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ORIGINAL ARTICLE

Autoimmune liver disease in patients with systemic lupus erythematosus: A retrospective analysis of 147 cases

CUMALI EFE[1], TUGRUL PURNAK[2], ERSAN OZASLAN[2], ZEYNEP OZBALKAN[3], YASAR KARAASLAN[3], EMIN ALTIPARMAK[2], PAOLO MURATORI[4] & STAFFAN WAHLIN[5]

[1]*Department of Internal Medicine, Ankara Numune Research and Education Hospital, Ankara, Turkey,* [2]*Department of Gastroenterology, Ankara Numune Research and Education Hospital, Ankara, Turkey,* [3]*Department of Rheumatology, Ankara Numune Research and Education Hospital, Ankara, Turkey,* [4]*Department of Clinical Medicine, Alma Mater Studiorum, University of Bologna, Bologna, Italy, and* [5]*Department of Gastroenterology and Hepatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*

Abstract

Objective. We aimed to investigate the characteristics of autoimmune liver disease (AILD) developed in patients with systemic lupus erythematosus (SLE), including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and the AIH/PBC overlap syndrome. We also evaluated the accuracy of diagnostic criteria and scoring systems for AILD in SLE. ***Methods.*** A retrospective analysis of patients attending the rheumatology and gastroenterology clinics in Ankara, Turkey, between 1999 and 2010. SLE patients with elevated liver enzymes were investigated for liver diseases. ***Results.*** A total of 147 SLE patients were identified and 36 of them had liver enzyme abnormalities. AILD was diagnosed in 4.7% of all SLE patients, in 19.4% of those with elevated liver enzymes. Of patients with liver enzyme abnormalities, 72.3% fulfilled the criteria for AIH proposed by the International Autoimmune Hepatitis Group (IAIHG), whereas 66.7% had AIH by using the simplified criteria. Yet, only 13.8% of these patients had liver biopsy findings consistent with AIH. Patients with AILD were treated with conventional therapy including ursodeoxycholic acid, prednisolone, azathioprine or combinations of these. Treatment failure and subsequent advanced liver disease developed in one patient. ***Conclusions.*** AILD may occur during the course of SLE. Due to biochemical similarities between AIH and SLE, AIH could be considered very probable by using both IAIHG scoring system and simplified criteria. For definitive diagnosis of AIH, liver biopsy should be performed in all SLE patients with chronic enzyme abnormalities. The response to therapy is favorable in these patients, and early diagnosis is important for preventing advanced liver disease.

Key Words: *Autoimmune hepatitis, overlap syndromes, primary biliary cirrhosis, revised original scoring system, simplified criteria, systemic lupus erythematosus*

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease classically affecting multiple organ and systems [1]. Autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC), the main autoimmune liver diseases, are characterized by specific autoantibodies, hypergammaglobulinemia and characteristic histological changes in the liver [2]. Clinical and subclinical liver diseases are common in SLE, although the liver is not a major target organ for damage in SLE patients [3]. Hepatotoxic drugs, coincident viral hepatitis, autoimmune liver disease (AILD) and non-alcoholic fatty liver disease are the main causes of liver disease in SLE [4]. Liver involvement in patients with SLE has previously been studied in combined cohorts including several collagen and connective tissue

Correspondence: Cumali Efe, MD, Ankara Numune Research and Education Hospital, Dept of Internal Medicine and Gastroenterology, Yazgan sokak 21/12 Cebeci, Ankara, Turkey. Tel: +90 3123635589; Fax: +90 312315026; E-mail: drcumi21@hotmail.com

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diseases [5,6] as well as in smaller SLE cohorts [7,8], but diagnostic findings, therapy regimes and patient outcomes were not stated in detail. There are several clinical and serologic similarities between the SLE and AILD and this may lead to diagnostic difficulties. The purpose of the present retrospective study was to investigate the prevalence and detailed characteristics of hepatic involvement due to AIH and PBC, the treatment options, the outcome and the value of International Autoimmune Hepatitis Group (IAIHG) scoring system and simplified criteria in patients with SLE.

