Liver involvement in systemic lupus erythematosus: incidence, clinical course and outcome of lupus hepatitis

M. Piga, A. Vacca, G. Porru, A. Cauli, A. Mathieu

Chair of Rheumatology and Rheumatology Unit, University and AOU of Cagliari, Cagliari, Italy.

Abstract

Objective

The aims of this study were to assess the spectrum of liver disease occurring in systemic lupus erythematosus (SLE), primarily the incidence, clinical course and outcome of lupus hepatitis (LH).

Methods

The records of 283 SLE out-patients referred to our Unit between 1994 and 2008 were reviewed to identify clinical or laboratory evidence of liver involvement. Liver enzyme values were considered abnormal when a sustained increase in serum transaminase levels above the normal value was observed for a period of at least three months or when the increase was confirmed in two consecutive assessments. Study inclusion criteria were a follow-up of at least 12 months and three liver function tests per year over the course of disease.

Results

A total of 242 patients with a mean follow-up of 72.2±59.1 months were identified. Liver enzyme abnormalities were observed in 45 (18.6%) patients. Of these, only 14 cases (5.8%) could be attributed to LH. Clinical course and response to therapy enabled the identification of three different patterns: remitting, unremitting *and* relapsing forms. *Acute hepatitis and liver failure were not observed. Low serum alanine transaminase levels at diagnosis and high doses of prednisone were associated to resolution of LH. Clinical course or response to therapy did not appear to be affected by liver histology or serological findings.*

Conclusions

LH is generally sub-clinical with a fluctuating course and responds well to moderate to high doses of prednisone without progression to end-stage liver disease.

Key words

Systemic lupus erythematosus, lupus hepatitis, autoimmune liver disease, liver disease

Matteo Piga, MD
Alessandra Vacca, MD
Giovanni Porru, MD
Alberto Cauli, PhD, MD
Alessandro Mathieu, MD

Chair of Rheumatology and Rheumatology Unit, University and AOU of Cagliari, Cagliari, Italy.

Please address correspondence and reprint requests to:
Dr Matteo Piga, MD
Chair of Rheumatology and Rheumatology Unit,
University Clinic AOU of Cagliari
SS 554, 09 042 Monserrato,
Cagliari, Italy.
E-mail: matteopiga@alice.it

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory multisystem disorder with a broad range of clinical manifestations (1).

Clinical manifestations of liver involvement in SLE are rare, while liver enzyme abnormalities are common (23-55%) and may have concomitant causes, such as drug or alcohol toxicity (2).

SLE-related hepatitis, also known as Lupus hepatitis (LH), is a distinct manifestation in 3–8% of patients affected by lupus. Clinical presentation is usually asymptomatic with a sub-clinical course but, on rare occasions, can mimic acute viral hepatitis (3, 4). LH has been described in association with the serum detection of anti-ribosomal-P-protein antibodies (anti-Rib-P), although there is little evidence to support their role in pathogenesis (4). The histological appearance of LH is protean and, although certain changes are characteristic, no findings specific to the disease have been observed to date. Matsumoto *et al*. reported a high incidence of histological liver disease (80-90%) in their autopsies of SLE patients, suggesting a silent hepatic involvement (5, 6). In the presence of antiphospholipid antibodies, disease course can be complicated by thrombosis of the portal and hepatic veins and by thrombosis of the small hepatic vessels leading to HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and non-thrombotic nodular regenerative hyperplasia (7).

However, whether and how disease course, in the absence of other liver pathologies, is complicated by LH, remains unclear and few data are available in the literature on long term follow-up.

In order to assess the spectrum of liver disease occurring in SLE and the incidence, clinical course and outcome of LH, a cohort of patients referred to our Unit between 1994 and 2008 was retrospectively reviewed.

Materials and methods

Patients

The records of 283 out-patients who satisfied the 1982 ACR classification criteria for SLE were reviewed to identify clinical or laboratory evidence of liver involvement (8). Liver enzyme values were considered abnormal when a sustained increase in serum transaminase levels above the normal value (NV) was observed for a period of at least three months or when the increase was confirmed in two consecutive assessments. Study inclusion criteria were a follow-up of at least 12 months and three liver function tests per year over the course of the disease.

