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CASE REPORT

Association of autoimmune hepatitis and systemic lupus erythematodes: A case series and review of the literature

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Abstract

Liver test abnormalities have been described in up to 60% of patients with systemic lupus erythematodes (SLE) at some point during the course of their disease. Prior treatment with potentially hepatotoxic drugs or viral hepatitis is commonly considered to be the main cause of liver disease in SLE patients. However, in rare cases elevated liver enzymes may be due to concurrent autoimmune hepatitis (AIH). To distinguish whether the patient has primary liver disease with associated autoimmune clinical and laboratory features resembling SLE - such as AIH - or the elevation of liver enzymes is a manifestation of SLE remains a difficult challenge for the treating physician. Here, we present six female patients with complex autoimmune disorders and hepatitis. Patient charts were reviewed in order to investigate the complex relationship between SLE and AIH. All patients had coexisting autoimmune disease in their medical history. At the time of diagnosis of AIH, patients presented with arthralgia, abdominal complaints, cutaneous involvement and fatigue as common symptoms. All patients fulfilled the current diagnostic criteria of both, AIH and SLE. Remission of acute hepatitis was achieved in all cases after the initiation of immunosuppressive therapy. In addition to this case study a literature review was conducted.

Key words: Systemic lupus erythematodes; Elevated liver enzymes; Autoimmune hepatitis

Core tip: Hepatic involvement in patients with systemic lupus erythematodes (SLE) is considered to be rare. The differences between hepatic involvement caused by hepatotoxic drugs, coincident viral hepatitis, non-alcoholic fatty liver disease or concurrent autoimmune hepatitis (AIH) as independent disease has not been defined clearly in patients with SLE. This case report describes six patients who fulfill the current diagnostic criteria for both SLE and AIH, and thus represents the largest case series in the literature.

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INTRODUCTION

Systemic lupus erythematodes (SLE) is a multisystem autoimmune disorder involving various organs such as kidneys, skin and the central nervous system. Liver involvement is normally not part of the spectrum of SLE, but is seen in up to 60% of SLE patients[1]. Hepatotoxic drugs, coincident viral hepatitis and non-alcoholic fatty liver disease (often induced by steroids) are the most commonly described causes of elevated liver enzymes in SLE[2].

Table 1 Review of literature

Author	Year of publication	Patients (*n*)	Sex	Age (in year)	Clinical presentation	Liver enzymes	Outcome
Chattopadhyay *et al*[15]	2011	1	Female	20	Fever, polyarthritis, jaundice	Elevated	Remission
Choi *et al*[16]	2008	1	Female	Unknown	Butterfly-type facial erythema	Elevated	Remission
Chowdhary *et al*[8]	2008	6	Unknown	Unknown	Unknown	Unknown	Unknown
Deen *et al*[17]	2009	4	3 female 1 male	Median 11 Range 11-13	Jaundice, splenomegaly, cutaneous involvement, articular involvement, proteinuria (> 0.5 g/d), cardiopulmonary involvement	Elevated	Remission in all cases
Efe *et al*[18]	2011	4	Female	Median 35 Range 27-40	Unknown	Elevated	Unknown
Iwai *et al*[19]	2003	1	Female	60	Elevated liver enzymes	Elevated	Remission
Kaw *et al*[20]	2006	1	Female	34	Arthralgia, myalgias, skin rash, nausea	Elevated	Remission
Kooy *et al*[21]	1996	1	Unknown	Unknown	Unknown	Elevated	Remission
Koshy *et al*[22]	2012	1	Female	30	Jaundice, abdominal distention	Elevated	Exitus letalis[1]
Mackay *et al*[11]	1999	1	Female	16	Failure to thrive, jaundice, non-erosive arthritis, oral aftous lesions	Elevated	Progress
Moriwaki *et al*[23]	1987	1	Unknown	Unknown	Unknown	Unknown	Unknown
Satoh *et al*[24]	1997	2	Unknown	Unknown	Unknown	Unknown	Remission
Suzuki *et al*[25]	1993	1	Female	33	Intermittend fever, polyarthralgia, cutaneous involvement, pericardial effusion	Elevated	Remission
Takahashi *et al*[26]	2007	1	Female	69	Fever, cough, pleural and pericardial effusion	Elevated	Remission
Tojo *et al*[27]	2004	5	Female	Median 43 Range 21-56	Raynaud's phenomenon, arthralgia, butterfly-type facial erythema, dry mouth, jaundice, edema, ascites, pleural effusion, struma, skin ulcer, fatigue, fever	Elevated in 4 of 5 cases	Remission in all cases
Usta *et al*[28]	2007	1	Female	12	Jaundice, hepatosplenomegaly, polyarthralgia, malaise, butterfly-type facial erythema, arthritis	Elevated	Stable
Yamasaki *et al*[29]	2004	1	Female	48	Ascites	Elevated	Remission
Yoon *et al*[30]	2003	2	Female	Unknown	Unknown	Elevated	Unknown

[1]Patient died due to acute liver failure.

