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Association of autoimmune hepatitis and systemic lupus erythematous: A case report and review of the literature

Charelle Salem; Elie Makhoul; Tony El Murr*

***Tony El Murr**

Department of Internal Medicine, Middle east institute of health, Lebanese University, Faculty of Medical Sciences, Lebanese university, Hadath, Lebanon
Phone: (961) 334-7473; Email: drtonimurr@hotmail.com

Abstract

Autoimmune hepatitis (AIH) is a autoimmune disease of the liver causing an necroinflammatory processus with an unknown etiology. Systemic lupus erythematous (SLE) is a autoimmune disease of unknown etiology, with chroinic inflammation affecting multiple organs including the liver, kidney, and CNS [1].

AIH has been considered to occur infrequently in SLE. We report a 42 year old female patient with an overlap syndrome involving Autoimmune Hepatitis (AIH) and Systemic Lupus Erythematous (SLE). The patient presented with jaundice, arthralgias, fatigue, jaundice, mild fever, and abdominal disconfort. Laboratory tests revealed severe liver dysfunction, a positive ANA/anti-dsDNA test. A liver biopsy showed acute hepatitis with severe inflammatory activity that goes with autoimmune hepatitis. The patient satisfied the international criteria for both SLE and AIH. Clinical symptoms and laboratory findings of SLE improved with appropriate treatment by corticosteroids and azathioprine, and remission of the liver disease was achieved as well.

Keywords

hepatitis; liver; kidney; jaundice; mild fever

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune inflammatory disorder that involves multiple systems such as kidneys, skin and the central nervous system. Liver involvement is seen in up to 60% of SLE patients [2]

Autoimmune Hepatitis (AIH) is also an autoimmune disease causing a necroinflammatory liver disease. It is characterized by the histological changes seen on liver biopsy, plasma cell infiltration of the portal tracts, hypergammaglobulinemia, and specific autoantibodies [3] The clinical presentation of AIH can range from asymptomatic disease to a fulminant hepatitis; with a female predominance and two peaks in early adult life and I the 4th decade of life [2].

Although, liver involvement is not a major target in SLE, there are common clinical and biochemical liver abnormalities. Only few case reports reported the co-occurrence of autoimmune hepatitis (AIH) and SLE [2].

In this report, we present a patient with an overlap syndrome involving autoimmune hepatitis AIH and SLE. It is still unclear if AIH and lupus hepatitis remain a different entities. And as such several clinical and histological features are used to distinguish AIH from SLE.

Case Report

A 42 year old female patient was admitted to the Emergency Department at Middle East Hopsital in June 2017 with complaints of malaise, jaundice, polyarthralgia, abdominal distention, discomfort, and low grade fever, evolving since 3 weeks. The patient had a history of arthralgia since few months and was treated by an orthopedic surgeon by non steroidal anti inflammatory and myorelaxant drugs without improvement.

The patient is known to have hypothyroidism treated by Eltroxine 200microgs/ d since 5 years. She was married at 18 years old and have three kids. Family history was negative for rheumatic or inherited liver disease, including SLE and AIH. She had no risk factor for blood transmitted disease.

On physical examination, the patient was conscious cooperative and oriented. She had an icteric sclera, with poorly injected conjunctiva. she had a history of photosensitivity with redness and itchy eruptions on her face. She had no palpable lymphadenopathy. Her lungs were clear with good bilateral air entry, and with regular S1 S2 on heart auscultation with no added murmur. On abdominal exam, the skin was intact. She had a palpable hepatomegaly and splenomegaly. She had no Peripheral edema and pedal pulses were positive. Neurological exam was within normal limits.

Complete blood count revealed hemoglobin of 96 g/L, white blood cell count 9800/mm3 and platelet count 208.000/mm3, a peripheral blood smear showed no specific features. Microscopic examination of the urine was normal. Biochemical tests showed evidence of liver dysfunction. Serum alanine aminotransferase (ALT) was 572 IU/L (N: 5-40 IU/L), aspartate aminotransferase (AST) 650 IU/L (N: 8-33 IU/L), gamma-glutamyl transpeptidase 320 IU/L (N: 5-40 IU/L), alkaline phosphatase 215 IU/L (N: 35-129 IU/L), total bilirubin 61 mg/L (N: 1-12 mg/L), conjugated bilirubin 52 mg/L (N: 0-3 mg/L), and prothrombin activity 89% with International normalized ratio 1.32 (N: 0-1).Serum creatinine, BUN and fibrinogen were normal.

