Hepatitis C Virus Infection in Systemic Lupus Erythematosus: a Case-Control Study

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ABSTRACT. ***Objective***. Viruses might be one of the elements that trigger systemic lupus erythematosus (SLE). Steroid therapy may influence the natural history of virus infections. The most frequent extrahepatic manifestations of hepatitis C virus (HCV) including arthralgia, myalgia, sicca syndrome, and antinuclear antibodies, may mimic a connective tissue disease, particularly SLE. Reports on the association between SLE and HCV infection are scarce. We investigated the association of HCV infection and SLE.

Methods. Retrospective case-control monocentric study of 19 patients with SLE and anti-HCVantibodies versus 42 randomized SLE patients without anti-HCV antibodies, matched for age and sex, coming from our cohort of 700 patients with SLE. SLE and HCV-infection features were reviewed.

Results. Mode of infection was blood product transfusion, drug addiction, or unknown. Prevalence of lupus clinical manifestations, antinuclear, anti-dsDNA, anti-extractable nuclear antigen antibodies, and complement levels was not different between HCV positive and negative SLE patients. Prevalence of cryoglobulin was higher in SLE patients with anti-HCV antibodies ($p < 0.04$), but none had a mixed cryoglobulinemia syndrome. ALT activity was increased in 11 HCV positive patients and 13 had detectable HCVRNA. Liver biopsy showed cirrhosis in 2 and mild fibrosis and activity in 5. One patient treated with interferon-alpha had a sustained virological response without SLE flare. Steroid therapy did not seem to alter HCV course.

Conclusion. SLE in HCV positive patients shows higher prevalence of cryoglobulin without mixed cryoglobulinemia syndrome. HCV infection has moderate signs of biochemical and liver pathological severity. SLE by itself or treated with steroids does not seem to worsen HCV infection. (J Rheumatol 2003;30:1473–8)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a frequent connective tissue disease. Its prevalence is estimated at 15 to 200 cases per 100,000 people[1,2]. Pathophysiology of SLE is still under debate. Some suggested mechanisms may involve abnormalities in T cell maturation[3]. Viruses might also be one of the elements that trigger SLE. One of the main characteristics of SLE is the broad spectrum of clinical and immunological manifestations[4]. Production of numerous autoantibodies, particularly antinuclear and anti-dsDNA antibodies, is the biological hallmark of SLE[5].

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Hepatitis C virus (HCV) infection is a major health problem in developed countries, where it is the most frequent cause of chronic active hepatitis. The major risk of HCV chronic infection is the development of cirrhosis with an estimated prevalence of 2%[6]. Several cofactors play a role in the development of cirrhosis: age at time of infection, alcoholism, co-infection with hepatitis B virus, or human immunodeficiency virus, in which immunosuppression may worsen infection[7]. Numerous extrahepatic manifestations have been reported with HCV infection including mixed cryoglobulinemia syndrome, porphyria cutanea tarda, membranoproliferative glomerulonephritis, sicca syndrome[8,9], thyroiditis, and high prevalence of autoantibodies[4,9-11]. Some of the most frequent HCV extrahepatic manifestations such as arthralgia, myalgia, sicca syndrome, and antinuclear antibodies may mimic a true connective tissue disease, particularly SLE[12]. Moreover, SLE is an immunosuppressive condition, especially since steroid therapy is widely used.

Data on the association between HCV infection and SLE are scarce[12-15], while an interaction between these 2 conditions seems possible. We investigated patients with SLE

chronically infected with HCVin a large, case-control study, by comparing the clinical, biological, and immunological characteristics of SLE in HCV positive and negative patients. We analyzed virological characteristics of HCV infection and liver pathology. Treatments for SLE and HCV infection were reviewed.

MATERIALS AND METHODS

Patient selection. Among patients with SLE seen in our internal medicine department since 1990, a positive third generation HCVELISA(ELISA-3) was found in 19 cases. Forty-two patients from our database of SLE patients followed in our department and having a negative HCV ELISA-3 were randomly selected and matched for sex and age at the time of the study. The patients negative for HCVantibodies were studied as controls.

Data collection. For HCVinfection, epidemiological factors including age, sex, mode of infection, duration of infection, organ transplantation, and treatment were studied. For SLE, rheumatological, dermatological, renal, neurological, and cardiac clinical manifestations were studied. Clinical severity was defined as the presence of at least one of the following: myocarditis, endocarditis, central nervous system involvement, type III or IV proliferative glomerulonephritis, and antiphospholipid syndrome. Presence of antinuclear (ANA), anti-dsDNA, anti-extractable nuclear antigen (anti-ENA), anticardiolipin autoantibodies (aCL), cryoglobulinemia, and hypocomplementemia (low C3, C4 or CH50 levels) were also reviewed as described[4,11,16,17].

