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Case Report
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Autoimmune Hepatitis-Induced Cirrhosis due to Long-Term Methotrexate Therapy for Rheumatoid Arthritis

*Habeeb Salameh[1], Jack Johnson[2], Kaled Diab[2], Hamzeh Saraireh[1], Shehzad N. Merwat[1] and Heather L. Stevenson[3]**

[1]Department of Internal Medicine, University of Texas Medical Branch at Galveston, USA

[2]School of Medicine, University of Texas Medical Branch, USA

[3]Department of Pathology, University of Texas Medical Branch at Galveston, USA

Abstract

Methotrexate (MTX) is commonly used to treat rheumatoid arthritis and can adversely affect the liver. Autoimmune hepatitis (AIH) is an extremely rare manifestation of MTX induced liver disease and has only been described in two previous cases. This report describes a patient that developed AIH, incomplete cirrhosis and portal hypertension after 10 years of MTX therapy. Liver function improved after discontinuation of MTX and proper treatment. Internists, family practitioners, gastroenterologists and hepatologists should be aware of the uncommon side effects of MTX and appropriately monitor patient's liver function tests. This will lead to earlier detection and prevention of bad clinical outcomes.

Keywords: Methotrexate (MTX); Autoimmune hepatitis; Rheumatoid arthritis; Liver cirrhosis

Introduction

Methotrexate (MTX) is commonly used to treatrheumatoid arthritis (RA) [1]. Abnormal liver function tests occur commonly with MTX, but serious hepatotoxicity is rare [2,3]. Therefore, liver function tests should be performed regularly to assess for hepatic injury.

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease primarily seen in young women [4]. The exact etiology and pathogenesis is unknown but is likely due to environmental factors and/or loss of immune tolerance in genetically susceptible hosts. Most cases are idiopathic with an unknown etiology. However, some known environmental triggers include medications, herbal agents, and viral hepatitis [4]. Herein, we report a MTX treated patient with RA who subsequently developed AIH that remained undetected until she developed incomplete cirrhosis and portal hypertension.

Case Presentation

We describe the case of a 66 year old African American female with a past medical history of being overweight (body mass index of 27.4 kg/m),having longstanding type-2 diabetes mellitus of 45 years duration, chronic kidney disease diagnosed 2 years prior to presentation, and anemia of chronic disease. In 2002 she was also diagnosed with erosive, non-deforming rheumatoid arthritis involving her bilateral wrists, elbows and knees. At that time she was prescribed MTX 7.5 mg weekly along with a folic acid supplement. While previously she had normal liver function tests, her liver enzymes (ALT, AST, and alkaline phosphatase) started to show intermittent mild elevations of less than 2 times the upper limit of normal between 2009 and 2011. She never consumed alcohol and her medications included metformin, folic acid, lisinopril, isosorbide dinitrate, nitroglycerin, mirtazapine and MTX (cumulative dose of 2.73 grams). Her viral serologies were negative but no further work up was pursued. She presented to the emergency department in July of 2012 with a 3-week history of abdominal swelling, abdominal pain, nausea, vomiting, weight loss, and fatigue. She reported her father had liver disease but further details were not known. Physical exam revealed as cites and splenomegaly. Abdominal ultrasound showed as cites, heterogeneous liver echogenicity and nodular contour, suggestive of cirrhosis. Her initial laboratory studies including an autoimmune liver disease panel are outlined in Table 1. Her Model for End-Stage Liver Disease (MELD) score was 14, which was primarily due to a creatinine of 1.5 mg/dl and an INR of 1.4. Her Child-Turcotte-Pugh score was class B. Ferritin levels were elevated at 1130 ng/mL and ceruloplasmin was normal at 36 mg/dL. Repeat viral serologies were negative.

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Correspondence:
Heather L. Stevenson, Department of Pathology, University of Texas Medical Branch at Galveston, 301 University Blvd 77555, Galveston, TX, USA 77555, USA,
E-mail: hlsteven@utmb.edu

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Table 1: Laboratory values.

