sciendo Acta Marisiensis - Seria Medica / Ahead of Print DOI: 10.2478/amma-2025-0034

CASE REPORT

Innovative approach on monitoring methotrexate induced hepatotoxicity in psoriasis patients – A case report

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Introduction: Methotrexate is often used as the first line of systemic treatment in patients with moderate to severe psoriasis and psoriatic arthritis.

Case report: We present the case of a 44-year-old male patient with moderate plaque psoriasis who was treated with Methotrexate and diagnosed with mild hepatic steatosis during the first month of treatment. Using FIB-4 (Fibrosis Index Based on 4 factors) as a noninvasive method for assessing the risk of liver fibrosis, the patient was able to take Methotrexate safely, with close monitoring of liver function.

Conclusions: FIB-4 can be used to assess the risk of liver fibrosis in psoriasis patients treated with Methotrexate to ensure better adherence to the treatment.

Keywords: methotrexate, psoriasis, hepatotoxicity, FIB-4

Received 26 April 2025 / Accepted 17 July 2025

Introduction

Methotrexate (MTX) is a dihydrofolate reductase inhibitor that was first used in 1948 to treat leukemia patients. To date, the possible side effects of MTX are well known. The most common reactions are gastrointestinal side effects (nausea, vomiting, diarrhea), liver and renal toxicity, myelosuppression and pulmonary fibrosis [1]. MTX is widely used for multiple conditions for its cytotoxic and anti-inflammatory effects, including moderate-to-severe psoriasis and psoriatic arthritis [2].

Psoriasis is a common, chronic, inflammatory dermatosis with variable prevalence worldwide, affecting 2-4% of the general population, and more frequently encountered in Caucasians [3]. Regarding treatment options, topical therapies consisting of steroids, vitamin D or calcineurin inhibitors are prescribed for localized, mild psoriasis, while systemic therapy is often required to control more severe forms of the disease, including articular involvement. The first line of systemic therapy for psoriasis is represented by conventional immunosuppressants such as MTX, failure or intolerance of this treatment option leading to innovative small-molecule therapies and biologic therapies [2].

Psoriasis patients are prone to developing metabolic dysfunction-associated steatotic liver disease (MASLD), with certain systemic therapies further increasing the risk of liver fibrosis [4]. MTX is the most prescribed systemic therapy in psoriasis patients and, considering drug hepatotoxicity being one of the main concerns, discussing the management of MTX-induced hepatotoxicity in psoriasis patients is necessary to ensure optimal medical care. To begin with, MTX may cause liver function impairment, while permanent damage indicated by fibrosis is less common and is mainly influenced by individual risk factors. To evaluate the risk of liver fibrosis in psoriasis patients treated with MTX several noninvasive tests have been validated [5,6].

Fibrosis Index Based on 4 factors (FIB-4) is a noninvasive test for assessing liver fibrosis which is calculated based on a formula that includes the patient's age, platelet count and liver enzyme levels - alanine transaminases (ALT) and aspartate aminotransaminases (AST). Initially designed for evaluating HIV (human immunodeficiency virus) patients co-infected with hepatitis C virus, it has become widely used in hepatology, high FIB-4 levels being associated with poor outcomes in chronic liver disease. In recent years, its use has extended to dermatology for assessing the risk of liver fibrosis in psoriasis patients treated with MTX [5,7].

Case report

We present the case of a 44-year-old male patient, with a history of generalized psoriasis vulgaris and psoriatic arthritis, diagnosed eleven years ago, without a family history of psoriasis or other associated diseases. The patient denied smoking and alcohol consumption and had a BMI (body mass index) of 24,5. Prior to his initial presentation, the patient had received local therapy with betamethasone and calcipotriol once daily for the past 6 months, with only

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slight improvement. A skin biopsy was performed and the histopathologic examination confirmed the diagnosis. The patient signed an informed consent form, permitting the use of personal medical data and images capturing the skin condition.