For HCVinfection, alanine aminotransferase (ALT) activity, viral load, genotype, and liver pathology were studied. Patient serological status was determined using 2 specific third generation immunoassays, a microparticle enzyme immunoassay (Axsym HCVversion 3.0, Abbott, Les Ulis, France), and an indirect immunoenzymatic technique (Monolisa anti-HCV Plus, Sanofi Diagnostic Pasteur, Marne la Coquette, France), each as recommended by the manufacturer. A patient was defined as positive when the 2 tests were positive according to each test specification. A test for HCV RNA was performed by polymerase chain reaction (PCR) on sera, which were stored at –80°C, and thawed prior to use. HCVgenome was detected by PCR using Amplicor HCV kit (Roche Diagnostics, Neuilly/Seine, France) as described[18]. In HCVRNApositive samples, HCVgenotype and subtype identifications were performed using a second generation Line Probe Assay (LiPA, Innogenetics, Brussels, Belgium). All sera were negative for hepatitis B surface antigen (HBsAg) and HIV using commercial immunoassays (Abbott Laboratories, Diagnostic Pasteur). Histological features of analyzed liver specimen were evaluated using validated METAVIR and Knodell scoring systems[19,20]. Treatments for HCVinfection and SLE and outcome were analyzed.

Statistical analyses. Conventional chi-square and Fisher's exact tests were used to analyze qualitative differences, and Student's test for the comparison of means. A p value of less than 0.05 was taken to indicate statistical significance.

RESULTS

Characteristics of SLE. Clinical, biological, and immunological manifestations of SLE in the 19 HCV positive patients are summarized in Table 1. All patients but 2 fulfilled the 1982 revised American College of Rheumatology criteria for SLE[21]. Specific anti-nucleosome antibodies were repeatedly positive in one of the patients who met only 2 SLE criteria (patient 14), and high levels of ANA and anti-dsDNA were found in the other patient (patient 4). Mean age of patients at the onset of SLE was higher in HCV positive patients (30 ± 13 yrs; range 15–64) versus control patients (24 ± 9 yrs; range 12-47) ($p < 0.04$). Sixteen were women and 3 were men. Arthritis was found in all cases. Eleven patients had cutaneous or mucosal involvement such as photosensitivity, Raynaud's phenomenon, subacute cutaneous lesions, and oral ulcerations. Ten patients had proteinuria higher than 0.5 g/day. A renal biopsy was performed in 7 cases and showed type II glomerulonephritis (WHO classification of SLE nephritis) in 1 patient, type III in 3, type IV in 2, and type V in 1. No patient had membranoproliferative glomerulonephritis. Pleuropericardial and central nervous system involvement occurred in 5 and 7 cases, respectively. ANAand anti-dsDNAwere found in 19 and 15 cases, respectively. Eight, 11, and 10 patients showed low levels of C3, C4, and CH50, respectively. Type II and III cryoglobulinemia was found in 3 and 7 cases, respectively. Thirteen patients had aCL. Among them, the antiphospholipid syndrome occurred in 7, presenting as retinal thrombosis in 2, and as stroke in 1. One patient had polyneuropathy. Steroid therapy was used in all patients. There was no relation between dose of steroid received and severity of HCV infection in terms of viral load or liver pathological score.

Comparison of clinical and immunological manifestations of SLE between patients with or without anti-HCV antibodies is summarized in Table 2. Prevalence of arthritis, cutaneous and mucosal involvement, and hemocytopenias was similar in HCV positive and negative patients ($p > 0.99$, $p > 0.77$, $p > 0.99$, respectively). Prevalence of severe clinical manifestations, i.e., myocarditis/endocarditis, central nervous system involvement, antiphospholipid syndrome, and type III or IV glomerulonephritis was not significantly different between HCV positive and negative patients. There was no difference in prevalence of ANA, anti-dsDNA, anti-ENA, and low levels of complement. Prevalence of cryoglobulinemia was higher in SLE associated with HCV infection than in SLE controls (53% vs 24%, $p < 0.04$). One out of four (25%) HCV-RNA negative patients showed cryoglobulinemia versus 8 out of 13 (62%) HCV-RNApositive patients. There was no difference in the cumulate dose of prednisone received, which was higher than 20 g per patient, whether patients were HCV positive or negative.

