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FULL PAPER

Hepatitis B and C virus infection in patients with Systemic and Cutaneous Lupus Erythematosus

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SUMMARY

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a multifactorial etiology. The primary aim of this study was to estimate HCV and HBV infection prevalence in a cohort of SLE and Cutaneous Lupus Erythematosus (CLE). We assessed the frequency of these infections in our cohort and the possible associations with disease clinical/laboratory features and disease activity status.

The prevalence of chronic HBV infection was 2.2% in the CLE group, while no HBsAg positive patients were identified in the SLE group. Conversely, the prevalence of anti-HCV positive was 2.2% in the SLE group while no anti-HCV positive patients were identified in the CLE group. We found no significant association between anti-HBc positive status and clinical manifestations or disease activity status in either group of patients. Hemodialysis resulted significantly associated with anti-HBc positivity in SLE.

In the present study, we found HBsAg positivity in CLE patients but not in the Systemic form (SLE); conversely, a similar prevalence of anti-HBc antibodies in both groups was observed. A possible protective role exerted by SLE in HBV infection may be hypothesized. A higher frequency of HCV infection in SLE compared to CLE suggests a possible involvement of HCV in some SLE-related clinical and immunological features.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a multifactorial etiology in which genetic and environmental factors interplay, determining disease development (Tsokos, 2011, Ceccarelli *et al*., 2015). This disease primarily affects women of childbearing age, even though people of all ages can be affected; furthermore, some ethnic groups (e.g. African Americans, Asian, and Native Americans/Alaska Natives) seem to be affected more frequently than Caucasians (Tsokos, 2011; Stojan *et al*., 2020; Essouma *et al*., 2020; Danchenko *et al*., 2006).

From a pathogenic point of view, SLE is characterized by chronic inflammation, production of various autoantibodies, complement activation and immune-complex deposition, resulting in tissue damage (Tsokos, 2011). Indeed, any organ and system could potentially be involved, such as skin, joints, kidneys, central and peripheral nervous system (Tsokos, 2011; Bruce *et al*., 2015; Bengtsson *et al*., 2017; Rahman *et al*., 2001).

In addition to systemic disease, an exclusively cutaneous condition has been widely described: so-called Cutaneous Lupus Erythematosus (CLE) (Patel *et al.*, 2020; Garelli *et al.*, 2020).

Among the numerous environmental factors in-

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volved in SLE susceptibility, infections seem to play a crucial role in disease pathogenesis and several agents have been implicated in disease development and relapses (Pan *et al.*, 2019; Illescas-Montes *et al.*, 2019; Rigante *et al.*, 2014). In particular, viral infections have been implicated in autoimmune disease pathogenesis (Nelson *et al.*, 2014). Among these, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are plausible candidates (Toussirot *et al.*, 2008; Rölle *et al.*, 2014; Arcangeletti *et al.*, 2020). Furthermore, epidemiological evidences have been described for the human T lymphotropic virus type I, HIV, corona viruses, mumps, Coxsackie and herpesvirus-6 (Fox 2005; Höllsberg *et al.*, 1995; Banki *et al.*, 1994; Sekigawa *et al.*, 1998; Talbot 1985; Dahlquist 1995; Atkinson 1994).

To date, several hypotheses have been formulated about the potential impact of Hepatitis B (HBV) and C virus (HCV) infections on SLE-related manifestations, with controversial results. Nonetheless, significant heterogeneity has been described regarding HBV prevalence in SLE patients, viral reactivation and the impact on disease activity (Sumethkul *et al.*, 2017; Wang *et al.*, 2017).

Furthermore, even though HCV infection has been associated with various immune processes, the mechanisms linking HCV with autoimmunity are still unclear (Mcmurray, 1997). In particular, anti-HCV antibodies have been identified in 2% of SLE cohorts, but there are conflicting results regarding the association with disease phenotype and course (Wang *et al.*, 2017; Mercado *et al.*, 2005; Ahmed *et al.*, 2006; Vassilopoulos *et al.*, 2003).

To our knowledge, data on the prevalence of HBV and HCV infection in Italian Lupus cohorts are not available. Thus, in the present study, we aimed to estimate HCV and HBV infection prevalence in a cohort of patients affected by SLE and CLE attending at the Lupus Clinic of the Rheumatology Unit, Sapienza University of Rome. Moreover, by using a case-case study design, we aimed to assess possible associations between these viral hepatitis infections and epidemiological and clinical features of both conditions.