It should be noted that, in the presence of normal serum alanine transaminase (ALT) levels, patients with liver enlargement on clinical examination or patients with increased serum aspartate transaminase (AST) and alkaline phosphatase (ALP) levels were excluded because these manifestations could not be confirmed as an expression of hepatocellular damage (9).

Patients' clinical, serological, ultrasonographic (US) features and, when available, liver histology were carefully evaluated for toxic, hereditary, infective, metabolic, congestive, malignant and autoimmune organ specific etiology according to international guidelines. Drugs hepatotoxicity was defined as normalisation of the test after drug withdrawal. Tests were focused on viral hepatitis (HAV, HBV, HCV, CMV, EBV, and HIV), Autoimmune Hepatitis (AIH), Primary Biliary Cirrhosis (PBC) and primary sclerosing cholangitis.

Exclusion of these causes led to LH diagnosis in patients. Clinical course, response to therapy and whether LH led to end-stage liver disease were all evaluated.

Outcome definition

Patients with LH were divided into two groups depending on clinical course and response to therapy: group I comprised patients who achieved resolution and group II those who did not. Endpoints were identified according to the International Criteria for Diagnosis of Autoimmune Hepatitis (ICAIH), modified as follows (10).

Resolution was defined as an improvement of symptoms and a normalisation of serum transaminase level values within 12 months of beginning treatment and sustained for at least six months on maintenance therapy (*remitting form*).

Non resolution was defined as either: 1) no improvement of symptoms or non normalisation of serum transaminase levels within 12 months of beginning treatment (*unremitting form*); 2) recurrence of symptoms or a rise in serum transaminase levels requiring increased immunosuppression after *resolution* as defined above (*relapsing form*).
End-stage liver disease was defined as the development of cirrhosis, portal hypertension and hepatic encephalopathy.
SLE and liver disease features were compared in both groups to identify factors influencing clinical course and outcome.

Statistical analysis
All data were stored in a database. Continuous variables were expressed as Mean ± Standard Deviation (M±SD). The two-tailed Fischer's exact test or the Chi-square test were applied for comparison of categorical variables and Student's *t*-test for continuous variables with normal distribution. Relapse-free survival was calculated according to the Kaplan-Meier method and the differences between relapse-free survival curves were analysed using the log-rank test. Hazard Ratio (HR) and 95% Confidence Interval (95% CI) were calculated. A value of $p<0.05$ was considered statistically significant.

Results

Spectrum of liver disease occurring in our SLE cohort
A total of 242 Caucasian patients (227 women, 15 men) of whom 12 with juvenile-onset of SLE, with a mean follow-up of 72.2±59.1 months (median 60.0) for a total of 1456.5 patient years, were included in the study. Of these, 45 patients had liver enzyme abnormalities of hepatic origin (Table I).
Only one case of end-stage liver disease in a patient suffering from AIH-SLE overlap complicated by portal vein thrombosis in the setting of antiphospholipid syndrome was observed. This was the only hepatic manifestation due to these antibodies observed in our series.

Characteristics, clinical course and outcome of lupus hepatitis
Fourteen patients showed liver abnor-

Table I. Prevalence and causes of persistent serum transaminase values elevation.

Liver-tests abnormalities	n.	%
Sustained raised transaminase	45	18.6
a) Drug toxicity	18	7.5
- Methotrexate	8	–
- NSAIDs	3	–
- Cyclophosphamide	3	–
- Azathioprine	3	–
- Isoniazid	1	–
b) Lupus hepatitis	14	5.8
c) Autoimmune hepatitis type 1*	4	1.6
- Associated with PVT	1	–
d) Non alcoholic fatty liver disease	3	1.2
e) Viral hepatitis	3	1.2
- HCV	1	–
- HBV	1	–
- CMV	1	–
e) Alcoholic hepatitis	2	0.8
f) Focal nodular hyperplasia	1	0.4

*According to 1999 International Criteria for diagnosis of autoimmune hepatitis.
PVT: portal vein thrombosis; NSAIDs: Non-steroidal anti-inflammatory drugs.

Table. II. Demographic characteristics, clinical and serologic features of LH patients.

