Methotrexate-Induced Liver Cirrhosis in a Patient of Psoriasis
Gurcharan Avasthi*, Prashant Bhatt**, Jagdeep Singh***

Abstract
Methotrexate has been used for many years to treat refractory psoriasis. A case of methotrexate induced cirrhosis is being presented to emphasize the importance of strict adherence to published criteria for patient selection, monitoring of cumulative drug dosages, and the performance of serial liver biopsies.

Introduction
Methotrexate has become the cornerstone in the therapy of a variety of inflammatory disorders affecting the skin and joints. From the beginning, methotrexate was recognized as a highly efficacious and safe agent in the treatment of psoriasis and psoriatic arthritis. Its overuse in daily dosage schedules during the 1960s, however, led to the development of some serious toxicity, including liver cirrhosis and bone marrow suppression, resulting in concerns about its safety. However, presently, there are fewer case reports of methotrexate induced cirrhosis because of the efficacy of weekly low dosage schedules, and well established guidelines for monitoring toxicity.

Case
We present a 67 years old male who was a known case of psoriasis for last 35 years. He was on topical therapy initially and was subsequently shifted to methotrexate by the treating physician. His psoriatic lesions were within control on 7.5 mg weekly dose which he had been taking for last 15 years. His liver functions were being monitored periodically as evident by the reports which were essentially normal except for once when SGPT was raised less than twice the upper limit of normal. However, he had been taking alcohol in non-cirrhogenic doses (30-120 ml weekly, on an average) for last 25-30 years. He was not taking any non-steroidal anti-inflammatory drugs, vitamin A, psoralsens-UVa therapy or any other hepatotoxic drug.

He presented to us with complaints of abdominal distension, swelling feet and decreased appetite for last 3 months. He had no history of hematemesis or malena, neither he had abdominal distension in past. He had no history of jaundice, tuberculosis or contact with a tuberculosis patient. He was non-diabetic and non-hypertensive.

On examination, he was alert with stable vitals and there was mild pallor. His BMI was 23.9 kg/m². He had spider angiomata over upper trunk. Pitting pedal edema was present. He had psoriatic plaques over extensor surface of his legs and forearms, and over the back of chest. His abdomen was distended and shifting dullness was present. Liver span was 9 cms and spleen was moderately enlarged. Rest of the general and systemic examination was essentially normal.

His hemoglobin was 9.5 gm/dl, TLC were 8300/cu mm and platelets were 1.2 lakh/cu mm. PCV was 29%, MCV was 84 fl. Viral markers (HBSAg, Anti HCV) were non-reactive. Liver function studies were normal, with total bilirubin of 1.3 mg/dl, direct bilirubin 0.7 mg/dl, albumin 2.6 gm/dl, SGOT 44 IU/l, SGPT 33 IU/l, ALP 114 IU/l and GGT 72 IU/l. INR was 1.44. Ascitic fluid examination revealed high gradient ascites (SAAG 2.2), Ultrasonography of abdomen showed normal sized liver with coarse parenchymal echotexture and nodular surface outline. Portal vein diameter was 13 mm at porta. Spleen was enlarged with a span of 14.8 cms, splenic vein diameter was 8 mm at porta. Moderate amount of free fluid was seen in pelvis and paracolic gutters. Upper GI endoscopy showed 2 esophageal varices of grade III.

His methotrexate was tapered off, band ligation was done for the varices, and he was put on topical therapy for psoriasis after consultation with dermatologist and started on diuretics, beta blockers and hematinics.

Discussion
There have often been doubts to the possibility of psoriasis per se being the cause of cirrhosis, but unfortunately, not enough or recent studies are there to clear the air on this. In a study of 32 patients with psoriasis who had never been given methotrexate, 16 were found to have fatty liver and two had cirrhosis, but obesity and abuse of alcohol were common in this series and could have been partly responsible for these findings.1 Our patient was on weekly oral methotrexate therapy, taking 7.5 mg tablet every week for the past 15 years, amounting to total cumulative dose of 5.85 g till the presentation of symptoms related to cirrhosis. The long duration of therapy, and concurrent alcohol ingestion were the risk factors in our patient.

The duration of methotrexate therapy, age, daily oral methotrexate dosage schedule, risk factors for non-alcoholic steatohepatitis (obesity, diabetes mellitus, and glucose intolerance) and concurrent alcohol ingestion have been identified as significant risk factors in the evolution of hepatic fibrosis in patients taking methotrexate. By contrast long-term low-dose methotrexate therapy, in the absence of excess alcohol ingestion or other profibrogenic agents or diseases, have been reported as being relatively free of the risk of developing fibrosis.2 Concurrent psoralsens plus UVA therapy has also been suggested to cause derangements in liver function, but our patient was not on topical therapy for psoriasis for last more than 15 years, though he was on unknown topical therapy during the initial phase of his ailment.