Methods

The clinical records of patients diagnosed with of SLE between January 1999 and July 2010 at our clinics were reviewed for liver involvement. We collected data on SLE patients including age, sex, interval between first liver manifestation and diagnosis of SLE. Also on serological tests for antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), antibody for smith antigen (anti-Sm) and Ro antigen (anti-Ro), lupus anticoagulant (LAC) and antiphospholipid antibodies (aPL). Abnormal liver function tests were defined as elevation in serum levels of alanine aminotransferase (ALT) (normal, <42 IU/l), aspartate aminotransferase (AST) (normal, <34 IU/l), alkaline phosphatase (ALP) (normal, 64–160 IU/l), and gamma-glutamyltransferase (GGT) (normal, 20–64 IU/l). After discontinuation of possible hepatotoxic drugs such as hydroxychloroquine ($n = 3$) and non-steroidal anti-inflammatory drugs ($n = 1$), patients with liver function tests above upper normal limits presented for a period of at least 2 months were further investigated with a thorough work-up for liver diseases including serological and histological.

AIH was diagnosed based on the criteria of the IAIHG [9] and simplified criteria [10], AIH/PBC overlap syndrome was diagnosed according to the criteria suggested by Chazouilleres et al. [11] and SLE was diagnosed according to the criteria established by the American College of Rheumatology in 1997 [12].

The antimitochondrial antibody (AMA) and anti-M_2 fraction were measured by immunoblotting while ANA, smooth muscle antibody (SMA), soluble liver antigen (SLA) and dsDNA were evaluated by indirect immunofluorescence technique. Serum immunoglobulin G (IgG) level and viral markers were measured with a commercially available ELISA. Antibody testing for ANA, SMA, SLA and AMA-M_2 was considered positive at a titer of 1/40 or above. Liver biopsies were assessed by an experienced pathologist regarding activity of chronic hepatitis, stage of fibrosis and biliary changes.

Results

The hepatic diagnoses in 36 SLE patients with liver enzyme abnormalities are presented in Table I. Demography, immunological features, histology and therapy outcome in patients with SLE and AILD are summarized in Table II.

We found liver enzyme abnormalities in 36 (24.4%) of 147 SLE patients who were under long-term follow-up. Seven of these had serological and histological findings consistent with AILD. This is equivalent to 4.7% prevalence in SLE and 19.4% in SLE patients with liver enzyme abnormalities.

Standard work-up for other concurrent liver diseases was negative. None of the patients with AILD had a history of high alcohol consumption. Viral serologies (hepatitis B and C, cytomegalovirus, Epstein–Barr, herpes simplex and HIV) were negative, abdominal ultrasound and magnetic resonance cholangiopancreatography revealed normal biliary tracts. All SLE patients with AILD were positive for ANA while four were positive for anti-dsDNA, three for SMA, three for AMA-M_2 and one for SLA. All SLE patients with AILD were female. The mean age at the end of study was 40 years (range 27–56). The diagnosis of AIH was made by increased liver enzymes including, AST and ALT, elevated IgG levels (normal, 7–16 g/l), autoantibody positivity and consistent liver biopsy findings. The mean score of five patients with AIH was 19.8 (range 17–21) by IAIHG proposed diagnostic criteria. Of all SLE patients with liver enzyme abnormalities, 72.3%

Table I. Hepatic diagnosis in 36 SLE patients with liver enzyme abnormalities.

Diagnosis	*n* (%)
NAFLD	12 (33.3%)
Viral hepatitis	8 (22.2%)
HBV	5 (13.8%)
HCV	3 (8.4%)
AILD	7 (19.4%)
AIH	4 (11.1%)
PBC	2 (5.5%)
AIH/PBC overlap	1 (2.7%)
Indeterminate causes	7 (19.4%)
NRH	2 (5.5%)

Abbreviations: NAFLD = non-alcoholic fatty liver disease; HBV = hepatitis B virus; HCV = hepatitis C virus; AILD = autoimmune liver disease; AIH = autoimmune hepatitis; PBC = primary biliary cirrhosis; NRH = nodular regenerative hyperplasia.

Table II. Demography, immunological features, histology and therapy outcome of patients with SLE and AILD.