Here lab tests three months prior to presentation were unremarkable.

Wilson's disease was ruled out because of normal serum ceruloplasmin. C-reactive protein level were elevated (130 mg/L). Coombs-positive hemolytic anemia was detected. Serum immunoglobulin G and M levels were increased (2500mg/dl and 650 mg/dl respectively), serum plasma electrophoresis showed hypoalbuminemia with a polyclonal increase in total gamma globulins. Serological tests showed positive results for serum antibodies against nuclear antigen (ANA) 1/6400 IU/L and double-stranded DNA. The serum levels of C3 and C4 were normal. Tests for antiphospholipid antibody and anticardiolipin antibody were slightly positive (9U/ml). Antibodies against smooth muscle (SMA), Liver/Kidney Microsomes (LKM), anti-mitochondrial M2 antibody (M2-AMA), anti-soluble liver antigen/liver-pancreas (SLA/LP), anti-M2-E3, antibody to liver cytosol (LC-1) and Exractable Nuclear Antigen (ENA) were negative Viral serological tests including antibodies for hepatitis viruses A, B and C, Epstein Barr, Cytomegalovirus (CMV), Human Immunodeficiency Virus (HIV) were negative.

Abdominal ultrasonography and color Doppler ultrasonography showed hepatosplenomegaly

with mild perihepatic liquid indicating hepatitis.

Three days after symptomatic treatment, the patient's laboratory tests and clinical symptoms were worsening: Serum alanine aminotransferase (ALT) was 1105 IU/L (N: 5-40 IU/L), Aspartateaminotransferase (AST) 910 IU/L (N: 8-33 IU/L), total bilirubin 110 mg/L (N: 1-12 mg/L), Prothrombin activity 63% and international ratio 2.1, micro albumin ratio 80mcg/mg (Table 1).

Table 1: Follow up laboratory result of the case

Date	Admission June 1	June 3	June 13	June 23	July 3	July 13	July 28	August 8	August 9
Hemoglobin (g/l)	96	90	103	109	115	123	128	118	120
SGOT (IU/L)	650	910	358	222	104	102	80	45	43
SGPT (IU/L)	572	1105	731	513	247	205	136	51	35
GGT (IU/L)	320	320	387	317	307	226	152	112	97
Total BILIRUBIN (mg/l)	61	110	40	30	13.8	9.5	8	4.5	4.8
Prothrombin activity %	89	63	83	83	89	93	95	98	89
Prednisone (mg)	0	60	50	40	30	25	17.5	15	7.5
AZA (mg)	0	0	0	50	100	100	100	100	100

The patient showed 6 of 11 American College of Rheumatology (ACR) criteria for SLE which classified her as definite SLE.

Abdomino-pelvic CT scan showed no significant abnormalities. Liver biopsy showed acute hepatitis with severe inflammatory activity. The hepatic architecture is very reworked with 12 enlarged fibroadenomatous portal spaces, seat of fibrosis more or less important with a tendency to confluence (bridging) inter-portal. The lobules are dissociated by a polymorphic inflammatory infiltrate with extensive hepatocyte necrosis (<50% of the portal circumference) and Councilman body formation. The remaining hepatocytes are surrounded by edematous fibrosis (figure 1).