The co-occurrence of autoimmune hepatitis (AIH) and SLE is considered to be rare and only few case reports have been published so far (Table 1). Diagnostic criteria in accordance with the International Autoimmune Hepatitis Group and the "simplified criteria" are based on elevation of Immunglobulin G (IgG), demonstration of characteristic autoantibodies, histological features of hepatitis and the absence of viral disease[3,4]. The clinical presentation of AIH ranges from asymptomatic disease recognized only by incidentally ascertained biochemical abnormalities to an acute or even fulminant hepatitis. Female predominance and occurrence peaks in early adult life and in the 4th decade of life are characteristic[5]. In symptomatic cases patients are often affected by non-specific symptoms such as nausea, anorexia, abdominal discomfort and jaundice. A common extrahepatic manifestation of AIH may be arthralgias, which are also often seen in SLE.

A patient with SLE and elevated liver enzymes presents a demanding differential diagnosis for the rheumatologist. While elevated IgG and anti-nuclear antibodies (ANAs) are characteristic for both AIH and SLE[5], there are few serological markers, which are highly specific for the two different diseases. Anti-double stranded DNA (anti-dsDNA) antibodies are associated with SLE but are also found in patients suffering from AIH[6]. Data on sensitivity for the diagnosis of SLE range from 25%-85%[7]. Czaja *et al*[6] tested sera from 53 patients with AIH by enzyme immunosorbent assay and indirect immunofluorescence using the Crithidia luciliae substrate and detected anti-dsDNA in 30 patients (57%). Also anti-Smith antibodies are frequently found in SLE patients and approximately 99% of individuals with positive anti-SM match the diagnostic criteria for SLE[7]. Specific markers for AIH, which usually do not occur in SLE, are soluble liver antigen (SLA), Liver-pancreas, smooth-muscle antibody (SMA) with specificity for F-actin and microsomal autoantigens, such as anti-liver kidney antibodies (anti-LKM antibody)[5]. While these markers may help to segregate AIH coincident with SLE serologically, liver histopathology represents the key feature that distinguishes AIH in SLE from nonspecific hepatic involvement in SLE. In patients with AIH liver histopathology shows characteristic lesions, such as interface hepatitis, rosetting of hepatocytes, emperipolesis and - consecutive to inflammation - fibrosis (Figure 1)[5]. In contrast, liver histology in SLE usually shows changes attributable either to drug toxicity or non-specific liver involvement as *e.g.*, fatty degenera-

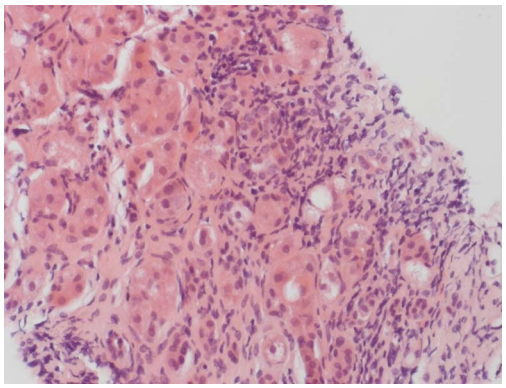

Figure 1 Typical histopathology of a patient with autoimmune hepatitis (case 1). Cirrhotic changes of the liver parenchyma with interface hepatitis. The portal and periportal inflammatory infiltrate is composed of lymphocytes, monocytes/macrophages and plasma cells (haematoxylin and eosin staining; × 200).

tion or hydropic hepatocytes[2,8].

As the diagnosis of AIH is relevant in SLE patients with regards to choices of immunosuppressants, long-term outcome and optimal surveillance of the patients, adequate attention should be taken to differentiate between "true additional" AIH or non-specific liver involvement.

In the following, we present six patients with SLE and the concomitant diagnosis of autoimmune hepatitis. All patients matched the current diagnostic criteria of both AIH as well as of SLE. A review of the literature was performed and published cases were summarized (Table 1).

CASE REPORT

Six female patients with arthralgias, elevated transaminases and additional symptoms were seen either at the I. Department of Medicine of the University-Medical Center Hamburg-Eppendorf or at the Johannes Gutenberg University Hospital Mainz, Germany, between 1991 and 2011. The median age at presentation was 44 years (range: 27-60 years). All patients presented with arthralgia (n = 6) as main complaint at time of diagnosis. Abdominal complaints (n = 4), cutaneous involvement (n = 4) and fatigue (n = 4) were the second most common symptoms. Jaundice (n = 1), fever (n = 1), photosensitivity (n = 1), sicca symptoms (n = 1) and myalgia (n = 1) were less often described. All patients presented with elevated liver enzymes (AST median: 238.5 U/L, range: 59-323 U/L; ALT median: 174.5 U/L, range: 53-413 U/L). Five of six showed increased levels of IgG (median 24.15 g/L; range 6.7-44 g/L) and ANA titers with a homogeneous pattern on immuno fluorescence diagnostics, (median 1:960, range 1:160-1:2560) (Table 2).