LABS	Admission	After 3 weeks	After 5 months	After 4 years
PT	16.5 sec ↑	14.2 sec	12 sec	13.0 sec
Platelets ($^{*}10^{3}$/ul)	106 ↓	116 ↓	154 ↓	123 ↓
Creatinine(mg/dl)/ estimated GFR (ml/min/1.73m^{2})	1.56 / 40.2	1.43 / 44.4	1.8 / 34.1	5.7 / 7
Albumin (g/dL)	2.6 ↓	2.7 ↓	3.5	3.6
Total bilirubin (mg/dL)	1.1 ↓	0.9	0.6	0.6
AST (IU/L)	34	48 ↑	26	21
ALT (IU/L)	27	39	38	27
AP (IU/L)	87	282 ↑	79	79
GGT (IU/L)	23	55 ↑	24	NR
ANA titer	Positive, 1:320	Positive, 1:320	NR	Negative
ASMA titer	Negative, <1:20	Negative, <1:20	NR	Negative, <1:20
F-Actin (units)	Positive, 36	Positive, 41	NR	Positive, 27
LKM-1	Negative, <1:20	Negative, <1:20	NR	Negative, <1:20
Gamma-globulin (g/dL)	2.0↑	NR	1.7	NR
IgG (mg/dL)	1700 ↑	1880 ↑	1670	1250
Revised AIH original scoring system	18	17	NA	6

Abbreviations: PT: Prothrombin Time; AST: Aspartate Aminotransferase; ALT: Alanine Amino Transferase; AP: Alkaline Phosphatase; GGT: Gamma-Glutamyl Transferase; ANA: Anti-Nuclear Antibodies; ASMA: Anti-Smooth Muscle Antibodies; LKM-1: Anti-Liver Kidney Microsomal Antibodies; NR: Not Reported; NV: Normal Value.

A liver biopsy was performed and histology is illustrated in (Figure 1). The biopsy showed chronic hepatitis with prominent interface activity, moderate portal lymphoplasmacytic portal inflammation, and frequent plasma cells were observed throughout the lobules. The modified hepatitis activity index (MHAI) was 10/18 and the Ishak fibrosis stage was 5/6, which was confirmed with a Masson's trichrome stain (data not shown) [5]. The biopsy also showed focal macrovesicular steatosis (involving less than 5% of hepatocytes), minimal bile ductular reaction, and there was no evidence of infiltrative disease, such as amyloidosis. The iron stain on the biopsy was negative indicating that the elevated ferritin was not associated with hepatic hemosiderosis. The AIH diagnostic score using the revised original scoring system [6] was 16 (>15= definite AIH) and the diagnostic score using the simplified scoring system [7] was 7 (≥6 = definite AIH).AIH was diagnosed and MTX therapy was subsequently discontinued. Treatment with prednisone (30 mg taper; decreased to 10 mg by week 4) and azathioprine (50 mg) was initiated. The latter was continued until 2015.

After four years her laboratory studies were repeated and are outlined in Table 1. Between her initial presentation and follow-up, she was diagnosed with end-stage renal disease secondary to uncontrolled diabetes. Her MELD score was 21due to a creatinine of 3.3 mg/dl and an INR of 1.1. She was now a Child-Turcotte-Pugh class A. The repeated autoimmune laboratory studies showed negative anti-nuclear antibodies (ANA), negative alpha-smooth muscle actin (ASMA) antibodies, borderline positive anti-F-actin antibodies, negative anti-LKM-1 antibodies, and normal IgG immunoglobulin levels. Her current sequelae of portal hypertension include thrombocytopenia and esophageal varices. According to the above AIH scoring systems; she no longer qualified for a diagnosis of AIH [6].

Discussion

Before considering drug-induced liver injury in patients presenting with elevated liver enzymes, a thorough work-up should rule out other etiologies including primary biliary cirrhosis, primary sclerosing cholangitis, and occult HBV or HCV infections, which we conduct in all of our patients. While lisinopril has been reported to be associated with cholestatic liver injury [8], none of her other medications have been reported to be associated with drug-induced liver injury or drug-induced auto-immune hepatitis. Furthermore, liver biopsy did not show typical findings of steatosis, non-alcoholic steatohepatitis, amyloidosis, or glycogen hepatopathy. Differentiation between true AIH and drug-induced AIH remains a diagnostic challenge [9]. A recent study found that most cases of drug-induced liver injury are attributed to nitrofurantoin or minocycline and that induced by methyldopa and hydralazine resembles auto-immune hepatitis in almost half of the cases [10].