Patient	Age/ gender	Period SLE to AILD	Features of SLE at diagnosis	Features of AILD at diagnosis	Liver biopsy findings	Current therapy/ follow-up years
1	27/F	AIH/1 year	ANA+, 1/160 dsDNA+ LAC+	ALT, 3 × UNL IgG, 2.5 × UNL ANA, 1/320 SMA, 1/80	Lymphoplasmacytic infiltration, interface hepatitis	Azt + Pred* + HCQ/6
2	33/F	AIH/5 years	ANA+, 1/80 ds-DNA+ anti-Sm+ anti-Ro+	ALT, 2.5 × UNL IgG, 2.7 × UNL ANA, 1/80 SMA, 1/160	Lymphoplasmacytic infiltration, interface hepatitis, fibrosis in portal areas	Azt + Pred* + HCQ/4
3	37/F	AIH/4 years	ANA+, 1/320 anti-Ro+ aPL+	ALT, 5 × UNL IgG, 1.8 × UNL ANA, 1/640	Lymphoplasmacytic infiltration, fibrosis in portal areas and minimal damage in bile ducts	Azt + Pred* + UDCA/3
4	40/F	AIH/2 years	ANA+, 1/640 anti-Sm+ anti-Ro+	ALT, 5 × UNL IgG, 1.6 × UNL ANA, 1/640 SLA, 1/80	Lymphoplasmacytic infiltration, fibrosis in porto-portal areas	Azt + Pred*/dead after 5 years
5	39/F	PBC/3 years	ANA+, 1/80 anti-Sm+	ALP, 4.1 × UNL IgG, 1.9 × UNL ANA, 1/160 AMA, 1/160	Non-suppurative destructive cholangitis	UDCA + HCQ/4
6	56/F	PBC/5 years	ANA+, 1/320 ds-DNA+ anti-Ro+	ALP, 3.7 × UNL IgG, 1.3 × UNL ANA, 1/320 AMA, 1/320	Destruction in bile ducts, granuloma formation	UDCA + HCQ/1
7	48/F	AIH/7 years AIH/PBC overlap/12 years	ANA+, 1/320 ds-DNA+	ALT, 5 × UNL ALP, 5.4 × UNL IgG, 2.1 × UNL ANA, 1/640 SMA, 1/160 AMA, 1/320	Lymphoplasmacytic infiltration, interface hepatitis	Azt + Pred* + UDCA/3

Abbreviations: ANA = anti-nuclear antibody; SMA = smooth muscle antibody; SLA = soluble liver antigen; AMA = anti-mitochondrial antibody; anti-Sm = antibody to Smith antigen; anti-Ro = antibody to Ro antigen; dsDNA = antibody to double-stranded DNA, LAC = lupus anticoagulant; aPL = antiphospholipid antibodies; Pred* = prednisolone low dose 5 mg/day; Azt = azathioprine 50 mg/day; UDCA = ursodeoxycholic acid 12–15 mg/kg/day; UNL = upper normal limit; HCQ = hydroxychloroquine.

fulfilled criteria for AIH proposed by IAIHG (n = 11 definite, with a score >15, n = 15 probable, with a score 10–15) but, only five patients had liver biopsy proven AIH. According to simplified criteria, 66.7% of all SLE patients with liver enzyme abnormalities had AIH (non-definitive, n = 24 probable, with a score 6). While, only five of these patients had liver biopsy findings consistent with AIH.

All patients diagnosed with PBC had elevated cholestatic enzymes including, ALP and GGT, positive AMA-M_2 titers and consistent biopsy findings. In one patient, an initial diagnosis of AIH was made by elevated liver enzymes, ANA and SMA positivity as well as characteristic biopsy findings. Five years after the AIH diagnosis, she developed elevated liver enzymes with a cholestatic pattern and serum AMA-M_2 turned positive. Although a second liver biopsy was not performed, AIH–PBC overlap (PBC sequential to AIH) was diagnosed based on the clinical and biochemical findings 12 years after presenting with SLE.