METHODS

Patient populations

Consecutive SLE and CLE patients, attending at the Lupus Clinic of the Rheumatology Unit, Sapienza University of Rome (*Sapienza Lupus Cohort*) were enrolled from September 2018 to September 2019. The diagnosis was performed according to the revised 1997 American College of Rheumatology (ACR) criteria (Hochberg *et al.*, 1997).

The study was approved by the local Ethical Committee (Prot. PRE-16/18, January 15, 2018 - Istituto Superiore di Sanità) and patients provided written informed consent. At the visit the SLE patients underwent a complete physical examination and clinical and laboratory data were collected in a standardized, computerized, and electronically filled form, including demographics, past medical history with date of diagnosis, co-morbidities, previous and concomitant treatments. Disease manifestations were recorded according to the above-mentioned ACR classification criteria (Rölle et al., 2014). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence assay (IIFA) on HEp-2, anti-dsDNA by IIFA on Crithidia luciliae, ENA (anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP), anti-cardiolipin (anti-CL) of IgG or IgM isotype and anti-Beta2glicoprotein I (anti-Beta2GPI) of IgG or IgM isotype by ELISA. Lupus anticoagulant (LA) was assessed according to International Society on Thrombosis and Hemostasis guidelines. For all subjects, complement C3 and C4 concentrations were determined by nephelometry.

Disease activity was assessed by using the SLE Disease Activity Index 2000 (SLEDAI- 2K); chronic damage by SLICC Damage Index (SDI) (Gladman *et al.*, 1996; Gladman *et al.*, 2002).

Each subject underwent peripheral blood sample collection; obtained sera were sent for virological testing to the Department of Infectious Diseases of Istituto Superiore di Sanità (ISS), where sera were stored at -80°C until serological and molecular assay were performed.

Serological and virological screening

Sera from patients were tested for HBV and HCV serological markers by chemiluminescent assays on the automated Cobas Elecsys e401 analyzer (Roche Diagnostics, Basel, Switzerland).

The Elecsys anti-HBc, Elecsys anti-HBs, Elecsys HBsAg II and Elecsys anti-HCV II kits were used according to the manufacturers' instructions. HBV-DNA levels in plasma were detected and quantified by COBAS AMPLIPREP/ COBAS TAQMAN HBV TEST, V2.0 with a claimed lower limit of detection of 20 IU/ml and a claimed upper limit of quantification of 1.7×10^8 IU/ml. HCV RNA quantitation was performed on anti-HCV positive sera using the High Pure System Viral Nucleic Acid Kit (Roche Diagnostics, Basel, Switzerland). Amplification and detection were carried out on a COBAS TaqMan 48 Analyzer using the COBAS TaqMan HCV Test v2.0 (Roche Molecular System Inc, Branchburg, NJ, USA); this test has a sensitivity of about 9.3 IU/mL and a linear range from 25 to 3.91×10^8 IU/mL.

Statistical analysis

SLE and CLE patients were described by clinical, serological, and laboratory variables. T-test or Mann-Whitney test, as appropriate, was applied to compare the two groups in case of continuous vari-

ables. When comparing categorical variables, chi-squared test or Fisher test was used. *P*-values lower than 0.05 were considered statistically significant. We estimated unadjusted and adjusted Odds Ratio (OR) of SLE (*versus* CLE) by applying logistic models, considering age and gender as possible risk factors.
Both HBV and HCV virus infection prevalence rates were estimated in the two groups of patients (SLE and CLE) and the respective unadjusted and adjusted OR for infection were calculated, applying a multiple logistic model and adjusting for age and gender.
In order to investigate possible associations between SLE or CLE specific clinical or laboratory features and positivity for HBV or HCV infection markers, two separate logistic models were run. For the assessment of risk factors potentially associated to anti-HBc positivity, the following variables were considered: transfusion, administration of blood derivatives, intervention/operations, teeth treatments, acupuncture, hemodialysis, endoscopy, hospitalizations, drugs, piercing, tattoo, manicure, family member with HBV. Descriptive and statistical analysis was performed for disease activity and chronic damage (assessed by SLEDAI-2k and SDI, respectively) in the SLE group to investigate a possible association between high SLE disease activity (defined for SLEDAI-2K values higher than 4), chronic damage (SDI ≥1) and HBV infection status.