MTX-induced liver injury has been reported to occur in patients treated for leukemia, psoriasis, rheumatoid arthritis and a variety of other diseases [11-16]. Transaminase elevation is the most frequently described hepatotoxicity [17]. Less common but significantly more dangerous side effects include hepatic steatosis, fibrosis, and even cirrhosis [18-20]. Kremer et al. [21] reported that patients with elevated liver enzymes due to MTX respond to dose adjustments, which reduced the likelihood of development of clinically significant liver disease. Paradoxically, MTX has been used successfully to treat AIH Type 1 that is refractory to standard therapy [22]. Another report described two pediatric patients who presented with steroid-dependent AIH disease that was refractory to 6-Mercaptopurine (6MP)/azathioprine (AZA) maintenance therapy that were successfully treated with MTX [23].

AIH is an extremely rare manifestation of drug-induced liver injury secondary to MTX and to our knowledge, has only been reported twice in the literature. The two previous cases are outlined in Table 2 [24,25]. Classically, AIH is characterized by elevated AST, ALT, IgG immunoglobulins, positive serum autoantibodies (ASMA/anti-F-actin), and prominent interface hepatitis with lymphoplasmacytic

Table 2: Summary of the two MTX-induced AIH cases in the literature.

Case 1: 57-year-old male who took MTX 15 mg/week from December 2000 – July 2003 and was treated for AIH with Methylprednisolone 80 mg/day [24].			
LABS	**Admission Labs**	**After 2 weeks**	**After 5 months**
PT	15 sec (69.9%) ↑	75.1% ↑	12 sec (112%)
Albumin (g/dL)	3.2 ↓	3.3 ↓	3.5
Total bilirubin (mg/dL)	3.3 ↑	4.3↑	0.6
AST (IU/L)	1242 ↑	216 ↑	26
ALT (IU/L)	1715 ↑	644 ↑	38
AP (IU/L)	167 ↑	163 ↑	79
GGT (IU/L)	196 ↑	176 ↑	24
ANA titer	Positive, 1:160	NR	NR
ASMA titer	NR	NR	NR
F-Actin (units)	NR	NR	NR
LKM-1	NR	NR	NR
Gamma-globulin (g/dL)	2.1 ↑	NR	1.7
IgG (mg/dl)	1890 ↑	NR	1670
Histology	Architectural distortion characterized by perivenular and lobular confluent and bridging necrosis, enlargement of portal tracts, intense parenchymal infiltration with plasma cells, interface hepatitis characterized by intra-acinar parenchymal hepatocellular damage, and early hepatic regeneration.		
Case 2: 53-year-old female who took MTX 15 mg/week from 2000-2005 and from 2009-2013. She was treated for AIH with Methylprednisolone 80 mg/day [25].			
LABS	**Admission Labs**	**After 1 week**	**After 4 months**
PT	71% ↑	88% ↑	NV
Albumin (g/dL)	3.5	NR	NV
Total bilirubin (mg/dL)	12.0 ↑	NR	NV
AST (IU/L)	580 ↑	270 ↑	NV
ALT (IU/L)	620 ↑	340 ↑	NV
AP (IU/L)	170 ↑	173 ↑	NV
GGT (IU/L)	146 ↑	122 ↑	NV
ANA titer	Positive, 1:640	NR	NV
ASMA titer	NR	NR	NR
F-Actin (units)	NR	NR	NR
LKM-1	NR	NR	NR
Gamma-globulin (g/dL)	1.7	NR	NV
IgG (mg/dl)	1690	NR	NV
Histology	Not mentioned in study		

Abbreviations: PT: Prothrombin Time; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; AP: Alkaline Phophatse; GGT: Gamma-Glutamyl Transferase; ANA: Anti-Nuclear Antibodies; ASMA: Anti-Smooth Muscle Antibodies; LKM-1: Anti-Liver Kidney Microsomal Antibodies; NR: Not Reported; NV: Normal Value.

inflammation by histology [7,26]. It is difficult to determine if AIH is idiopathic or drug-induced based on the histopathologic features alone; however, Suzuki et al. [27] reported that the presence of portal neutrophils and cholestasis are more commonly observed in drug-induced AIH, and these features were observed in our patient's liver biopsy (Figure 1). The diagnosis of drug-induced AIH is best confirmed by its resolution after removal of the inciting agent and the lack of requirement for long-term steroid therapy [28].