Characteristics	Lupus hepatitis (n=14)
Sex (M/F)	1/13
Age at SLE onset, years (range)	26.5 ± 10.8 (11–47)
Age at LH onset, years (range)	30.8 ± 15.3 (11–56)
Follow-up, months (range)	72.9 ± 45.1 (24–168)
Malar rash*	50% (7)
Discoid rash*	35.7% (5)
Photosensitivity*	35.7% (5)
Oral ulcers*	21.4% (3)
Arthritis*	78.5% (11)
Serositis*	28.5% (4)
Lupus nephritis*	35.7% (5)
Neurologic involvement**	50% (7)
Polyneuropathy	3
Stroke	2
Cognitive dysfunction	2
Haematologic*	78.5% (11)
Thrombosis/obstetric complication***	28.5% (4)
ANA high titer positive	100% (14)
ENA	85.7% (12)
Anti-SSA	7
Anti-RNP	5
Anti-SM	3
Anti-SSB	1
aDNAds high titer positive	78.5% (11)
Antiphospholipid antibodies**	35.7% (5)
ASMA positive	21.4% (3)
AMA anti-M2 positive	0% (0)
LKM positive	0% (0)
Cryoglobuline	7% (1)

*According to the 1982 ACR classification criteria for SLE.
**According to the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus syndromes.
***Included in the 2006 classification criteria for definite antiphospholipid syndrome.
ANA: Antinuclear antibodies (IFI Hep-2 with cut-off 1:640); ENA: Anti extractable nuclear antigens (immunoblotting); aDNAds: Anti-DNA double strand (RIA); Antiphospholipid antibodies, anticardiolipin IgG and IgM (ELISA) and/or lupus anticoagulant (aPTTc, DRVVT, DRVVT ratio); AMA: Antimitochondrial; LKM: anti Liver-Kidney Microsomal; ASMA: Anti Smooth-Muscle Antibodies (ELISA).
The three ASMA positive patients had titer equal to or lower than 1:80.

Table III. Details of liver histology in eight patients diagnosed as suffering from lupus hepatitis and their relationship with aminotransferase levels, autoimmune serology at the time of liver biopsy. All patients are ANA (IFI Hep-2) positive 1:640. All but patients 7 had high titer aDNAds (RIA).

	Portal tract infiltration	Interface hepatitis	Lobular hepatitis	Rosetting Cells	Biliary changes	Fatty liver	Fibrosis	ALT I.U./l (NV)	AST I.U./l (NV)
Resolution									
Pt 1 (SM+)	+	+	++	0	+++	0	+	165 (30-65)	137 (15-37)
Pt 2 (SSA+)	+	0	0	0	0	+	0	72 (0-41)	58 (0-38)
Pt 3 (ASMA 1:40)	++	0	0	0	0	+	0	57 (0-31)	51 (0-35)
Non resolution									
Pt 4 (SSA+; SSB+)	+	0	0	0	0	++	0	95 (0-31)	70 (0-35)
Pt 5 (RNP+;ASMA 1:80)	+	0	0	0	0	0	0	268 (30-65)	111 (15-37)
Pt 6 (SSA+)	++	+	+	+	++	0	+	49 (0-41)	32 (0-38)
Pt 7 (SSA+; aDNAds-)	+++	+	++	0	0	+	0	276 (0-41)	203 (0-38)
Pt 8 (ASMA 1:80)	+	+	+	0	0	+	+	72 (0-47)	47 (0-38)

Pt: patient; NV: normal value; I.U./l: international unit/liter; Cy: cyclosporine; Pred: prednisone; Grade: 0: absent; +: mild; ++: moderate; +++: severe.

malities that could only be attributed to lupus and were diagnosed with LH. Demographic and SLE features are described in Table II.

Due to the non-routine search for anti-Rib-P and the retrospective nature of our study, it was not possible to evaluate the incidence of this antibody.

Liver function test abnormalities were identified at SLE onset in 5 patients (36%). All patients were given a class A Child-Pugh score. Clinical manifestations were non-specific for hepatic disease and consistent with SLE activity, including malaise and fatigue. Two patients also complained of nausea and vomiting. AST/ALT ratio was less than 1 in all LH patients. In 6 out of 14 cases serum transaminase levels fluctuated between normal and slightly abnormal. Progressive increases in levels were seen in 2 cases whereas in the remaining patients steady abnormal values in levels were maintained. In 13 of the 14 patients, changes in ALT levels, but not absolute enzyme values, correlated with disease activity fluctuation calculated using the ECLAM score (11). Hepatomegaly without splenomegaly was confirmed by ultrasound examination of the liver in 5 patients. Percutaneous liver biopsy was performed in 8 of 14 patients as the remaining 6 patients, in agreement with hepatologists, were at high risk for complications. Histological findings did not correlate with the abnormalities revealed by the liver function tests (Table III).