Clinical evaluation revealed multiple erythematous, scaly plaques on trunk and limbs with mild involvement of the nails, scalp and palmoplantar areas (Figure 1, Figure 2). Due to the fact the initial PASI (Psoriasis Area and Severity Index) was 11.6 and the DLQI (Dermatology Life Quality Index) score was 18 and the lack of response to local therapy, the patient became eligible for systemic treatment. Since no abnormalities have been detected in routine laboratory tests, MTX therapy is initiated starting with a test-dose of 7.5 mg in the first week, followed by a course of 15 mg of MTX per week taken orally and 5 mg folic acid supplementation 72 hours after MTX.

At one month evaluation, the patient complains of nausea and abdominal pain after MTX administration, while routine laboratory results show mild elevation of ALT and gamma-glutamyl transferase (GGT). A gastroenterological consultation is carried out. Viral hepatitis is ruled out through testing hepatitis B antigen and hepatitis C antibody, and abdominal ultrasound found a subtle increased hepatic echogenicity, leading to the final diagnosis of mild hepatic steatosis. The gastroenterologist recommended hepatoprotective therapy with 1000 mg of silymarin per day (equivalent of 250 mg extract of Silybum marianum) for 3 months, while MTX treatment may be continued but with regular reevaluation of liver function.

At that time, the patient was not a candidate for innovative therapy since he had neither intolerance to the drug nor lack of response to treatment. Taking into account the gastroenterologist's suggestion and with the patient's consent, it was agreed to continue MTX therapy with close monitoring of liver function and hepatoprotective treatment, as recommended. Subcutaneous injections as route of administration was further chosen for this patient and as a result the gastrointestinal side effects improved.

Over the following months, liver enzyme levels gradually increased, with ALT levels increasing the most at 2.37 times higher than the upper normal limit. According to Joint American Academy of Dermatology – National Psoriasis Foundation (AAD-NPF) guidelines for the management of psoriasis with systemic nonbiologic therapies elaborated in 2020 by Menter A et al., FIB-4 is recommended to be used to further evaluate liver function and particularly the risk of developing liver fibrosis. FIB-4 is calculated based on age, platelet count and liver transaminases [5].

Although FIB-4 increased over time, it never exceeded the cut-off value of 1.3 [8], placing the patient at low risk of liver fibrosis (Table I). In this situation, the 2020 Joint AAD-NPF guidelines recommend periodic reassessment of liver enzymes and annual gastroenterology consulta-