While all patients tested negative for anti-LKM-1 as well as SLA/LP antibody, three patients tested positive for SMA. Four patients showed positive anti-dsDNA titers, only one patient tested positive for anti-Sm antibody (case 4).

Five of six patients had a history of Hashimoto's thyroiditis as coexisting autoimmune disease. Other concomitant autoimmune disorders like primary sclerosing cholangitis, psoriasis and Raynaud's phenomenon occurred in one patient respectively.

The diagnosis of SLE was established based on the American College of Rheumatology (ACR) classification criteria[3,9]. All patients fulfilled the simplified diagnostic criteria of AIH with a median score of 8 points (range 6-8 points)[4].

Liver biopsy was performed due to elevated transaminases in all cases and showed typical signs of AIH (Figure 1). Advanced fibrosis/cirrhosis was found in three patients.

Treatment was initiated in all cases with prednisolone pulse-therapy[10] and extended to a combination of azathioprine and hydroxychloroquine in four cases. A monotherapy with azathioprine or mycophenolate mofetil after prednisolone pulse-therapy was started in one patient, respectively. Two patients required a change of treatment due to azathioprine intolerance and switched to treatment with cyclophosphamide. Remission of acute hepatitis was achieved in all cases. Complete biochemical remission including normalization of transaminases as well as IgG levels was achieved in all patients after six months of treatment.

One patient (case 3) developed hepatocellular carcinoma (HCC) in 2012, six years after diagnosis of AIH. In her first liver biopsy in 2006, the patient showed liver cirrhosis. The patient was regularly seen at the outpatient clinic for follow-up visits and ultrasound screening for HCC was performed every six month. Multifocal HCC (barcelona clinic liver cancer-stadium C) was diagnosed six years after diagnosis of AIH. Surgical resection or liver transplantation as curative treatment option was not feasible due to advanced tumor stage. The patient underwent transcatheter arterial chemoembolization every three month. Since July 2013, the patient receives additionally systemic therapy with sorafenib due to tumor progression. Information of patient characteristics is given in Table 2.

DISCUSSION

Hepatic involvement in patients with SLE is well documented, but considered to be rare[11]. The differences between hepatic involvement caused by hepatotoxic drugs, coincident viral hepatitis, non-alcoholic fatty liver disease or concurrent AIH as independent disease has not been defined clearly in patients with SLE.

In this case series, we present six patients who fulfill the current diagnostic criteria for both SLE and AIH[3,9]. Interestingly, these patients presented with clinical and serological symptoms suggestive for AIH and liver disease was the leading disease in five of our patients. In addition to symptoms suggestive for AIH, the patients had distinctive features of SLE, supporting the interpretation of coexistence of the two conditions.

To our knowledge, only 35 cases of patients with the concurrent diagnosis of SLE and AIH have been published altogether (Table 1).

Table 2 Patient characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Demographic data						
Age at time of diagnosis (yr)	43	59	40	60	27	45
Sex	Female	Female	Female	Female	Female	Female
Year of diagnosis	2012	2003	2006	2001	1994 (SLE) 2005 (AIH)	1991
Laboratory tests						
Hemoglobin (g/dL)	10.7	NA	NA	14.7	13	13.4
Leukocytes (/μL)	0.7	NA	NA	8.9	4.84	8.7
Platelets (/μL)	21	NA	NA	291	232	181
AST (U/L)	316	170	59	307	125	323
ALT (U/L)	99	164	53	298	185	413
Total bilirubin (mg/dL)	8.9	1	1.8	0.83	0.9	4.1
IgG (g/L)	44	19.3	6.77	10.13	29	29
C3 (mg/dL)	4.1	Normal	Low	NA	0.14	NA
C4 (mg/dL)	4.1	Normal	Low	NA	0.14	NA
ANA, homogeneous pattern (titer)	1:2560	1:320	1:640	1:1280	1:160	1:1280
SMA (titer)	1:2380	1:320	Negative	1:60	1:160	Negative
Anti-dsDNA (units)	39	941	Negative	Negative	37	> 200
RNP-Sm (immunoblot)	NA	Positive	NA	NA	Positive	NA
Liver biopsy (Grading/staging[1])	Cirrhosis (G2/F4) Chronic hepatitis	Cirrhosis (G1/F4) Chronic hepatitis NASH	Cirrhosis (G3/F4) Chronic hepatitis	Fibrosis (G1/F3) Chronic hepatitis	Fibrosis (G2/F1) Chronic hepatitis PSC	Fibrosis (G3/F3) Chronic hepatitis
Clinical symptoms of SLE	Arthritis Photosensitivity Oral ulcers Serositis	Arthritis Malar rash	Arthritis	Arthritis Malar rash	Arthritis	Arthtitis Malar rash
Therapy regime	Prednisolone Azathioprine Hydroxychloroquine	Prednisolone MMF	Prednisolone Azathioprine Hydroxychloro-quine	Prednisolone Azathioprine Hydroxychloro-quine Cyclophospha-mide	Prednisolone Azathioprine	Prednisolone Azathioprine Cyclophospha-mide
Course of disease	Remission	Remission	Remission Diagnosis of HCC in 2012	Remission	Remission	Remission