After beginning treatment, 12 patients

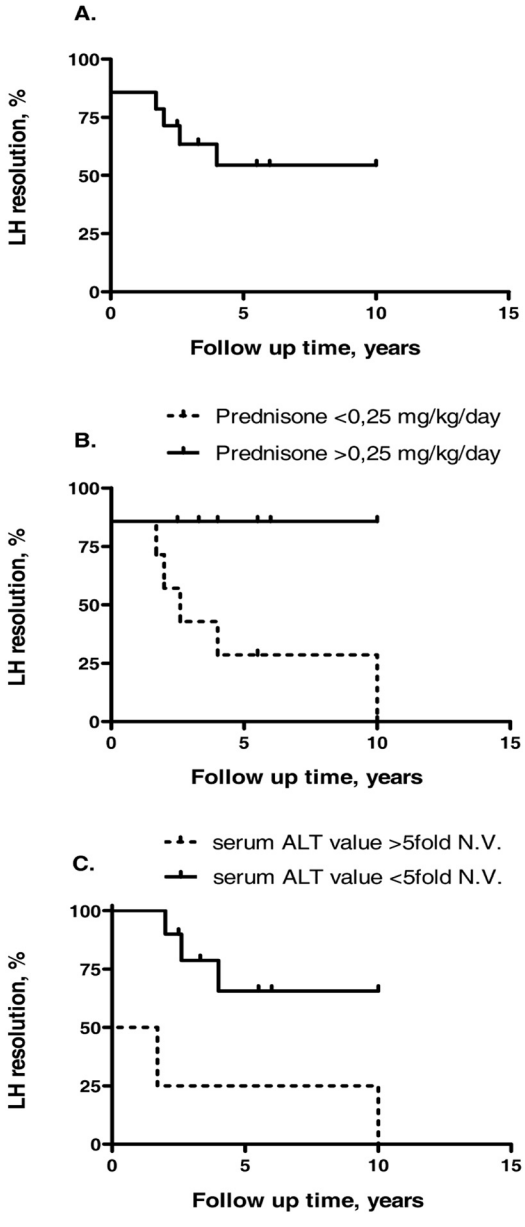

Fig. 1. (**A**) Kaplan-Meier plot showing survival rate of LH resolution over time. (**B**) Kaplan-Meier plot comparing differences in survival rate of LH resolution in function of serum ALT value at the time of diagnosis. (**C**) Kaplan-Meier plot comparing differences in survival rate of LH resolution in function of mean prednisone intake during follow-up. Number of subject at risk: Time 0=14; Time 5=5; Time 10=2. Ticks on curves correspond to the time when a subject's data was censored.

Table IV. Comparison of groups with resolution and not resolution of lupus hepatitis at the time of diagnosis.

Characteristics	Resolution group (n=7)	Non resolution group (n=7)	*p*-value
Age at SLE onset, years (range)	26.8 ± 13.0 (11–47)	26.3 ± 9.0 (14–39)	0.90[a]
Age at LH onset, years (range)	30.8 ± 15.3 (11–56)	29.6 ± 7.5 (20–42)	0.84[a]
Follow-up, months (range)	68.2 ± 41.4 (31–156)	77.5 ± 51.4 (24–168)	0.71[a]
C3 mg/dl (range)	80.2 ± 24.6 (38–112)	78.8 ± 28.8 (47–123)	0.88[a]
C4 mg/dl (range)	13.7 ± 7.2 (4–25)	18.1 ± 14.3 (8–49)	0.47[a]
Mean ALT I.U./l (range)	96.8 ± 51.3 (52–190)	276.4 ± 246.2 (61–801)	0.08[a]
Mean AST I.U./l (range)	63.7 ± 41.0 (33–155)	124.5 ± 65.3 (49–203)	0.06[a]
Mean ALP I.U./l (range)	327.4 ± 202.1 (181–726)	327.1 ± 216.8 (104–642)	0.99[a]
ALT >5foldNV	0 (0%)	4 (57.2%)	0.03[b]
Hepatomegaly, US scan	42.8% (3)	28.5% (2)	0.63[b]
Prednisone cumulative dose, g (range)	27.7 ± 20.6 (9.7–56.0)	14.5 ± 10.7 (3.0–34.9)	0.15[a]
Prednisone mean dose, mg/kg/d (range)	0.29 ± 0.13 (0.10–0.50)	0.16 ± 0.10 (0.10–0.35)	0.06[a]
Prednisone mean dose >0.25mg/kg/d	85.7% (6)	14.2% (1)	0.01[b]
Other treatment for SLE	100% (7)	85.7% (6)	0.50[b]
Hydroxychloroquine	2	3	–
Methotrexate	1	0	–
Azathioprine	2	1	–
Cyclophosphamide	2	2	–
Cyclosporine A	1	0	–
ECLAM score	3.5 ± 0.8	3.7 ± 1.8	0.85[a]
SLICC/ACR Damage score	0.6 ± 0.5	0.7 ± 1.4	0.81[a]