RESULTS

Characteristics of the study population

One hundred thirty-eight patients were enrolled, 92 (67%) affected by SLE and the remaining 46 by CLE. As expected, females were more represented in the SLE group than in the CLE group (91.3% *vs* 71.7% p-value: 0.003); moreover, the median age of CLE patients was slightly higher than those with SLE (52 *vs* 47 p-value: 0.038) (*Table 1*). The majority of patients were Italians, who were more represented in the CLE group (100% *vs* 88% p-value: 0.016) (*Table 1*). All the foreign patients (N=11) were affected by SLE; specifically, 54.5% were Caucasian (Hungary, Bulgaria, Romania and Albania), 27.3% Hispanics/South Americans (Peru and Brazil) and 18.2% Asiatic (China and Sri Lanka). All foreign patients had lived in Italy at least 12 years.
In the SLE cohort, anti-dsDNA antibodies were found in 62.0% and anti-SSA in 47.8%. Regarding CLE, ANA were found in 54.3% of patients and anti-SSA in 19.6%; as expected, anti-phospholipid antibodies were more frequently detected in SLE than in CLE patients (*Table 1*). Unsurprisingly, SLE patients experienced more treatment lines than CLE patients (*Table 1*). In particular, the prevalence of subjects treated by glucocorticoids was significantly higher in the SLE group (89.1%) than in the CLE group (23.9%, p<0.001). Furthermore, the proportion of patients treated by hydroxychloroquine was similar in the two groups (SLE 95.6% versus CLE 91.3%, p=NS, *Table 1*).

Hepatitis B and C seroprevalence in SLE and CLE patients

Table 2 reports data about HBV and HVC infection markers in SLE and CLE patients.
In detail, the prevalence of chronic HBV infection (i.e., patients testing HBsAg positive) was 2.2% in the CLE group (one patient), while no HBsAg positive patients were identified in the SLE group.
The HBV DNA concentration for the patient testing HBsAg positive was 133.0 copies/mL.
The anti-HBc prevalence was almost similar between SLE and CLE patients (9.8% *vs* 8.7%, p=1.00; unadjusted OR 1.14; 95% CI: 0.33 - 3.91, p=0.837). Even when adjusting for age and gender, SLE was not sig-

Table 1 - *Demographic, clinical, laboratory and treatment data for the SLE and CLE patients.*

	SLE N= 92	*CLE N= 46*	*p-value*
Sex, n (%)			
Female	84 (91.3%)	33 (71.7%)	*0.003*
Male	8 (8.7%)	13 (28.3%)	
Age (years)			
Median (IQR) [range]	47 (39-56) [18-72]	52 (42-62) [31-74]	*0.038*
Nationality, n (%)			
Italian	81 (88.0%)	46 (100%)	*0.016*
Foreign	11 (12.0%)	0	
Education*, n (%)			
Graduated	25 (29.1%)	9 (19.6%)	0.234
Not gradated	61 (70.9%)	37 (80.4%)	
Unknown	6 (6.5%)**	0	

