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Methotrexate Induced Nonaggressive Liver Cirrhosisin a Case of Psoriasis: A Rare Case Report

DrV.N.Dhadke, Dr Suraj Shrestha, Dr Prasad Jain, Dr Rashmi Rajur, Dr Shruti Nelekar,

Professor, Dr VMGMC, Solapur.
Junior resident, Dr VMGMC, Solapur
Junior resident, Dr VMGMC, Solapur.
Junior resident, Dr VMGMC, Solapur.
Junior resident, Dr VMGMC, Solapur.

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ABSTRACT
Since decades methotrexate has been used in treatment of psoriasis. Even after various adverse effects of this drug, methotrexate still remains one of the cornerstonedrugs in treatment of psoriasis. Out of various side effects like hepatotoxicity, haematological and pulmonary toxicity, hepatotoxicity is poorly studied in literature. We present you a case of methotrexate induced liver cirrhosis in a patient of psoriasis who was on low dose therapy for more than a decade.
Keywords:liver cirrhosis,methotrexate,psoriasis, liver biopsy, liver elastography

I. INTRODUCTION:

Methotrexate has been recognised as an efficacious agent even after recent advances in treatment of psoriasis and is still used due to its low cost and easy availability [1]. Methotrexate can cause minimal liver fibrosis or a nonaggressive type of liver cirrhosis on its long-term use [2]. High dose methotrexate therapy has been implicated in causing liver cirrhosis, but there are very few cases reported so far in which long term low dose of methotrexate caused liver cirrhosis [3].Symptoms are usually absent until cirrhosis and liver function tests are typically within normal limits. Routine monitoring of patients on methotrexate therapywith liver elastography for progression of liver fibrosisis required to detect liver toxicity in earlier stage.

Case

58 years old female a known case of psoriasis was on oral low dose methotrexate therapy for 15 years. Her disease was under well control on 2.5 mg methotrexate taken thrice weekly [Table 1]. Her liver functions were being monitored periodically which were essentially normal. She was not taking any non-steroidal anti-inflammatory drugs,vitamin A,psoralens-UVA or any other drugs which were proven to be hepatotoxic.

Table 1 shows total dose of methotrexate taken by patient over 15 years

Medication	Dose	Regimen	Duration	Total dose taken
Methotrexate	2.5 mg	Thrice a week	15 years	1350 mg
Folic acid	5 mg	Once a day	15 years	27000 mg

Patient had distention of abdomen, swelling of bilateral lower limbs and loss of appetite for3 months. She had no history of hematemesis, melaena or any similar complaints in the past. She was known diabetic on regular medications. Patient was non-alcoholic, or didn't had exposure to any hepatotoxic agents in past. She had no significant family history and similar complaints in the past.

She also had a history of CNS tuberculoma 12 days back. She was on anti-Koch's therapy for 12 days.Before diagnosis of CNS tuberculoma, she had history of fever, headache, one episode of convulsion, altered sensorium and giddiness. It might be due to immunosuppression effect of methotrexate. There was no history of tuberculosis either in herself or her family and immediate contacts. Patient did not remember having had any tuberculin skin test.

On examination patient was conscious and was well oriented to time, place and person. Her vitals were stable. She had mild pallor and bilateral pitting type of pedal oedema. There was no icterus, lymphadenopathy, clubbing, cyanosis and other peripheral signs of liver cell failure seen on general examination. Extensor surfaces of back and legs

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had multiple psoriatic plaques [figure 1]. Her abdominal examination revealed moderate splenomegaly with nonpalpableliver. Her abdomen was distended and had moderate ascites.

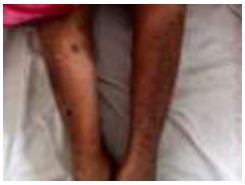

Figure 1 shows bilateral pitting oedema with psoriatic plaques

She had low haemoglobin with normal mean corpuscular volume. Her total leucocyte counts were normal with low platelets (Table 2). She had normal serum electrolytes and liver enzymes. Her international normalizing ratio was in normal range. She had serum albumin ascitic ratio on higher side which was suggestive of transudative ascites (Table 2). ANA western blot test was done which was negative. Patient was also negative for Hepatitis C and Hepatitis B.