[1]Scheuer classification for grading and staging of chronic hepatitis. AIH: Autoimmune hepatitis; ALT: Alanine aminotransferase; ANA: Anti-nuclear antibodies; anti-dsDNA: Anti-double stranded DNA; anti-KLM-1: Anti-liver-kidney microsome type 1; anti-SMA: Anti-smooth muscle; AST: Aspartate transaminase; HCC: Hepatocellular carcinoma; MMF: Mycophenolate mofetil; NASH: Non-alcoholic steatohepatitis; NA: Not applicable; PSC: Primary sclerosing cholangitis; SLE: Systemic lupus erythematodes.

AIH and SLE are considered distinct diseases, which can be associated like other autoimmune diseases. This is supported by the fact, that five of our six patients had coexisting autoimmune disorders, as *e.g.*, Hashimoto's thyroiditis.

Differential diagnosis of elevated liver enzymes in patients with SLE as non-specific hepatic involvement or as AIH is demanding. While serological markers, such as ANA, anti-dsDNA or raised IgG can be strongly overlapping in SLE and AIH, histology is all the more essential to distinguish AIH in SLE from non-specific hepatic involvement in SLE. In accordance with the revised simplified criteria of AIH, histological demonstration of hepatitis compatible with AIH[12] is the essential diagnostic criterion of AIH[3,5]. We suggest that AIH needs to be considered in the differential diagnosis of any SLE patient with elevated liver enzymes. Liver biopsy is therefore crucial in these patients.

Treatment strategies are determined by the predominant disease, which in our case series was AIH. The recommended treatment for both, AIH and SLE, are immunosuppressive strategies with therapeutic success. Except one, all published cases responded well to immunosuppressive treatment (Table 1). It has been shown for AIH, that complete biochemical remission is crucial for long-term prognosis of these patients[13]. There is no data available for the prognosis of AIH with concomitant SLE but publications suggest, that achievement of complete remission is crucial not only for long-term survival in these patients but also regarding quality of life. However, AIH has a more aggressive histology pattern and prognosis of untreated symptomatic autoimmune hepatitis is poor with a five-year survival rate below 25% in untreated patients versus 80% in those treated with corticosteroids[14].

To summarize, 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. In our view, AIH needs to be considered in the differential diagnosis of any SLE patient with elevated liver enzymes, and liver biopsy should

become mandatory in such patients.

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COMMENTS

Case characteristics

Authors report six female patients with systemic lupus erythematodes (SLE) and autoimmune hepatitis (AIH).

Clinical diagnosis

Current diagnostic criteria for both SLE and AIH were fulfilled.

Differential diagnosis

Hepatic involvement caused by hepatotoxic drugs, coincident viral hepatitis or non-alcoholic fatty liver disease.

Laboratory diagnosis

All patients presented with elevated liver enzymes. Five of six showed increased levels of IgG. While all patients tested negative for anti liver kidney-1 as well as soluble liver antigen/LP antibody, three patients tested positive for smooth muscle. Four patients showed positive anti-double stranded DNA titers, only one patient tested positive for anti-Sm antibody.

Pathological diagnosis

Liver biopsy was performed due to elevated transaminases in all cases and showed typical signs of AIH. Advanced fibrosis/cirrhosis was found in three patients.

Treatment

Treatment was initiated in all cases with prednisolone pulse-therapy and extended to a combination of azathioprine and hydroxychloroquine in four cases. A monotherapy with azathioprine or mycophenolate mofetil after prednisolone pulse-therapy was started in one patient, respectively. Two patients required a change of treatment due to azathioprine intolerance and switched to treatment with cyclophosphamide.

Experiences and lessons

Autoimmune hepatitis needs to be considered in the differential diagnosis of any SLE patient with elevated liver enzymes, and liver biopsy should become mandatory in such patients.

Peer review

This is a case series and literature review paper of patients with AIH-SLE overlap. It is very important to clarify the characteristics of these patients.

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