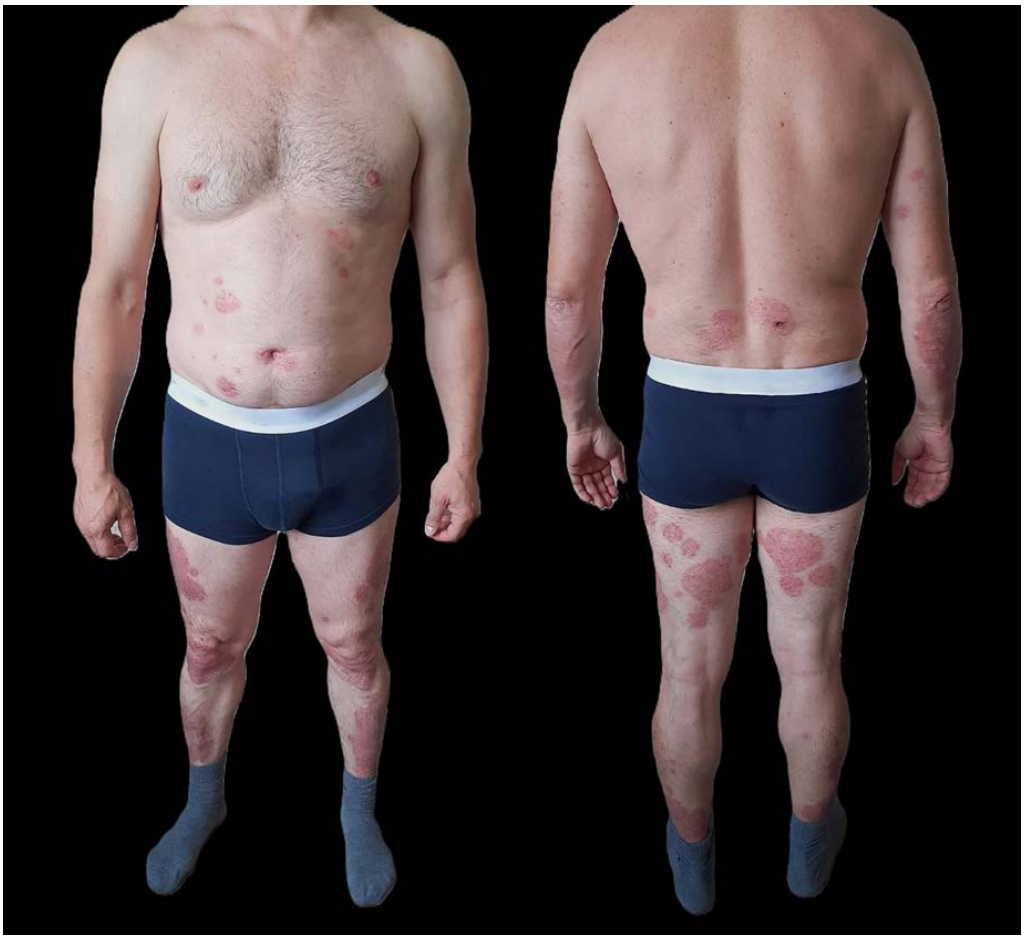

Fig. 1. Patient before systemic therapy

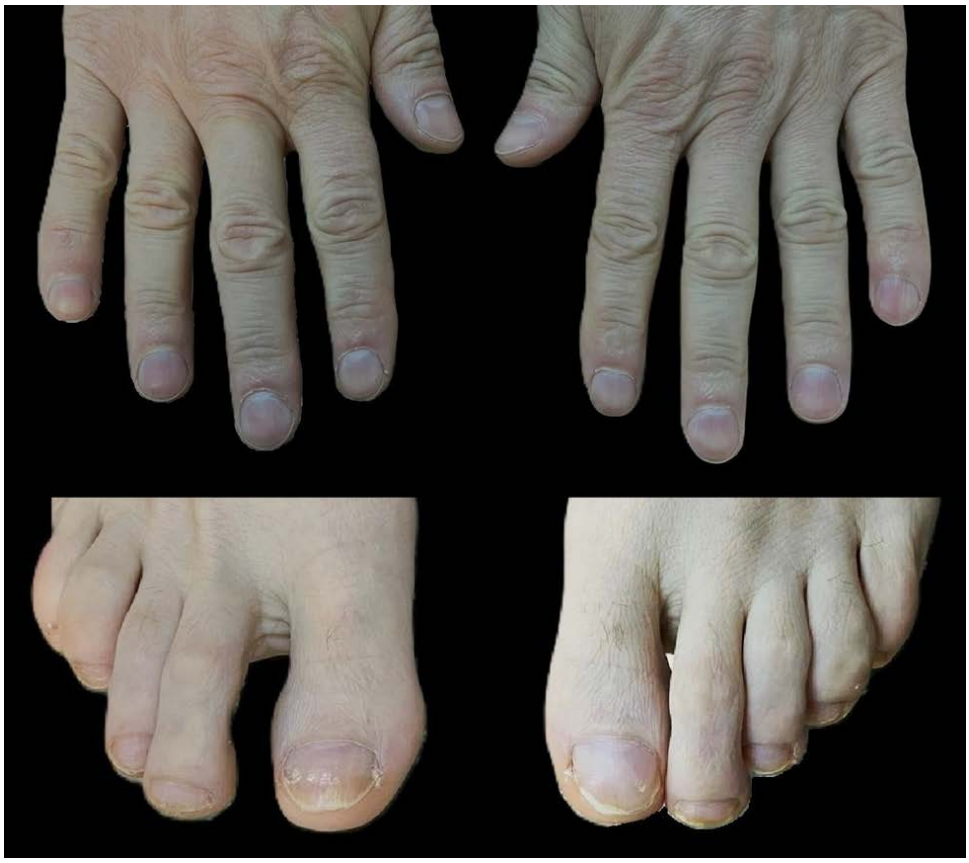

Fig. 2. Nail involvement before systemic treatment

Table I. Evolution of liver enzymes and FIB-4 during MTX treatment

	Normal range	Baseline (before MTX)	One month evaluation	Four months evaluation
ALT	0-45 U/L	36	50	107
AST	11-34 U/L	23	24	40
GGT	0-55 U/L	54	76	81
FIB-4 index	< 1.3	0.73	0.68	0.91

ALT – alanine transaminases; AST – aspartate aminotransaminases; GGT - gamma-glutamyl transferase.

tion or reevaluation of FIB-4 or other minimally invasive markers of liver fibrosis [5]. The patient continued MTX treatment safely with periodic evaluation of liver function, despite developing hepatic cytolysis.

Discussions

Hepatotoxicity is a well-known side effect of MTX use and occurs more frequently in psoriasis patients treated with MTX than in rheumatoid arthritis patients following the same treatment [4]. The molecular pathways of MTX induced hepatotoxicity starts with MTX conversion to MTX polyglutamates inside the hepatocyte, further inducing intracellular oxidative stress, generating persistent inflammation. Moreover, MTX interacts with adenosine metabolism, creating an excess of adenosine which further promotes fibrosis [9]. Histologically, MTX toxicity to the liver is described as steatosis with 5% of the patients developing fibrosis and 1% cirrhosis [10]. Acute liver failure is less common and occurs after exposure to high doses of MTX, presenting with a profound impairment of general health. However, it has been reported that certain gene polymorphisms affecting the metabolism of MTX may increase the patient's risk to liver failure even at low doses of the drug [11,12].