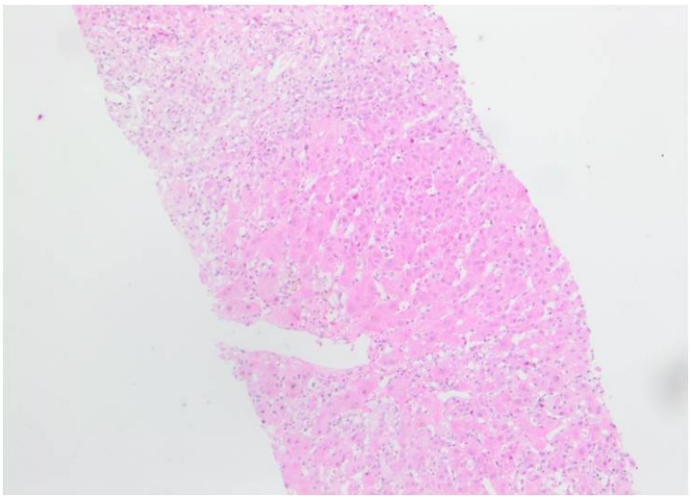

Figure 1 : Beginning of cirrhotic lobulations related to a very active hepatitis, compatible with an autoimmune origin.

These findings suggested an overlap syndrome involving SLE and autoimmune hepatitis.

The patient was started on treatment with oral prednisolone 1 mg/kg per day (60 mg/d). Because of the ongoing high transaminase levels, azathioprine (AZA) was added (50 mg/kg per day for the first week and than 100 mg/day for 6 months), prednisolone was gradually tapered (by 10 mg/week till 30 mg daily, than tapered by 5 mg/week till 20 mg daily, than tapered by 2.5 mg/week till 5 mg daily for 6 months).

Clinical symptoms and laboratory findings of SLE improved, and a remission of acute hepatitis was achieved in the case. Complete biochemical remission including normalization of transaminases as well as IgG levels was achieved after four months of treatment.

The patient was regularly seen at the outpatient clinic for follow-up visits.

Discussion

Systemic Lupus Erythematous (SLE) is a autoimmune disorder that involve multiple system including various organs such as kidneys, skin and the central nervous system [2].

The liver is not usually one of the classically involved organ in the spectrum of SLE, but is seen in up to 60% of SLE patients [2].

The hepatic involvement in SLE and AIH has different similarities in the clinical and biochemical features, and the difference is not clear [3].

As such, patients with AIH are suggested to be at an increased risk of developing systemic connective tissue disease, and furthermore the presences of systemic connective tissue disease will increase the risk of AIH [3].

Despite considering AIH and SLE-associated hepatitis two different entities [3], both have features of an autoimmune disorder. Both entities are diagnosed by the presence of of polyarthralgia, hypergammaglobulinemia and specific positive tests such as ANA, SMA, anti ribonucleoprotein antibody, and anticardiolipin antibodies [2]. Otherwise, several clinical features can differentiate between SLE and AIH. AIH is characterized by the presence of cirrhosis or periportal hepatitis, with necrosis and rosette formation of the liver cells (figure 2). SLE is more likely in the presence of lobular hepatitis. Whereas in the association of AIH and SLE “lupus hepatitis” , it is characterized by an inflammatory infiltrate, mainly consisting of lymphocytes [3].

Our patient had acute hepatitis with severe inflammatory activity characterized a hepatic architecture with 12 enlarged fibroadenomatous portal spaces, seat of fibrosis more or less important with a tendency to confluence (bridging) inter-portal. The lobules are dissociated by a polymorphic inflammatory infiltrate with extensive hepatocyte necrosis (<50% of the portal circumference) and Councilman body formation.

ANA and Anti-DsDNA were the only positive serological markers; its positivity is sufficient to diagnose AIH. The patient was also evaluated for all disease that can suggest an autoimmune features such as hereditary (Wilson's disease), infectious including hepatitis A, B, C, CMV and EBV, and for drug-induced liver injury [3]. When the simplified scoring system for AIH was applied, patient had a score of 8, which is sufficient for a definite diagnosis of AIH [4] (table 2).

Table 2: simplified criteria for diagnosis of autoimmune hepatitis [6].

Simplified criteria for the diagnosis of autoimmune hepatities		
Variable	Cut-off	Points
ANA or SMA	≥ 1:40	1
ANA or SMA	≥ 1:80	2*
or anti-LKM-1	≥ 1:40	
or SLA	positive	
lgC	≥upper limit of normal	1
	≥1.10 times upper limit of normal	2
liver histology	Compatible with AIH	1
	Typical of AIH	2
Absense of viral hepatities	Yes	2

Score >6: Probable AIH: > : define AIH.