Table 2 shows laboratory parameters

Parameters	Results	Units	Normal range
WBC	4.2	g/L	4.0–10.0
Haemoglobin	102	g/L	120–150
MCV	87.4	fL	83–101
Platelets	61000	10^9/L	150–410
Sodium	136	mmol/L	133–146
Potassium	3.9	mmol/L	3.5–5.3
Bilirubin	0.6	µmol/L	0.0–21
ALT	40	U/L	0.0–40
ALP	68	U/L	30–130
Albumin	23	g/L	35–50
INR	1.24		0.8–1.2
SAAG	**2.1**	g/L	Less than 1.1 – low More than 1.1 - high

ALT: Alanine transaminase; AST: Aspartate transaminase; SAAG: Serum Albumin Ascitic Gradient; WBC: White Blood Count; INR: International normalized ratio.

Her ultrasonography revealed raised echogenicity of liver parenchyma with surface irregularity with presence of moderate amount of free fluid in abdomen with portal vein diameter of 13 mm at porta hepatis with enlarged spleen of 12.8 cm which was suggestive of liver cirrhosis with portal hypertension. Her oesophageal endoscopy revealed oesophageal varices of grade II.Liver elastography was done which was suggestive of altered echotexture of liver with raised shear wave velocities on ARFI consistent with f4 fibrosis(cirrhosis).

On diagnosis of nonaggressive liver cirrhosis her methotrexate therapy was tapered off, band ligation was done for oesophageal varices and was put on topical therapy for psoriasis.

II. DISCUSSION

Methotrexate is one of the first line treatment in management of psoriasis [1, 4]. Methotrexate can cause liver fibrosis or nonaggressive liver cirrhosis on long term use [2]. Methotrexate is an inhibitor of dihydrofolate reductase enzyme. It causes depletion of folate reserve in body which leads to inhibition of RNA and DNA synthesis thus arresting the cell growth.It is used extensively in the therapy of leukaemia, lymphoma and several solid organ tumours. It also has potent immunomodulatory activity against psoriasis, inflammatory bowel disease and the inflammatory arthritis. Methotrexate is available in generic forms and under the brand names of Rheumatrex and Trexall in tablets of 2.5, 5, 7.5, 10 and 15 mg, and in both powdered and liquid-for-injection forms in vials of various strengths for intravenous, intramuscular or intrathecal injection [3]. The dose regimen varies by indication; high, short-term doses being used in treatment of cancer and chronic, lower doses for autoimmune conditions. The typical maintenance dose used to treat psoriasis and rheumatoid arthritis is 7.5 to 25 mg once weekly either orally or by injection. Side effects are mostly dose related and include stomatitis, oral ulcers, hair loss, fatigue, headache,

gastrointestinal upset, nausea, diarrhoea and bone marrow suppression. Severe adverse events include bone marrow suppression, severe infections, severe liver and lung disease, lymphomas, severe skin reactions, tumour lysis syndrome, fatal death and congenital abnormalities [3].

It also increases stellate cells in liver which leads to initiation of fibrosis which ultimately leads to liver cirrhosis [1, 3]. Earlier it was considered that high dose methotrexate therapy is implicated in causing liver cirrhosis and use of low dose for long term therapy is less likely to cause fibrosis or liver cirrhosis [3]. Long term therapy with methotrexate has been associated with development of fatty liver and hepatic fibrosis and, in rare instances, portal hypertension and symptomatic cirrhosis. Symptoms are usually absent until cirrhosis is present, and liver tests are typically normal or minimally and transiently elevated. But in recent studies it has been cleared that even long-term low dose therapy can lead to liver fibrosis or nonaggressive liver cirrhosis [2, 5]. Presence of comorbidities like diabetes mellitus, alcoholic liver disease, dyslipidaemia and chronic viral hepatitis can increase risk of liver cirrhosis in patients on methotrexate therapy [6].Chronic liver disease is characterized by progressive hepatic fibrosis with the development of cirrhosis. Liver biopsy has been the gold standard test for assessing hepatic fibrosis for many years. It is an invasive and painful procedure, with rare potential life-threateningcomplications, limiting its acceptance and repetition in usually asymptomatic patients. Because of invasive and painful procedure of liver biopsy, Transient elastography is now emerging test for evaluation of liver cirrhosis by measurement of liver stiffness [7].

III. CONCLUSION

This case concludes that methotrexate can cause liver fibrosis or nonaggressive liver cirrhosis without having much clinical signs and symptoms and deranged liver enzymes.Symptoms are usually absent until cirrhosis and liver tests are typically normal or minimally and transiently elevated. Even low dose long term therapy is known to cause liver cirrhosis hence it is advisable that periodic monitoring of these patients with liver elastography for evaluation of liver cirrhosis by measurement of liver stiffness is needed for early detection and timely alteration in treatment to prevent further progression of liver cirrhosis.

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