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Prolonged Cholestatic Liver Disease Secondary to Methotrexate

Yahya Atayan[1], Yasir Furkan Cagın[1], Mehmet Ali Erdogan[1], Yılmaz Bilgic[1], Remzi Bestas[2], Murat Aladag[1]

[1] Inonu University, Faculty of Medicine, Department of Gastroenterology, Malatya, Turkey

[2] Education and Training Hospital, Department of Gastroenterology, Diyarbakir, Turkey

Abstract

Methotrexate (MTX) is a folate antagonist which damages the DNA and classified as an antimetabolite antineoplastic agent. It is the most commonly used drug in the treatment of rheumatoid arthritis (RA) and its efficiency and reliability were well established. Drug-induced hepatotoxicity varies from non-specific liver changes to acute fulminant failure, cirrhosis and liver cancer. The mechanism in which methotrexate causes liver damage is not known. It may cause acute increase in transaminase enzymes, and on the long-term it may lead to liver fibrosis and cirrhosis. Whether it is used in high doses (eg, cyclic use of 1 gram or more) or on low doses (eg, weekly doses of 7.5 to 25 mg), MTX may lead to life threatening conditions like hepatotoxicity. Presented in this case report, a 52 year old male patient was diagnosed with rheumatoid arthritis. in which hepatic fibrosis and prolonged cholestatic liver disease occurred secondary to prolonged usage of MTX

Keywords: Methotrexate, liver disease, cholestasis

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Corresponding Author*:* Yahya Atayan, Inonu University, Faculty of Medicine, Department of Gastroenterology, Malatya, Turkey
E-mail: yahyaatayan@hotmail.com **Phone**: +90 505 3476757

Introduction

Drug-induced hepatotoxicity varies from non-specific liver changes to acute fulminant failure, cirrhosis and liver cancer. Methotrexate (MTX) is a folate antagonist which damages the DNA and it is classified as an antimetabolite antineoplastic agent. It was shown to produce anti-inflammatory effects through adenosine, by decreasing the secretion of tumor necrosis factor, a proinflammatory cytokine, and by increasing the secretion of interleukin 10 [1]. It is the most commonly used drug in the treatment of rheumatoid arthritis (RA) and its efficiency and reliability were well established. In general, it shows its effects within 3-6 weeks, and it is well tolerated by patients. The mechanism in which methotrexate causes liver damage is not known. MTX reduces the amount of folate stored in the liver thus, it is recommended to offer oral folinic acid replacement during the therapy [2,3]. The association between folate deficiency and hepatotoxicity was not well established. Providing a daily intake of 1mg of folic acid, or a weekly intake of 2.5mg of folinic acid was shown to reduce the incidence of high liver enzymes [4,5]. In this case report, we introduce a case in which hepatic fibrosis and prolonged cholestatic liver disease occurred secondary to prolonged usage of MTX.

Case

A 52 year old male patient was diagnosed with rheumatoid arthritis 4 years ago. He was started on MTX tablet (7.5mg/week),folic acid, leflunomide, and prednol 32mg/day. He used this regimen for 2 years. The regimen was changed to subcutaneous injections, 10-15 mg/week, which he used for 2 more years. About 3 months ago, the patient started having jaundice all over his body. He presented to a medical center where endoscopic retrograde cholangiopancreatography was performed for a prediagnosis of extrahepatic cholestasis. 3 weeks after the procedure his INR and bilirubin levels continued to increase. The patient was referred to our center with a diagnosis of fulminant hepatitis to be evaluated for liver transplantation. The patient's laboratory findings were as follows: WBC: 3.5 10°3/ml, hemoglobin: 9.5gr/dl, thrombocytes; 155 10°3/ml, HbsAg; negative, anti Hbc IgM; negative, antiHbsAg; negative, antiHCV; negative, anti HAV IgM; negative, immunoglobulin A, G, M normal, autoantibodies negative, RF: 158 IU/ML, ceruloplasmin normal, iron: 55, iron binding capacity: 45, ferritin; 1500ng/ml and transferrin saturation index was above 100%, total bilirubin: 32 mg/dl, ALT: 85 U/L, AST: 56 U/L, ALP; 233, GGT; 255, albumin:

2.1gr/dl, INR: 2.7 and HFE gene mutation was negative. Liver biopsy was performed. Pathologic evaluation reported the presence of diffuse parenchymal cholestasis, lobular regenerative changes, moderate necroinflammatory activity, mild portal fibrosis and minimal pericellular fibrosis (1/6) According to the Roenigk classification score was 4 (Figure 1, 2). No iron accumulation was seen. Therefore, the diagnosis of hepatic fibrosis and cholestatic liver disease secondary to prolonged methotrexate usage was considered. Ursodeoxycholic acid and N-acetylcysteine were given. 2 sessions of plasmapheresis with fresh frozen plasma were performed. The patient's bilirubin level started decreasing and the patient was discharged and he was subsequently followed up as an outpatient. The patient has just been informed that his case would be published.