ANA, anti- nuclear antibody : Sms, anti-smooth muscle antibody; anti-lkm-1, anti- liver kidney microsomal antobody type 1: SLA, soluble liver antigen: lgC, immunoglobulin G: AIH, autoimmune hepatities.

*Addiction of points achieved for all auto antibodies cannot exceed a maximum of 2 points adopted from hennes em, zeniya M et al. hepatology. 2008; 48: 169-176.

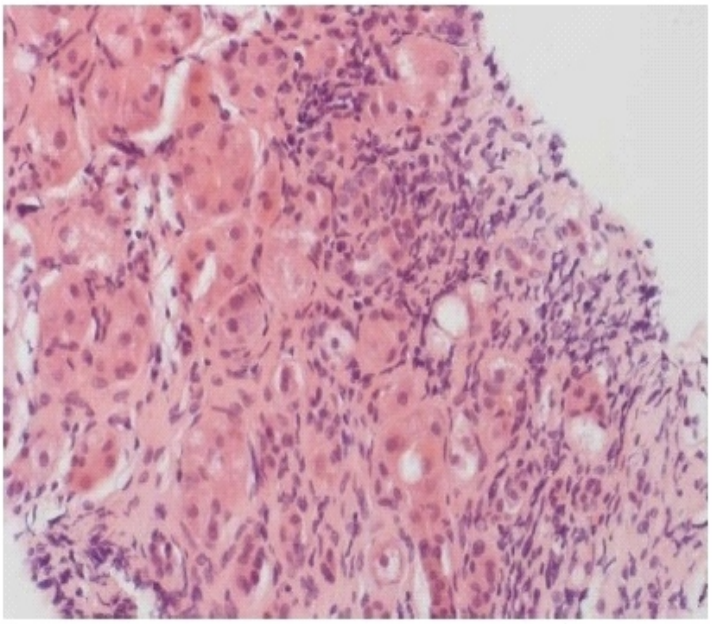

Figure 2: Typical histopathology of a patient with autoimmune hepatitis. Cirrhotic changes of the liver parenchyma with interface hepatitis. The portal and periportal inflammatory infiltrate is composed of lymphocytes, monocytes/macrophages and plasma cells (haematoxylin and eosin staining; × 200). Loshe AW, mieli-vergani G et al [7].

Several Specific markers can be used to segregate the coincident AIH with SLE, such Soluble Liver Antigen (SLA), liver-pancreas, Smooth Muscle Antibody (SMA). But liver biopsy for histopathology will remain the best feature that distinguishes lupus hepatitis from non specific liver involvement in SLE [2].

The criteria for the diagnosis of SLE and AIH have been proposed by respectively the American College of Rheumatology [4], and the International Autoimmune Hepatitis Group (IAIHG) [5], and our patient met those criteria. She had the characteristic photosensitivity, polyarthralgia, arthritis, renal disorder, hematologic disorder, and was positive for antibodies against native DNA and nuclear antigen. She was started on prednisolone and azathioprine and achieved complete remission for her SLE and her liver disease.

We believe that our patient has the AIH-SLE overlap syndrome. This syndrome was well reported to have a good response to steroid therapy with a good prognosis. The combination of prednisone and AZA is preferred for steroid sparing [3]. The relapse is common. A long term low dose prednisone or AZA therapy will be required after several relapses; but even after relapse, remission can be achievable [3].

In conclusion, AIH and SLE are distinct diseases, whose combination of clinical symptoms and diagnostic markers overlap. While SLE and AIH are rarely diagnosed as concomitant diseases in one patient, hepatic involvement in patients with SLE is sometimes observed during the course of disease. As such we suggest that in SLE patient presenting with elevated liver enzymes, AIH should be considered. Liver biopsy is crucial in such patients. The goal is to obtain complete remission with the appropriate regimen of steroids and azathioprine, to prevent the disease progression, and to maintain a long-term survival on low dose of medication if possible.

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Authors Information: Charelle Salem; Elie Makhoul; Tony El Murr*

Department of Internal Medicine, Middle east institute of health, Lebanese University, Faculty of Medical Sciences, Lebanese university, Hadath, Lebanon

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