Characteristics of HCV infection. Table 3 summarizes the main HCV infection features in SLE patients. The mode of HCV infection was blood transfusion in 9 cases, drug addiction in 1 case, and unknown in 9 patients. Serum ALT activity was increased in 11 patients (mean 2.3 ± 0.8 upper limit of normal value). Quantitative HCV-RNA was performed in all cases but 2. Four patients had undetectable HCV-RNAby PCR and 13 were positive. Among the latter, 4 patients had a viral load lower than 0.2×10^6 copies/ml and 9 were higher. Genotypes were 1 and 3a in 10 and 3 cases, respectively. A liver biopsy was performed in 11 patients. One patient had no liver fibrosis. Portal fibrosis without or with rare septa was found in 8 cases and cirrhosis

Table 1. Features of SLE in patients with positive anti-hepatitis C virus antibodies.

Patient	Sex	Age	SLE Criteria	ANA	ENA	dsDNA	aCL	Cryo	Hypocomp
1	F	62	Arth, Nephr, Hem	10,000	Y	Y	Y	N	Y
2	M	34	Arth, Nephr, Ser, Hem	320	N	Y	Y	III	Y
3	F	35	Arth, Ulc, Nephr, Nrl, Hem	2000	Y	N	Y	II	Y
4	F	65	Hem	10,240	N	Y	N	III	N
5	F	34	Arth, Nephr, NP, Ser	1000	Y	Y	ND	N	N
6	F	70	Arth, Nephr, Hem	100	Y	Y	Y	II	N
7	F	31	Arth, Photo, Nephr	5000	Y	Y	Y	III	Y
8	F	36	Arth, Ulc, Malar, Hem	2500	N	N	N	N	Y
9	F	37	Arth, Subac, Malar, Hem	160	Y	N	Y	N	N
10	M	45	Arth, Ulc, Malar, Ser, Hem	320	N	Y	Y	N	N
11	F	53	Arth, Ser, Ulc, Subac, NP	1000	N	Y	N	III	N
12	M	52	Arth, Ser, Hem	5000	Y	Y	Y	III	N
13	F	33	Arth, Nephr	640	N	Y	Y	N	N
14	F	36	Hem	1280	N	N	N	II	N
15	F	46	Arth, Subac, Nephr, Hem	1000	Y	Y	N	III	Y
16	F	20	Arth, Photo, Nephr, Hem	1280	N	Y	Y	N	Y
17	F	46	Arth, Subac	1280	Y	Y	Y	N	N
18	F	25	Arth, Subac	1280	N	Y	Y	III	Y
19	F	30	Arth, NP, Photo, Hem, Nephr	1280	N	Y	Y	N	N

ANA: antinuclear antibodies; ENA: anti-extractable nuclear antigen antibodies; dsDNA: anti-double stranded DNAantibodies (1/); aCL: anticardiolipin antibodies; Cryo: type of cryoglobulin; Hypocomp: hypocomplementemia; Arth: arthritis; Nephr: nephropathy; Hem: hemocytopenias; Ser: serositis; Ulc: oral ulcer; NP: neuropsychiatric manifestations; Photo: photosensitivity; Malar: malar rash; Subac: subacute cutaneous lesions; Y: presence; N: absence; ND: not done.

Table 2. Comparison of SLE features in patients with and without HCV infection. Values represent the number (%) of patients.

Feature	SLE Patients Without HCV, n = 42	SLE Patients With HCV, n = 19	p
Age at onset of SLE, yrs	24 ± 9	30 ± 13	< 0.04
Myocarditis/endocarditis	6 (14)	4 (22)	NS
Central nervous system involvement	19 (45)	7 (39)	NS
Antiphospholipid syndrome	14 (33)	7 (37)	NS
Type III or IVglomerulonephritis	10 (24)	5 (28)	NS
ANA	40 (98)	19 (100)	NS
Anti-dsDNA	35 (85)	15 (79)	NS
Anti-ENA	19 (45)	9 (47)	NS
Anticardiolipin	24 (58)	13 (68)	NS
Low C3	18 (43)	8 (42)	NS
Low C4	24 (57)	11 (58)	NS
Low CH50	28 (67)	13 (68)	NS
Mixed cryoglobulinemia	8 (19)	10 (53)	< 0.04

in 2 cases. The mean Knodell score was 5.5 ± 2.9. According to the METAVIR system, the mean activity score was 1.1 ± 0.8 and the mean fibrosis score was 1.5 ± 1.3. There was no correlation between histological score and viral load.

