

## CASE REPORT

## Hepatology

# Methotrexate induced hepatotoxicity in metabolic dysfunction-associated steatotic liver disease

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## Abstract

Hepatotoxicity is an under-recognized and potentially fatal side effect of high-dose methotrexate (HDMTX) chemotherapy, and this risk is compounded in children with metabolic dysfunction-associated steatotic liver disease and/or metabolic-associated steatohepatitis. We present the case of a 12-year-old obese, Hispanic male with elevated hepatic transaminases of unknown etiology at initiation of high-risk B-cell acute lymphoblastic leukemia chemotherapy. He developed acute kidney injury within 24 hours of receiving intravenous HDMTX which progressed to acute hepatic failure. Liver biopsy confirmed methotrexate toxicity aggravated by undiagnosed metabolic dysfunction-associated steatotic liver disease. Rapid deterioration precluded liver transplantation, and he died 21 days after HDMTX treatment. This case highlights the need for comprehensive hepatic evaluation in patients with known or suspected liver disease when administering HDMTX. Dialysis should be considered if delayed methotrexate clearance occurs due to potential for rapid, irreversible hepatotoxicity.

## KEYWORDS

liver, obesity, pharmacotoxicology

## 1 | INTRODUCTION

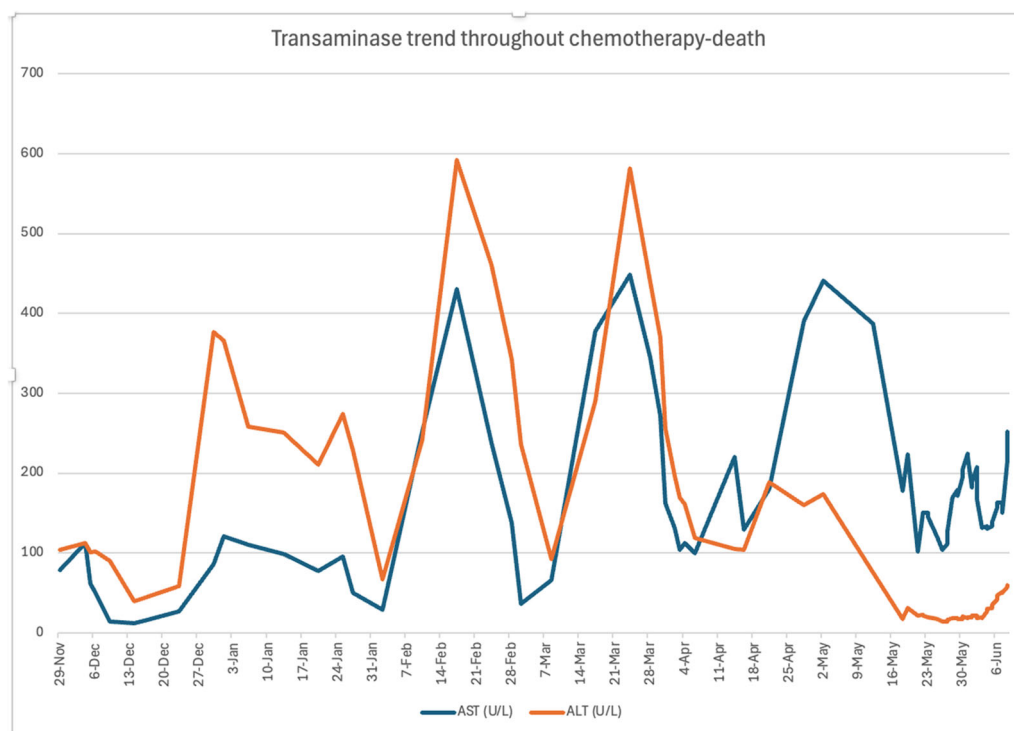
Hepatotoxicity is an under-recognized, potentially fatal side effect of high-dose methotrexate (HDMTX) chemotherapy.<sup>1</sup> In patients with underlying metabolic dysfunction-associated steatotic liver disease (MASLD) and/or metabolic-associated steatohepatitis (MASH), methotrexate (MTX) accumulates in adipose tissue and can induce uptake of hepatic lipids, slowing MTX clearance and increasing hepatotoxicity risk.<sup>2</sup> This case emphasizes the need for a comprehensive hepatic evaluation in patients with known or suspected liver disease when receiving a potentially hepatotoxic medication.