Continuous variables are expressed as Mean ± Standard Deviation (M±SD); [a] Student's *t*-test; [b] Fisher's exact test.

achieved complete *resolution*. However, 5 of them suffered a recurrence *(relapsing form)* after 49.2±40.9 months due to SLE flare-up and required increased immunosuppression. Two cases, in which normalisation of serum transaminase levels was not achieved within 12 months of beginning treatment, were classified as *unremitting form*. The estimated relapse-free survival rate was 54.4% of cases over 10 years of follow-up (Fig. 1A).

No significant differences in demographic, serological, clinical data or liver histological findings (Table IV) were revealed when characteristics between *resolution* and *non resolution* patients were compared. However, all 7 patients in group I reported serum ALT values five times lower than NV compared with only 3 in group II (100% *vs*. 42.8%; p=0.03).

All patients took oral steroids and 8/14 immunosuppressants. No differences were observed in patients on immunosuppessive therapy, while a mean dose of prednisone >0.25mg/kg/day was found as statistically significant in group I (85.7% *vs*. 14.3%; p=0.01). Serum ALT levels five times lower than NV at the time of diagnosis and mean daily prednisone doses higher than 0.25mg/kg/day during follow-up gave estimated relapse-free survival rates of 65.6% (p=0.01; HR:10.2; 95%CI: 1.5–68.8) and 85.7% (p=0.04; HR 4.8; 95%CI: 1.0–21.6) respectively, over 10 years of follow-up (Fig. 1B and 1C).

At the end of follow-up, no end-stage liver disease was observed and all the patients were given a class A Child-Pugh score. One patient in group I died of a heart attack.

Discussion

Our results confirm that liver involvement in SLE is due to causes other than lupus in most cases, but 6% of patients show abnormalities of liver function tests that could only be caused by lupus. LH occurs as subclinical hepatitis showing ALT fluctuation parallel to the activity of SLE, without progression to end-stage liver disease. Acute hepatitis was not observed. Clinical course and response to therapy enabled the identification of three different patterns: *remitting*, *unremitting* and *relapsing forms*.

Several studies have sought to systematically examine the incidence and nature of liver disease in patients with SLE. Runyon *et al*. reported that 60% of 206 SLE patients had at least one abnormal liver function test during disease course (12). Gibson and Myers speculated that "unexplained" elevation in hepatic enzyme levels (29%) and inflammatory infiltrate of the portal area were features of SLE (13). Miller *et al*. assessed the relationship between abnormal liver tests and SLE in a prospective 24-month study on 260 lupus patients and 100 controls affected by other rheumatic diseases. Liver enzyme levels were found to be higher in 23% of patients and in 8% no cause other than SLE was identified. None of the control group had abnormal liver function tests related to their disease. In 12 out of 15 patients changes in serum ALT values were concordant with disease activity, suggesting that subclinical liver disease may be a manifestation of SLE, and 4 patients had a persistent rise in transaminase levels beyond the study period. The authors did not report end-stage liver disease (3). Arnett and Reichlin proposed the term "lupus hepatitis" to portray an under recognised SLE feature occurring in 3% of cases, strongly correlated with anti-Rib-P serum detection. The contrary does not appear to be true, since the majority of lupus patients with anti-Rib-P do not show evidence of liver involvement. They described six patients, all positive for anti-Rib-P, with hepatic manifestations ranging from subclinical remitting or a persistent rise in serum transaminase values to acute hepatitis, liver failure and death (4). Chowdhary

et al. revealed end-stage liver disease is rare in lupus unless associated with primary liver disease such as AIH, non alcoholic fatty liver disease (NAFLD) and viral hepatitis (14).