Four SLE patients were treated for HCV infection. One patient (patient 12) was treated with amantadine for 12 months but no biochemical or virological response was observed. A 12 month course of ribavirin (1200 mg/day) was given to patient 4 but showed no biological or virological response. A 6 month combination treatment with interferon-α 3×10^6 IU thrice weekly plus ribavirin 1200 mg/day in patient 18 did not lead to any response. These 3 patients were infected by a genotype 1 virus. Patient 2 was infected by a genotype 3 virus; in this case, a 6 month course of interferon-α 3×10^6 IU thrice weekly permitted a sustained virological response. SLE was not affected by any anti-HCV treatment. In particular, no SLE flare occurred in the 2 patients treated with interferon-α. One patient had positive HCV ELISA-3 test and detectable HCV-RNA by PCR (patient 15). HCV-RNA became undetectable in this patient in subsequent years whereas anti-HCV antibodies were still present, suggesting spontaneous recovery of HCV infection.

Table 3. Hepatitis C infection features in patients with systemic lupus erythematosus.

Patient	Source of Infection	ALT	Genotype	PCR before Treatment (viral load in million copies/ml)	Knodell Score	METAVIR Score	HCV Treatment
1	?	N	ND	–	2	A0F1	ND
2	?	N	3a	+ (< 0.2)	4	A1F1	IFN
3	T	N	1	+ (< 0.2)	ND	ND	ND
4	?	N	1b	+ (1.5)	9	A2F1	Ribavirin
5	T	2N	3a	+ (< 0.2)	5	A1F1	ND
6	T	2N	3a	+ (< 0.2)	9	A1F4	ND
7	?	2N	1b	+ (1.1)	2	A0F1	ND
8	?	3N	ND	–	ND	ND	ND
9	IVDA	2N	ND	–	2	A0F1	ND
10	T	2N	1b	+ (3)	ND	ND	ND
11	?	1.5N	ND	ND	ND	ND	ND
12	T	4N	1	+ (13.9)	4	A2F4	Amantadine
13	T	N	1b	+ (5)	ND	ND	ND
14	?	N	1b	+ (16)	6	A1F1	ND
15	?	N	ND	–	ND	ND	ND
16	?	N	ND	ND	ND	ND	ND
17	T	1.2N	1b	+ (2.9)	ND	ND	ND
18	T	2N	1b	+ (9.5)	10	A2F2	IFN+ribavirin
19	T	4N	1b	+ (1.6)	7	A2F0	ND

ALT: serum alanine aminotransferase activity (results are expressed as number of times the upper limit of normal value); IFN: interferon-α; ND: not done; T: transfusion; IVDA: intravenous drug abuser; ?: unknown; –: negative; +: positive.

DISCUSSION

HCV infection has been associated with numerous extrahepatic manifestations, the most frequent being mixed cryoglobulinemia[4]. Many HCV-infected patients have other extrahepatic diseases such as autoimmune thyroiditis[22], sicca syndrome[8], leukocytoclastic vasculitis, and pruritus[11]. These manifestations might be linked to HCV infection of peripheral blood mononuclear cells[23]. SLE pathophysiology also involves B and T cell functions. However, reports on the association of HCV infection in SLE patients are scarce[12-14]. In a previous study in 62 SLE patients, we found 7 patients positive for anti-HCV antibodies by ELISA-2 but only 2 had detectable HCV-RNA[24]. Kowdley, *et al* reported 5/42 SLE patients positive for anti-HCV antibodies by ELISA-2 but only 2 had detectable HCV-RNA[14]. In both studies, no patients had chronic liver disease symptoms. In a recent study, Ramos-Casals, *et al* showed that prevalence of HCV infection in SLE patients was higher (13%) than that observed in blood donors from the same geographic area (1%)[12]. Moreover, in 115 consecutive SLE patients followed in our department, 4 (3.5%) were found to be HCV positive (unpublished observations). Altogether, our data suggest that HCV infection prevalence in patients with SLE is higher than in healthy subjects.