## 2 | CASE REPORT

A 12-year-old obese (Class II, body mass index [BMI] z-score 2.29), vaccinated, Hispanic male presents with elevated hepatic transaminases of aspartate aminotransferase (AST) 104 U/L and alanine transaminase (ALT) 79 U/L, (reference ranges 10–40 U/L) and thrombocytopenia of 79 K/UL (reference range 150–400 K/UL) at the onset of high-risk B-cell acute lymphoblastic leukemia chemotherapy (Figure 1). Before chemotherapy, he did not undergo a baseline laboratory or imaging assessment to establish cardio-metabolic risk factors or explore potential liver dysfunction, however, coagulation and metabolic panel

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**FIGURE 1** Pictorial graph depicting the laboratory trend of patient's hepatic transaminases (AST, ALT) from the onset of chemotherapy through patient's death. ALT, alanine transaminase; AST, aspartate aminotransferase.

including bilirubin and albumin levels were normal at chemotherapy onset. He also did not have documented hepatomegaly or splenomegaly per imaging or physical exam. Throughout treatment, he had previously received intrathecal and intravenous HDMTX with appropriate MTX clearance, but fluctuations of transaminase elevation (AST 378 U/L, ALT 290 U/L) attributed to MTX. Within 24 hours of planned intrathecal chemotherapy followed by intravenous HDMTX, he developed new onset stage 3 acute kidney injury (AKI) based on tripled creatinine levels with preserved urine output on diuretics. His estimated glomerular filtration ratio (eGFR) was 201 mL/min/1.73 m<sup>2</sup> (reference range 120–130 mL/min/1.73 m<sup>2</sup>), stage 1, and he was not on concurrent medications that could impair urinary MTX excretion. This AKI resulted in poor MTX clearance, with an unfractionated MTX level of 110 µmol/L at 24 hours postinfusion (reference range <5.0 µmol/L). Within 48 hours, he had received two doses of glucarpidase, and his MTX level decreased to <1.0 µmol/L over 7 days.<sup>3</sup>

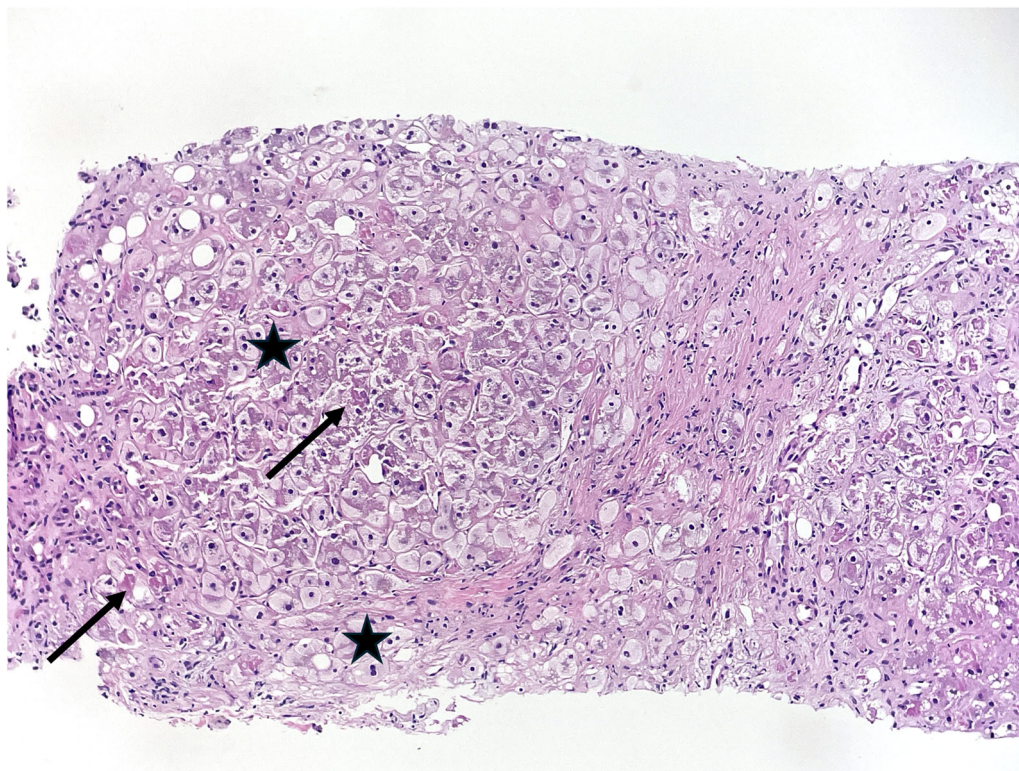
During this interval of slow MTX clearance, he developed new acute hepatic failure with peak international normalized ratio of 3.4 s (reference range 0.8–1.2 s) and conjugated bilirubinemia to 7–9 mg/dL (reference range <0.3 mg/dL). Simultaneously, his ALT level was normal, and his AST level was elevated to 130–250 U/L. Liver biopsy revealed florid, panlobular hepatocyte ballooning with prominent Mallory-Denk