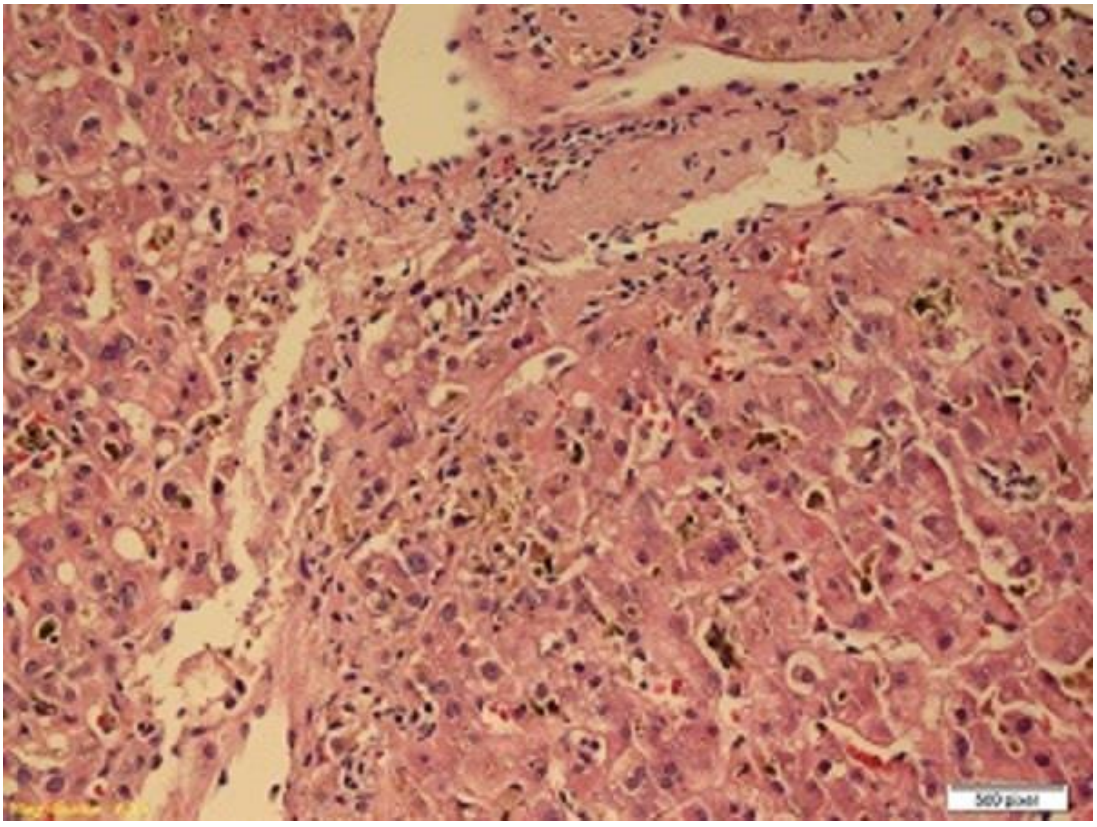

Figure1. Diffuse parenchymal cholestasis and anisonucleosis. HE x 200

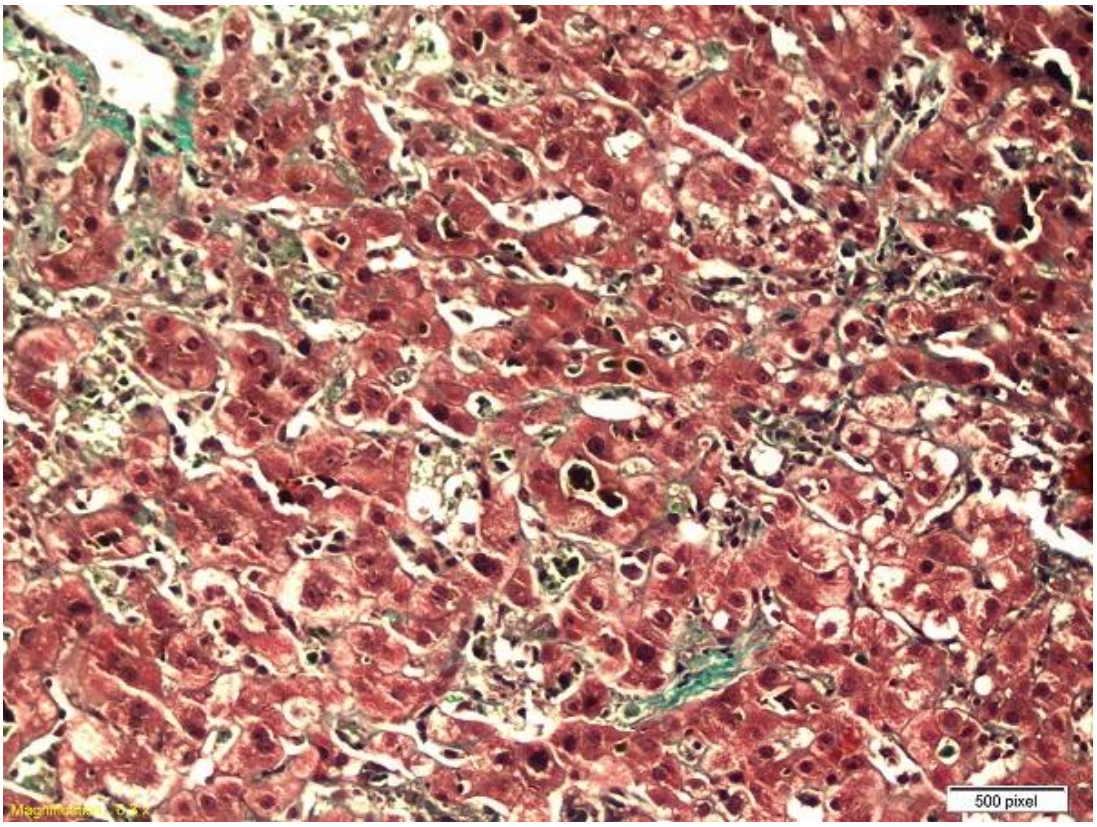

Figure 2. Pericellular / sinüsoidal fibrozis. M. trikrom x 200

Discussion

MTX competitively inhibits the metabolism of folic acid. It is a competitive inhibitor of the dihydrofolate reductase enzyme in the S phase of DNA synthesis. Therefore, the production of tetrahydrofolic acid is blocked and purine synthesis is inhibited. It may cause acute increase in transaminase enzymes, and on the long-term it may lead to liver fibrosis and cirrhosis. Because liver damage does not correlate with the increase in liver enzymes, it was recommended to obtain a liver biopsy once a cumulative dose of 1.5 grams is consumed [6]. Whether it is used in high doses (eg, cyclic use of 1 gram or more) or on low doses (eg, weekly doses of 7.5 to 25 mg), MTX may lead to life threatening conditions like hepatotoxicity, pulmonary complications and myelosuppression. The enzymes come back to the normal levels one month after stopping the drug. The other side effects of MTX are not as dangerous as liver hepatotoxicity. Its most commonly seen side effects are loss of appetite, nausea, vomiting, diarrhea and oral aphthous ulcers. 5% of the patients may develop hematologic toxicity (leukopenia, thrombocytopenia, pancytopenia, megaloblastic anemia). It

is also a teratogenic drug. In males, it may cause reversible oligospermia [7]. Histologically, it may cause fatty liver, stellate (Ito) cell hypertrophy, anisonucleosis, hepatitis and fibrosis. In our case, despite the irregular usage of the drug, we performed a liver biopsy because the cumulative dose was over 1.5 grams. Diffuse parenchymal cholestasis and minimal pericellular fibrosis were seen in the biopsy (1/6) and According to the