One study (Tilling et al) focused on alcohol as a confounding factor, and found that there was no direct relationship between consumption of alcohol and liver injury in psoriatic patients on methotrexate.3 This further advocates that alcohol consumption might not be the direct contributory factor towards cirrhosis in such patients, and might just be another risk factor for development of cirrhosis in a patient on long term methotrexate therapy. Although our patient was taking alcohol in non-cirrhogenic dose, but looking at the longer duration of alcohol intake, the possibility of alcohol acting as a contributory factor is quite likely.

Many studies have found that abnormal liver function tests are often encountered during the treatment of psoriasis with methotrexate. The incidence of these abnormalities varies widely in individual series.4 But studies as early as in 70’s have found
that clinical signs of serious hepatic damage may be the first indication of cirrhosis and that liver function studies might not be reliable indicators of pathologic changes found on liver biopsy. At least one study showed that early fibrosis and cirrhosis seem to appear, with very minor abnormalities in laboratory results, which indicates the necessity of performing liver biopsies in psoriatics on long-term methotrexate therapy.  

Although our patient was being monitored for liver toxicity by periodic liver function tests, which incidentally were normal throughout the duration of therapy, except for one reading which had SGPT value of 68 IU/ml, so the patient might have been continued on therapy without considering liver biopsy.

This underlines the need of proper selection of patients and monitoring of therapy based on periodic liver biopsy, without banking solely on liver function tests. Methotrexate treatment schedules should be adjusted for each patient in order to control psoriasis symptoms at the lowest possible dose. Due to the risk of serious cumulative toxicity, it has been recommended that methotrexate be reserved for patients with severe, life-ruining psoriasis that cannot adequately be controlled by topical therapies, and that methotrexate treatment regimens should include dose reductions and periods off treatment. Methotrexate therapy is contraindicated in psoriasis patients with significantly impaired liver function. Frequent monitoring of viral markers, renal, hepatic and haematological parameters is necessary for all patients with psoriasis receiving methotrexate. Not all cases of methotrexate-induced hepatotoxicity may be detected by liver function tests, and liver biopsy is still considered the most reliable method of detecting hepatotoxicity in patients treated with methotrexate.

The American Academy of Dermatology recommends that sequential liver biopsies should be performed at a cumulative dose of 1-1.5 g and repeated at cumulative dose intervals of 1.5 g thereafter. For patients at increased risk of hepatotoxicity, liver biopsy may be justified earlier during therapy. The evidence indicates that in patients with no risk factors for liver disease on long-term, low-dosage (<20 mg), once-weekly methotrexate, liver biopsy is justified after an initial cumulative dosage of 4 g. The presence of pathologic changes detected by the liver biopsy should direct the decision of whether or not to continue methotrexate therapy. Patients with grade I or II histological changes (without fibrosis) can continue methotrexate; patients with grade IIIA changes (mild fibrosis) can continue methotrexate with a repeat liver biopsy after 6 months; patients with grade IIIB changes (moderate to severe fibrosis) or grade IV changes (cirrhosis) should discontinue methotrexate. However, liver biopsy is an invasive procedure, which itself may cause liver damage. Recently it has been found that normal serum type III procollagen aminopeptide (PIIINP) levels correlate with low risk of developing liver fibrosis, and this alternative noninvasive test is gaining acceptance in some parts of Europe. In future serial PIIINP measurement may obviate the need of repeated biopsies for patients with normal initial biopsy results. Liver biopsy may be required in patients with persistently elevated PIIINP levels.

The patient under discussion was being treated by the local physician with methotrexate therapy over a long period (cumulative dose in excess of 5 g over 15 years) relying on liver function tests, without undergoing serial liver biopsies, contrary to well-established treatment guidelines mentioned earlier. By the time we received the patient, he had already developed liver cirrhosis. Because of the obvious evidence of cirrhosis, coupled with patient’s reluctance to undergo any invasive procedure, liver biopsy was not performed.

The authors re-emphasize the need to guard against the false sense of security rendered by normal results of liver function tests and to perform serial liver biopsies starting at cumulative dose of 1.5 g in patients on methotrexate therapy, besides of course stressing on the abstinence from alcohol and avoiding hepatotoxic agents.

References