These studies are in agreement with our findings but they did not address the questions of LH clinical course and outcome. To our knowledge this is the first study which investigates the contributing factors to LH resolution. We report that low serum alanine transaminase levels at diagnosis and high dose of prednisone are associated with resolution of lupus hepatitis, even though *unremitting* or *relapsing forms* have been observed with very low increases in serum ALT levels. Treatment of LH is based on immunosuppressant and steroids commonly used in SLE. Our study confirms the previous observations that prednisone at high or moderate doses improves laboratory test results and must be considered to avoid relapse, while the efficacy of immunosuppressants has not been fully demonstrated (3, 4, 12).

LH is associated with several histological pictures but mild portal inflammatory infiltrate, lobular necrosis and fatty infiltration are considered characteristics (15-16). Eight patients in our cohort showed various degrees of portal area infiltration, 5/8 fatty infiltration and 4/8 low degrees of chronic active hepatitis. Six of our patients did not undergo percutaneous liver biopsy, which is one of the limits of this study. Therefore we were unable to prove if liver histology influence clinical course and response to therapy in patients with LH. However, chronic active hepatitis was more frequent among patients with *no resolution*.

Liver biopsy should be performed to help in differential diagnosis and to accurately stage the disease. Patients with confirmed SLE showing chronic active hepatitis could be suspected of suffering from AIH. In the 1950's Mackay *et al*. proposed the term "hepatic lupus" to differentiate from "lupoid hepatitis", which was used to indicate AIH (17). To date, the differences and concordance between SLE related hepatitis and AIH have not been fully defined (18). AIH presentation may be asymptomatic or insidious with mild non-specific symptoms only. It may also mimic acute viral hepatitis and show a higher rate of progression to cirrhosis than LH. Patients with AIH may show ANA and occasionally mild clinical features of SLE such as arthralgia, but rarely more severe complications such as nephritis and neuropsychiatric syndromes (19). Liver histology showing interface hepatitis with a predominantly lymphoplasmacytic infiltrate is characteristic but not pathognomonic of AIH and cannot exclude LH (20-21). The existence of classification criteria for the diseases may help to differentiate between them (8, 10). The presence of autoantibodies plays a central role in diagnosis and classification of SLE and autoimmune liver disease. ANA and ASMA characterise type 1 AIH but are also present in SLE (22). On the contrary, aDNAds, ENA and anti-Rib-P are associated to SLE and virtually absent in AIH (22-24). The presence of liver kidney microsomal constituent antibodies (anti-LKM) and anti liver cytosol type 1 (anti-LC1) define patients with type 2 AIH. PBC is indicated by antimitochondrial antibodies (AMA) reacting to the M2 antigen in contrast to M1, which is the target of anticardiolipin antibodies (25). SLE is rarely associated with PBC and type 2 AIH while type 1 AIH-SLE overlap is more frequent than believed, as demonstrated by several reports (26, 27). Our series show an overlap incidence similar to those reported in other surveys (1.7–2.7%) (12, 28). It should be noted that a higher incidence of AIH is seen in patients affected by juvenile-onset SLE (28).

Another limit of this study is represented by the small number of cases. It would be interesting to verify our findings in a larger cohort through a multi-centre study involving both rheumatologists and gastroenterologists. We cannot exclude that a number of SLE patients with severe liver disease went directly to a Gastroenterology Unit thus determining an inaccurate prevalence of these disorders. Another limit regards the follow-up period, which although long enough to differentiate between LH *resolution* and *non resolution*, might be insufficient to highlight slow progression to hepatic failure. Theoretically, it is possible that repeated and prolonged hepatic damage may lead to liver failure, however large multi-centre studies of mortality in SLE have shown that liver disease does not influence morbidity or mortality (29).

In conclusion, careful liver assessment must be performed in SLE patients manifesting serum transaminase abnormalities to ascertain that LH is effectively the cause of these abnormalities. LH is generally subclinical with a fluctuating course which responds well to moderate to high doses of prednisone without progression to end-stage liver disease. Treatment with suitable doses of corticosteroids and if necessary additional immunosuppressants such as azathioprine, as corticosteroids sparing, should be considered to avoid relapse in LH patients, especially in those showing chronic active hepatitis and high serum ALT level values at diagnosis.

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