Prevalence of severe clinical or biological manifestations of SLE was not higher in HCV positive than in HCV negative patients. Age at onset of SLE was slightly higher in HCV positive patients. The reasons for this difference are not clear, especially in this small number of patients. Extrahepatic manifestations of patients with HCV infection may have led to a delayed diagnosis of SLE. The immunological pattern between the 2 groups of patients was slightly different. Prevalence of mixed cryoglobulinemia was higher in HCV-infected compared to HCV negative patients. A similar increase was also observed in HCV-infected patients with extrahepatic manifestations and was associated to systemic vasculitis[4,11]. These results suggest that HCV infection rather than SLE by itself was responsible for the increased prevalence of cryoglobulin and confirm in a larger cohort the observations of Ramos-Casals, *et al*[12]. On the other hand, these authors reported a higher prevalence of hypocomplementemia and anti-dsDNA antibodies in HCV positive patients, which was not observed in our cohort. The presence of mixed cryoglobulinemia syndrome with severe asthenia, peripheral nerve involvement, or membranoproliferative glomerulonephritis[25,26] was not found in SLE patients with HCV infection (Reference 12 and our study).

SLE and HCV infection share many common clinical, biological, and immunological features such as arthralgia, arthritis, myalgia, low white cell counts, hypocomplementemia, and autoantibodies (i.e., ANA and aCL). There may be confusion regarding clinical and immunological signs of HCVinfection and SLE in some patients[11,27-29]. This underscores the necessity, in patients presenting arthralgia, arthritis, myalgia, sicca syndrome, or low white cell counts who are suspected of SLE, to test for anti-HCV antibodies using ELISA-3. Conversely, extrahepatic manifestations of HCV infection may mimic SLE[12]. Therefore, we suggest

physicians consider a true SLE diagnosis in HCV positive patients only if highly specific antibodies for SLE diagnosis such as anti-dsDNA and anti-nucleosome are found.

In our study, HCV infection in SLE patients showed a low activity index: 7/19 patients with anti-HCV antibodies had normal ALT levels, 4 had undetectable HCV-RNA, and liver histological activity and fibrosis scores were low. False positive results of first or second generation HCV-ELISA tests can occur in patients with autoimmune diseases, especially those with hypergammaglobulinemia, but are unlikely with third generation ELISA.

Recently it was demonstrated that patients with serum anti-dsDNA showed a Th1 pattern of intracellular cytokines[30]. Patients who develop chronic HCV infection show a predominant Th2 response, but a weak Th1 response[31], the effects of Th1 cytokines being crucial for protection against HCV infection[32]. Therefore, Th1/Th2 polarization might play a role in the low or absent viremia of HCV positive patients with SLE. We found no clinical or immunological difference in terms of autoantibody prevalence between HCV-RNA positive and negative patients, suggesting the absence of false positive ELISA-3 test. Increased ALT activity associated with anti-HCV antibodies and undetectable HCV-RNA was found in 2 cases. A liver biopsy performed in one of these patients showed no activity. We cannot exclude the role of steroid therapy or steatosis in the increased ALT activity in these 2 HCV-RNA negative patients[33]. There was no correlation between liver histological activity and fibrosis (Knodell and METAVIR scores) and the level of viral load. Mean Knodell and METAVIR system scores were low, and only 2 patients showed cirrhosis. These patients were 52 and 70 years old whereas the mean age of the cohort was 42 ± 13 years (range 25-70). Thus, HCV infection in SLE patients does not seem to lead to a high rate of fibrosis progression in young patients. Only some of the oldest patients showed a high fibrosis score. Although longterm followup of our patients is not available, the natural history of liver fibrosis progression in HCV-infected patients with SLE does not seem to differ from non-SLE patients[6].

Due to SLE multivisceral involvement, steroid therapy has been used in all HCV-infected patients in our study. There has been some controversy about the effect of steroid therapy possibly leading to increased ALT activity and HCV replication, and to liver necrosis[34]. High doses of corticosteroids received by our patients did not seem to alter the course of chronic HCV. However, we did not have pre and post steroid HCVviral load to ascertain the absence of influence of steroid therapy in lupus patients with chronic HCV infection. Overabundance of extrahepatic manifestations in HCV infection, with a general tendency to develop autoimmune or lymphoproliferative phenomena, might be induced through a primary action on the lymphoid system[4,11]. Steroid-induced immunosuppression in these patients might be useful[35]. Usually, interferon-α is contraindicated in autoimmune diseases. Other antiviral molecules such as ribavirin[36] or amantadine[37] do not lead to longterm viral response. These data explain why only 4/19 SLE patients were treated for their HCV infection. It is interesting to note that one patient was treated with interferon-α without worsening of SLE.

SLE may be associated with HCV infection. SLE in HCV-infected patients does not show a different clinical pattern, but is associated with higher prevalence of mixed cryoglobulinemia, whereas HCV infection has moderate signs of biochemical and liver pathological severity. SLE by itself or treated with steroids does not seem to worsen HCV infection.

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