Roenigk classification score was 4. Roenigk > 3b were considered to signify advanced fibrosis [8] Other side effects of MTX are nodulosis, rash, alopecia, headache after taking the drug, dizziness and increased joint pain [9]. In our case, the patient had loss of appetite and hair loss. Kirnap et al. reported that MTX was effective in the treatment of RA and that it was very well tolerated at low doses [10]. A systematic review of literature reported that the low dose MTX monotherapy has a high long-term reliability [11]. There is no evidence that the simultaneous use of MTX and leflunomide increases the risk of hepatotoxicity, and this combination was used successfully in the treatment of active RA [12]. In our case, hepatotoxicity didn't occur for a long period of time while the patient was using leflunomide simultaneously. But after he used MTX alone hepatotoxicity occurred. Prospective studies carried out by rheumatologists after starting MTX in diseases like RA showed that AST and albumin levels are correlated with liver damage. It was reported that adjusting the MTX dose according to the levels of AST and albumin can take liver damage under control and thus, allow the usage of this drug for years. It was reported that using folic acid or folinic acid to replace the deficiency may limit the rise in liver enzymes. The risk of liver damage is higher in patients who drink alcohol, who have type 2 diabetes and who are obese.

Conclusion: MTX is successfully used in the treatment of RA. Even though it was reported that MTX is reliable in the treatment of rheumatologic diseases on the long-term, it may still cause liver toxicity, which should be further evaluated with a liver biopsy to clarify the diagnosis. Although methotrexate used safely in rheumatic diseases

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