bodies and less than 5% steatosis, consistent with established pathology criteria for methotrexate toxicity<sup>4</sup> (Figure 2). Interestingly, there was also extensive sinusoidal fibrosis from each central vein and focal bridging fibrosis, histopathology more reflective of prior undiagnosed MASH<sup>4</sup> (Figure 3). He rapidly deteriorated with refractory septic shock, anasarca, and hepatorenal syndrome requiring continuous renal replacement therapy (CRRT). This precluded his candidacy for liver transplantation, and he died 21 days after receiving HDMTX.

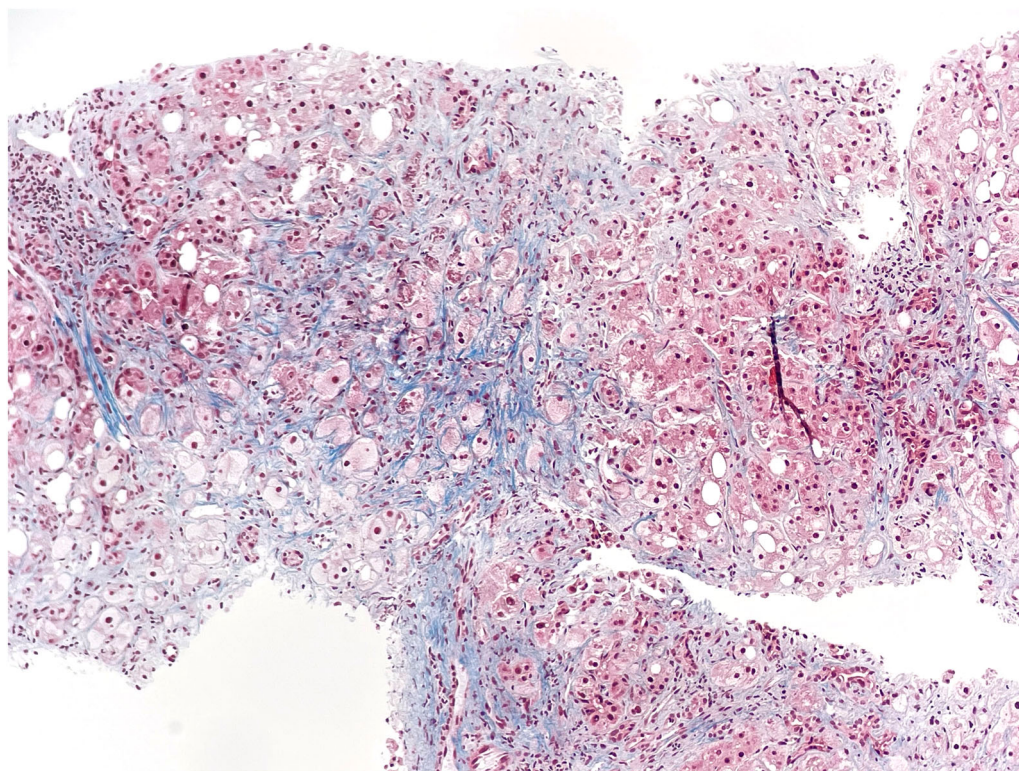
### 3 | DISCUSSION

MASLD and MASH are leading causes of pediatric liver dysfunction with rates rising parallel to the obesity epidemic. MASLD, defined as steatosis in >5% of hepatocytes, is an umbrella term describing hepatic dysfunction. MASH, an advanced form of MASLD, exhibits histologic ballooning, degeneration of hepatocytes, and inflammation.<sup>4</sup> Hispanic children have a four-fold risk of MASLD/MASH development with male sex, obesity, and/or metabolic syndrome being other known associated co-morbidities.<sup>4</sup> Induction of cytochrome P450 2E1 (CYP2E1), a metabolizing membrane-bound protein and enzyme, provokes the production of reactive oxygen species and promotes oxidative stress, both of which are key features of MASH.<sup>5</sup> Neuman et al. studied





**FIGURE 2** Hematoxylin and eosin histologic stain of this liver biopsy section demonstrates extensive, panlobular hepatocyte ballooning containing ballooned hepatocytes (star), and Mallory-Denk bodies (arrow). There is minimal (<5%) macrovesicular steatosis and scant lobular or portal inflammation. There is mild hepatocellular and canalicular cholestasis.



**FIGURE 3** Trichrome histologic stain of this liver biopsy section confirms the preservation of normal liver architecture. It also shows extensive sinusoidal fibrosis (blue staining) emanating from each of the central veins with focal, bridging fibrosis.



the effects CYP2E1 inducers Tylenol and ethanol on MTX-induced hepatotoxicity, concluding that CYP2E1 induction promotes cytokine upregulation and apoptosis, thus linking the development and progression of MASLD and magnifying MTX hepatotoxicity.<sup>6</sup> A troubling aspect of MASLD/MASH is they are relatively asymptomatic diseases until the development of cirrhosis, leading to later diagnosis and intervention. Therefore, clinicians should have a low threshold for initiating a diagnostic work up if liver dysfunction is suspected especially in the setting of MASLD/MASH risk factors.

