatobiliary ultrasound revealed increased liver parenchymal echogenicity, consistent with grade 2 hepatic steatosis, and hepatosplenomegaly, measuring 19 cm and 17.3 cm, respectively. These findings were further confirmed by contrast-enhanced magnetic resonance imaging, demonstrating significant hepatic damage. Due to the severity of the condition, emergent plasmapheresis was initiated to manage the patient's acute liver injury.

III. DISCUSSION

The interaction between methotrexate (MTX) and alcohol represents a significant clinical concern due to their synergistic potential to cause liver injury. While MTX is an important medication, hepatotoxicity remains one of its most serious adverse effects, especially when risk factors such as alcohol consumption are present. This case highlights a rare and severe manifestation of MTX-induced hepatotoxicity in a patient with a history of alcohol abuse, necessitating plasmapheresis and supportive measures. Chronic low-dose MTX therapy has been associated with a spectrum of hepatic adverse effects ranging from transient transaminase elevations to fibrosis and, in rare cases, hepatic failure [7-9]. Alcohol use is a well-established risk factor that may potentiate the hepatotoxic effects of MTX. While older guidelines often discouraged any alcohol use, a study in 2017 suggested that low-to-moderate intake may be safer than previously believed. A large prospective study by Humphreys et al. demonstrated that consuming less than 14 units of alcohol per week (≈ 112 g/week ≈ 16 g/day) was not significantly associated with elevated liver enzymes in MTX users, whereas intake above 21 units (≈ 168 g/week ≈ 24 g/day) increased the risk considerably [10].

Our patient's history of chronic alcohol use, even if not quantified precisely, likely contributed to hepatic vulnerability. It is believed that alcohol and MTX exert synergistic toxicity, via shared pathways, including mitochondrial dysfunction, increased oxidative stress, and disruption of folate metabolism [2]. A review by Ezhilarasan discusses how MTX induces hepatotoxicity through apoptosis, oxidative stress, and cytokine-mediated inflammation, mechanisms which are also aggravated by alcohol [2]. Additionally, histologic abnormalities such as hepatic steatosis, fibrosis, and cirrhosis have been well documented in long-term MTX users. A meta-analysis by Whiting-O'Keefe et al. found a significantly higher prevalence of hepatic fibrosis in patients on long-term MTX, particularly those with other risk factors such as alcohol use [9]. While the American College of Rheumatology has issued guidelines for liver function monitoring—initially every 2–4 weeks for a couple of months, then every 8–12 weeks—there is variability due to the lack of evidence-based methodology in creating those guidelines. This highlights the need for individualized patient monitoring based on risk factors such as alcohol use, pre-existing liver disease, or elevated baseline liver enzymes. Hepatotoxicity related to MTX use can range from asymptomatic elevation of liver enzymes to more severe manifestations, including hepatic steatosis, fibrosis, and cirrhosis. Alcohol intake adds to this risk by placing an additional metabolic burden on the liver, exacerbating MTX-related hepatic damage [6].

What makes our case especially notable is the rapid onset and severity of hepatotoxicity, requiring not only drug cessation but also plasmapheresis [11]. Plasmapheresis may be beneficial in cases of severe drug-induced liver injury by removing circulating toxins or immune complexes. This therapeutic decision was based on the patient's deteriorating condition and failure to improve with conventional supportive therapy. The American College of Rheumatology recommends routine liver function monitoring during MTX therapy, yet this may be insufficient in patients with additional risk factors such as alcohol use, especially if the extent of alcohol consumption is underreported. Kremer et al. suggest more frequent liver enzyme monitoring or even liver biopsy in patients at high risk [6]. This case underscores the importance of thorough pretreatment screening, including honest assessment

of alcohol use, and individualized risk-benefit analysis when prescribing MTX. In ambiguous or borderline cases, alternatives such as biologic disease-modifying antirheumatic drugs (DMARDs) or non-hepatotoxic immunosuppressants may be considered.

Guidance on alcohol use during MTX therapy is uniformly cautious, with jurisdiction-specific nuances that shape practice. The Turkish Society of Rheumatology recommends complete abstinence [12], aligning with European Medicines Agency (EMA) requirements for product information, which list alcohol misuse as a contraindication and advises against concurrent intake [13]. In contrast, UK guidance from the British Society for Rheumatology and the NHS permits consumption within national limits—up to 14 units per week, ideally spread across several days—provided there are no additional hepatic risk factors and liver function is monitored regularly [14].

Synthesizing these positions highlights the need for a pragmatic, risk-stratified approach. For high-risk patients—such as those with a history of alcohol-related liver disease, metabolic comorbidities, viral hepatitis, or concomitant hepatotoxins—abstinence should be compelled. For selected low-risk patients with robust monitoring, limited intake within UK thresholds (≤14 units per week) may be reasonable, provided counselling is explicit and limits are documented. Intakes exceeding 21 units per week, or sustained heavy drinking, should be avoided given the substantial increase in risk of liver enzyme derangement and fibrosis.

In conclusion, alcohol exposure increases the risk of MTX-related hepatotoxicity in a dose-dependent manner. The safest course is abstinence, particularly where any hepatic risk is present. Where alcohol is consumed, it should be kept within ≤14 units per week, liver function should be monitored regularly, and shared decision-making should be embedded, tailored to local standards and individual risk profiles.

IV. ETHICAL APPROVAL

The patient was informed about the study and consented to its publication. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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Table 1. Summary of patient's biochemical analysis by date

Date	Day 1	Day 4	Day 7	Day 8	Reference range
AST	73	42	56	42	5 – 34 (U/L)
ALT	128	65	57	30	0 – 55 (U/L)
γ-GTP	1490	682	320	-	9 – 36 (U/L)
TB	30.19	41.47	40.27	28.06	0.2 – 1 (mg/dL)
DB	17.48	22.82	22.77	14.63	0 - 0.2 (mg/dL)
PT (INR)	1.33	-	1.26	-	0.8 - 1.2

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; γ-GTP: Gamma-Glutamyl Transpeptidase; TB: Total Bilirubin; DB: Direct Bilirubin; PT: Prothrombin Time; INR: International Normalized Ratio