The most common autoantibodies seen in AIH are ASMA, anti-F-actin, ANA and anti-LKM-1. Our patient had positive ANA and anti-F-Actin antibodies with negative ASMA and anti-LKM-1 antibodies. F-Actin is a component of the smooth muscle complex and has been shown to be more sensitive and more specific for the diagnosis of AIH when compared to ASMA [29]. Thus, even though ASMA serology was negative, the diagnosis of AIH can still be made by the presence of positive anti-F-Actin antibodies.

The presence of incomplete cirrhosis and portal hypertension in our patient resulted in abnormally low liver enzymes when compared to the classic presentation of AIH. As hepatocytes are lost, the liver loses its ability to synthesize proteins, such as albumin, transaminases, and clotting factors [30]. At least a third of patients with AIH already have cirrhosis at presentation, indicating the disease has progressed unrecognized for a period of time prior to diagnosis [31]. In hindsight, she started having intermittent, mild elevations in her liver injury tests approximately 7 years after starting MTX, at which time she had an incomplete work-up that was negative for infection with hepatotropic viruses (i.e., HAV, HBV, and HCV).

After resolution of AIH, our patient's albumin level increased, but still remained slightly below normal, and her hepatic transaminases have remained within the normal range for more than four years.

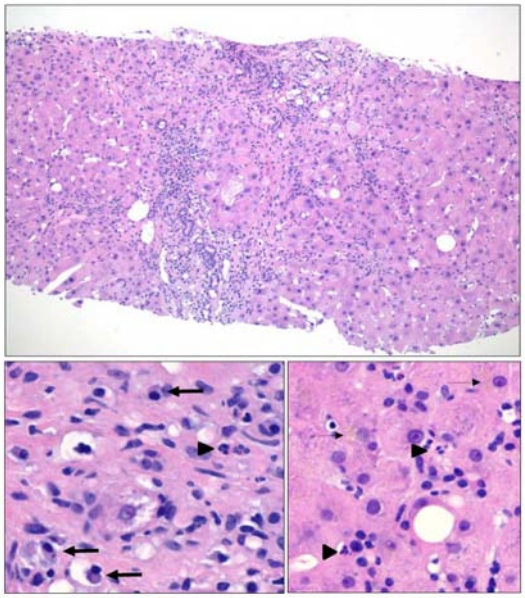

Figure 1: The liver biopsy showed moderate lymphoplasmacytic portal inflammation with frequent neutrophils (arrow heads), prominent interface and lobular inflammatory activity with abundant plasma cells (thick arrows), hepatocyte rosette formation (all panels), and mild hepatocellular cholestasis (thin arrows). The modified hepatitis activity index score was 10/18. Frequent bridging fibrosis, areas of subsinusoidal fibrosis and focal nodule formation were also observed. These features are consistent with incomplete cirrhosis (Ishakfibrosis stage: 5/6).

Since withdrawing MTX treatment, her autoantibodies have been undetectable or within the normal range, her liver enzymes have remained normal, and her hepatic synthetic function has improved, which strongly supports that this medication was the inciting agent in our case of drug-induced AIH [32]. A follow up liver biopsy was not performed, as there was no clinical indication.

In summary, patients on long-term MTX therapy should be monitored for the development of AIH by monitoring liver enzymes. If patients are noted to have abnormal elevations, a further work-up, including laboratory studies for AIH should be considered. If serologic studies are suggestive of AIH, a liver biopsy may be indicated for confirmation and determination of fibrosis stage. Clinicians need to be aware of the potential side effects of MTX therapy and should appropriately monitor patients for drug-induced liver injury, including AIH, which will lead to earlier detection and prevention of poor clinical outcomes.

Author Contribution

J Johnson, K Diaband H Saraireh wrote the manuscript and reviewed the literature. H Salameh, S Merwat and H.L. Stevenson critically revised the manuscript for important intellectual content, supervised the process and approved the final draft.

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