Asymptomatic elevation of liver enzymes is a common, self-limiting side effect of MTX treatment, occurring in up to 50% of patients. Most patients manage to return to normal enzyme levels with dose adjustment or discontinuation of the drug, or in some cases without changing the course of treatment. However, it is important to note that most studies underline the role of other risk factors such as alcohol consumption, obesity or diabetes mellitus in the development of hepatotoxicity during treatment with MTX, thereby questioning the real contribution of the drug to developing MASLD [10,13]. However, the 2020 Joint AAD-NPF guidelines note that there are certain situations in which MTX therapy should be discontinued, such as a significant and sustained elevation of liver enzymes, hypoalbuminemia or high cumulative dose of MTX in a patient with underlying fibrosis [5].

To overcome the side effects of MTX, plenty of supplements have demonstrated their effectiveness against drug-induced hepatotoxicity. First of all, folic acid supplementation is widely recommended to reduce the side effects

of MTX and can be prescribed along with MTX, without compromising drug efficacy. Studies have shown that folic acid is able to overcome MTX toxicity, including decreasing elevated liver enzymes and reducing gastrointestinal side effects, maximizing the adherence of patients treated with MTX. Furthermore, it has been found that a low dose of 5 to 10 mg of folic acid is sufficient to overcome these side effects [6,14].