PBC patients were treated with only ursodeoxycholic acid (UDCA) 12–15 mg/kg/day, three patients with AIH were treated with prednisolone 30 mg/day plus azathioprine 50 mg/day, one AIH patient with cholestatic features and AIH/PBC overlap syndrome patient were treated with prednisolone 60 mg/day, azathioprine 50 mg/day and UDCA 12–15 mg/kg/day combination. The dose of prednisolone was gradually tapered to 5 mg/day in patients with AIH and overlap syndrome when clinical and biochemical remission was achieved. Azathioprine and UDCA were maintained at stable doses in all patients. Hydroxychloroquine therapy was used in four patients in addition to this therapy, in three before diagnosis and in one after AILD was diagnosed. The mean time between SLE and AILD diagnosis was 4.5 years (range 1–12 years) and seven patients were followed for an average of 3.7 years after diagnosis of AILD (range 1–6 years). Six patients are in remission with standard therapy but treatment failure lead to advanced liver disease and

eventually death from staphylococcal septicemia in one patient after 5 years follow-up.

Discussion

Hepatic lesions due to pathogenetic processes initiated by SLE are thought to be rare but several studies have shown that SLE patients have a 25–50% chance of developing abnormal liver tests in their life time [3]. Hepatotoxic drugs, coincident viral hepatitis, non-alcoholic fatty liver disease, hepatic arteritis and nodular regenerative hyperplasia are common causes of liver enzyme abnormalities in SLE patients [5]. AILD is considered to be a rare condition in SLE patients. In a study, 377 adult and 92 juvenile SLE patients were evaluated and the prevalence of AILD was reported 1.3% ($n = 5$) and 9.8% ($n = 9$), respectively [13]. In current study, the prevalence of AILD was 4.7% among SLE patients but, AILD was found in 19.4% of SLE patients who had liver enzyme abnormalities. Similar to our study, the prevalence of AILD was reported 22.5% in 40 SLE patients with liver enzyme abnormalities [7].

AIH was previously called lupoid hepatitis due to striking similarities with SLE, but histological examination of the liver shows specific changes in AIH. Interface hepatitis, piecemeal necrosis associated with lobular activity and rosette formation of liver cells appear only in AIH which confirms that these are two different diseases [14].

We found the prevalence of AIH among 36 SLE patients with enzyme abnormalities to be 11% ($n = 4$). In two previous studies on 40 and 46 SLE patients with liver enzyme abnormalities, AIH was diagnosed in 15% ($n = 6$) and 11% ($n = 5$) of patients, respectively [7,8]. These studies confirm that AIH is not an uncommon cause of liver enzyme abnormalities in SLE patients.

Both IAIHG proposed diagnostic criteria and simplified criteria for AIH [9–10] use a numerical scoring system based on a selection of biochemical, serologic, and histological findings. Although, ~70% of SLE patients with liver enzyme abnormalities fulfilled (definitive or probable) the IAIHG and the simplified criteria, only 13.8% had liver biopsy proven AIH in the present study. These findings suggest that relying merely on the IAIHG scoring system and the simplified criteria may lead to diagnostic confusion. ANA positivity and elevated IgG levels, components of the two scoring systems mentioned above, are frequently encountered in patients with SLE. Therefore, a definitive diagnosis of AIH cannot be made without liver biopsy. Histological findings should be consistent with AIH, the presence of moderate or severe interface hepatitis activity with a predominantly lymphoplasmacytic necroinflammatory infiltrate, with or without lobular involvement and portal–portal or portal–central bridging fibrosis, with the formation of liver cell rosettes [15].

PBC is a common cause of liver enzyme abnormalities in rheumatic diseases such as systemic sclerosis and Sjögren's syndrome. In two studies, Sjögren's syndrome patients with elevated liver enzymes were evaluated and the prevalence of PBC was 70% and 53%, respectively [6,16]. Similarly, PBC was diagnosed in 76.1% of 21 systemic sclerosis patients with liver enzyme abnormalities [6]. But, such association in SLE is rare, and only a few cases have been reported [17]. In a case report and literature review based study, the authors identified 12 SLE patients associated with typical AMA-positive PBC. In this study, the titer of AMA decreased in nine patients and turned negative in four of these nine during the follow-up [18]. Matsumoto et al. also reported 2 (5.4%) cases with AMA-negative PBC among 73 SLE patients [5]. With these findings, same authors think that the coexistence of SLE and AMA-negative PBC may be more common, but this was not observed in our AMA-positive patients (two PBC, one AIH/PBC overlap) during 1, 3 and 4 years follow-up. Moreover, the titer of AMA increased from 1/160 to 1/640 in a patient with PBC 4-years after diagnosis.