MTX is hypothesized to cause high cellular turnover in hepatic tissues and transaminase elevation through its mechanism as a folate antagonist.<sup>2</sup> This folate antagonism makes HDMTX an indispensable chemotherapeutic agent in childhood oncologic protocols through inhibition of the division of normal and malignant cells. Regarding HDMTX and hepatotoxicity, a prospective study of a 24-patient cohort with psoriasis receiving long-term MTX therapy concluded that MTX administration aggravates existing MASH, causing microscopic MASH-like liver injury of steatosis, necroinflammation, zone 3 pericellular fibrosis, and/or hepatocyte ballooning.<sup>7</sup>

Mechanistically, MTX is 70%–90% renally cleared and excreted intact in the urine.<sup>3</sup> Nephrotoxicity secondary to HDMTX is potentially life-threatening, manifesting as an AKI from the intratubular deposition of MTX crystals.<sup>3,8</sup> Consensus guidelines for use of rescue medications leucovorin and glucarpidase in the setting of MTX toxicity define absolute MTX concentrations associated with risk for severe or life-threatening toxicity at different time points after HDMTX infusion. Glucarpidase is indicated if serum creatinine is elevated compared to baseline and/or the 48-h MTX concentration is  $>5 \mu\text{mol/L}$ , both of which were present in this case.<sup>3</sup> If left untreated, MTX nephrotoxicity can lead to multisystem organ complications such as hepatotoxicity due to increased MTX accumulation in adipose tissue and its mechanism as a folate antagonist.<sup>2</sup> If rescue medications are unsuccessful, dialysis modalities may be used for MTX clearance.<sup>9</sup>

This case demonstrates that while MTX levels predict nephrotoxicity, progression to hepatotoxicity is dependent on the individual's baseline hepatic function. We suspect our patient had undiagnosed MASH complicating his acute HDMTX hepatotoxicity based on liver pathology, and his baseline characteristics of Hispanic ethnicity, Class II obesity, and initial asymptomatic transaminase elevation and thrombocytopenia. In this context, MTX-induced hepatotoxicity can quickly progress to liver failure, necessitate transplantation, or result in death. Dialysis should be considered if delayed MTX clearance occurs due to potential for rapid, irreversible hepatotoxicity.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## ETHICS STATEMENT

The parents/guardians of the patient provided informed consent for publication of this case report.

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