While folic acid is mitigating several side effects of MTX, it fails to effectively reduce the oxidative stress caused by MTX-derived polyglutamate buildup in hepatocytes [9]. As a result, several supplements have been investigated, including silymarin, which was prescribed to our patient. The main mechanism underlying silymarin's hepatoprotective effect is its antioxidant activity [15]. A few studies have assessed silymarin supplementation in patients receiving MTX, showing promising results in improving both hepatic and renal function, yet there is no dosing regimen for these patients [16,17]. A 2025 meta-analysis attempted to standardize silymarin administration and proposed an optimal daily dosage of silymarin between 140 and 400 mg, depending on the specific liver condition, for short-term use. After two months of treatment, the efficacy of silymarin should be evaluated through measuring liver enzyme levels [15]. Despite these benefits, the EASL-EASD-EASO (European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity) 2024 guidelines on MASLD management emphasize that while silymarin may improve liver enzyme levels, however, based on the limited data available, it may not improve histological alterations in MASLD patients [8].

In terms of patient monitoring, the focus shifted towards minimally invasive tests, leaving behind the previous gold-standard – liver biopsy. Several noninvasive tests (NITs) were developed for estimating liver fibrosis, aiming to reform the MASLD staging system which relied on biopsy. They include serum biomarkers such as FIB-4 or FibroTest, which is calculated by a formula using haptoglobin, GGT, total bilirubin and alpha 2-macroglobulin, as well as imagistic methods such as transient elastography also known as FibroScan. A 2023 meta-analysis comparing the prognostic accuracy of NITs and liver biopsy found that the 5-year time-dependent area under the curve (tAUC) was slightly higher for FIB-4 (0.74) and elastography (0.76) than for histology (0.72), indicating that NITs have similar prognostic value to biopsy [18]. Another meta-analysis highlighted that magnetic resonance elastography (MRE) and shear-wave elastography had the highest diagnostic accuracy for staging MASLD, with area under the receiver operating characteristic curve (AUROC) values of 0.96 and 0.95, respectively. FIB-4 performed well, with an AUROC of 0.84. Based on these findings, the authors recommended using FIB-4 in combination with elastography to improve accuracy of liver fibrosis assessment [19].

Several studies have investigated MTX-induced hepatotoxicity in patients with psoriasis and rheumatoid arthritis receiving low-dose MTX over prolonged periods. Although FIB-4 has demonstrated utility in identifying liver fibrosis, it has certain limitations and should not be used as the sole method for fibrosis assessment [20-22].

In psoriasis patients treated with MTX, current guidelines recommend using FIB-4 for identifying population at risk of liver fibrosis that may need further tests. Combining FibroScan or FibroTest with collagen peptide type III measurement is the ideal method for evaluating liver fibrosis in these patients [5]. Both FibroScan and FibroTest have gained popularity due to their minimally invasive approach and proven effectiveness in fibrosis assessment [6,23]. However, type III procollagen peptide serves only as an adjuvant marker to estimate liver stiffness since it reflects only active fibrogenesis and lacks organ specificity [24].

Unlike other NITs, FIB-4 is calculated using patient`s age and routine laboratory tests (platelet count and liver transaminases), making it both easily accessible and cost-effective [5]. Despite its limitations, FIB-4 remains a valuable tool for assessing the risk of liver fibrosis in psoriasis patients treated with MTX, as it is a reliable, widely available, inexpensive method that minimizes unnecessary testing.

Conclusion

MTX often causes a temporary increase of liver enzymes, without permanent liver damage. Therefore, a proper assessment of the real risks faced by patients is mandatory to avoid premature discontinuation of the drug. The addition of minimally invasive tests like FIB-4 to dermatology guidelines is helpful because it guarantees better access for the evaluation of liver fibrosis and provides valuable information for determining the patient's risk and directing the course of treatment.

Authors' contribution

SAM (Writing – original draft; Data curation; Investigation)
TOM (Writing – review & editing; Methodology; Conceptualization)
SR (Data curation; Resources; Software)
RAM (Investigation; Validation; Visualization)
TRA (Data curation; Resources; Software)
COS (Validation; Visualization; Methodology)
MSH (Supervision; Validation; Writing – review & editing)

Conflict of interest

None to declare.

Ethical statement

Informed consent was provided by the patient for the publication of this case.

Funding

No external funding was received.

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