PBC was reported in 3 cases among 60 SLE patients with liver enzyme abnormalities [6]. Chowdhary et al. [7] also described 3 PBC cases in 40 SLE patients. In another study, a PBC patient reported among five adult SLE patients with AILD [13]. These reports together with our findings show that PBC is a rare but increasingly reported cause of liver enzyme abnormality in SLE patients.

The AIH/PBC overlap syndrome has been reported in a few SLE patients [19]. In a recent study, positive anti-dsDNA, also very common in SLE, was found in 60% ($n = 9$) of 15 non-SLE patients with AIH/PBC overlap syndrome [20]. In a previous study, we found positive anti-dsDNA in 58% ($n = 7$) of 12 non-SLE patients with AIH/PBC overlap syndrome [21]. Furthermore, anti-dsDNA was detected in 34% of patients with pure AIH and interestingly, these patients showed a poorer response to corticosteroid treatment [22]. Similarly, Agmon et al. found anti-dsDNA positivity in 22% of pure PBC patients [23]. These results suggest that similar immunologic mechanisms are involved in SLE, AIH and PBC.

Clinical and biochemical remission was achieved in six of seven patients. None of these seven patients had clinical or laboratory findings indicating renal or neuropsychiatric disease which are important causes

of mortality and morbidity in SLE. Thromboembolic events were observed in patients either positive or negative for aPL and LAC. All SLE patients with AILD were treated with conventional immunosuppressive therapy regimes including azathioprine, prednisolone, UDCA or a combination of these. When clinical and biochemical remission was achieved, hydroxychloroquine was administered in four SLE patients with AILD. No hepatoxic side effects were noted during follow-up. Hydroxychloroquine is effective in inflammatory conditions by blocking the activation of Toll-like receptors on plasmacytoid dendritic cells. Toll-like receptors recognize DNA-containing immune complexes, this leads to the production of interferon-α and causes the dendritic cells to mature and present antigen to T cells. Hydroxychloroquine reduces the activation of dendritic cells thus alleviating the inflammatory process by decreasing Toll-like receptor signaling [24–25]. Hydroxychloroquine is used extensively in the treatment of SLE, not only for cutaneous and musculoskeletal lupus, but also for its role in preventing flares, preventing renal and central nervous system involvement, and improving survival rates. Based on these findings, we think that hydroxychloroquine can be used safely in SLE patients with AILD; therefore, the presence of underlying AILD does not seem a reason for complete discontinuation of hydroxychloroquine. Treatment failure and hepatic decompensation occurred in a patient after 5 years diagnosis of AIH. She died of multiorgan failure from staphylococcal septicemia and related complications but, it is also important to note that, SLA positivity was found in only this patient and the presence of SLA may partly explain poor prognosis in this patient. Although it is not conclusive, therapy response and clinical out come of SLE patients with AILD seems favorable under conventional therapy.

The cause of liver enzyme abnormalities could not be determined in 19.4% of the patients. Other diseases, such as hemochromatosis, Wilson's disease, alpha-one-antitrypsin deficiency and celiac disease were not found. Several reports have described SLE patients with liver enzyme abnormality but no diagnostic findings [26]. The cause of liver enzyme abnormalities in these studies has been reported as SLE itself, with biochemical abnormalities correlating with disease activity [27,28]. But, we found no correlation between the liver enzyme abnormalities and SLE activity among our patients.

Female predominance, genetic susceptibility, hypergammaglobulinemia, autoantibody positivity and response to immunosuppressive therapy suggest that similar immunologic mechanisms are responsible for the development of both AILD and SLE. In addition to serologic and biochemical similarities, immunosuppressive therapy during the course of SLE may disguise an underlying AILD. This may lead to confusion or delayed diagnosis. AILD is not rare in SLE. Both hepatologists and rheumatologists should be aware of this association since early diagnosis and appropriate therapy is essential to prevent progress into advanced liver disease in the later course of SLE.

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