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	SLE N= 92	*CLE N= 46*	*p-value*
Work activity*, n (%)			
Intellectual	30 (37.0%)	15 (32.6%)	0.616
Not Intellectual	51 (63.0%)	31 (67.4%)	
Unknown	11 (12.0%)**	0	
Disease duration (years)			
Median years (IQR) [range]	11 (6- 22) [0-40]	10 (4-18) [0.5-38]	0.185
Clinical manifestations #, n (%)			
Joint involvment	67 (72.8%)	0	
Skin involvment	61 (66.3%)	46 (100%)	*< 0.001*
Gilliam classification of CLE			
acute cutaneous	0	33 (71.7%)	
subacute cutaneous	0	9 (19.6%)	
Lupus profundus	0	1 (2.2%)	
Lupus tumidus	0	3 (6.5%)	
Neuropsychiatric involvment	19 (20.6%)	0	
Hematological manifestations	49 (53.3%)	0	
Sierositis	18 (19.6%)	0	
Renal involvment	25 (27.2%)	0	
Laboratory manifestations #, n (%)			
Antinuclear antibodies (ANA)	92 (100%)	25 (54.3%)	*< 0.001*
Anti-dsDNA	57 (62.0%)	0	
Anti-Sm	17 (18.5%)	0	
Anti-SSA	44 (47.8%)	9 (19.6%)	*0.001*
Anti-SSB	20 (21.7%)	0	
Anti-RNP	16 (17.4%)	0	
Anti-cardiolipin IgG/IgM	26 (28.3%)	2 (4.3%)	*0.001*
Anti-β2Glicoprotein I IgG/IgM	18 (19.6%)	0	
Lupus anticoagulant	11 (12.0%)	1 (2.2%)	*0.061*
Low C3 level < 70 (mg/dl)	11 (12.0%)	1 (2.2%)	*0.061*
Low C4 level < 10 (mg/dl)	8 (8.7%)	0	
Treatments #, n (%)			
Corticosteroids	82 (89.1%)	11 23.9%	*<0.001*
Hydroxychloroquine	88 (95.6%)	42 91.3%	0.44
Cyclosporine A	20 (21.7%)	0	
Methotrexate	17 (18.5%)	0	
Cyclophosphamide	12 (13.0%)	0	
Mycophenolate mofetil	19 (22.8%)	0	
Azathioprine	26 (28.3%)	0	
Rituximab	7 (7.6%)	0	

presence of clinical, laboratory manifestations and used treatments. Therapies are related to disease history.
*percentages and p-value unknown excluded; ** percentages of unknown on the total (n=92)

nificantly associated with anti-HBc prevalence (adjusted OR 1.41; 95% CI: 0.37-5.29). Similarly, we did not find any difference in terms of median anti-HBc titer in SLE and CLE patients (0.015 *vs* 0.011 IU/ml, p=0.074; IQR: 0.015-0.111 *vs* 0.010-0.017). Regarding anti-HBs, the proportion of positive patients was similar in the SLE and CLE groups (35% *vs*. 37%, p-value=0.801), with median anti-HBs titers of 163.5 for SLE and 397.0 mIU/mL for CLE patients (p-value=0.313; IQR: 16.8-664.5 *vs* 8.8-1000.0). Meanwhile

Table 2 - *Prevalence of HBV and HCV infection markers in SLE and CLE patients.*

Markers	*SLE*	*CLE*	*p*
	(N=92)	*(N=46)*	
	N (%)	N (%)	
HBsAg+	0 (0)	1 (2.2)	0.333
Anti-HBc+	9 (9.8)	4 (8.7)	1
Any HBV marker+[a]	33 (35.9)	18 (39.1)	0.708
HBV DNA+	0 (0.0)	1 (2.2)	0.333
Anti-HBs+ (total)	32 (34.8)	17(37.0)	0.801
Anti-HBs+ (alone[b])	24 (26.1)	14 (30.4)	0.687
Anti-HCV+	2 (2.2)	0 (0)	0.552
HCV RNA	0	0	-

[a]Any HBV positive marker: patients testing HBsAg+ (with or without anti-HBc and/or HBV DNA) or anti-HBc+ alone or anti-HBs+/anti-HBc+ or anti-HBs alone.
[b]Anti-HBs positive alone patients: individuals vaccinated against HBV.

only one SLE patient resulted anti-HBs negative and anti-HBc positive.

A similar proportion of anti-HBs negative and anti-HBc negative individuals was identified in SLE and CLE patient groups (64% and 61%, respectively, p=NS).

Furthermore, the proportion of HBV-immunized individuals (i.e., anti-HBs positive and anti-HBc negative - Anti-HBs+ alone, *Table 2*) was similar (SLE: 26.1%, CLE: 30.4%; p=0.687).

The prevalence of anti-HCV positives was 2.2% in SLE groups and 0.0% among the CLE group (p=0.552). The two SLE patients testing anti-HCV positive were both HCV RNA-negative, suggesting a past resolved HCV infection or previous treatment for HCV.

Association of clinical and laboratory features with anti-HBc positive status in SLE and CLE patients

No clinical manifestations resulted associated with anti-HBc positive status in SLE patients. Likewise, no association between skin manifestations and HBV infectious status was found in CLE patients. Finally, no laboratory features (i.e., autoantibodies) were significantly associated with anti-HBc positivity in both groups (data not shown).

Disease activity and damage in SLE

The median SLEDAI-2k value in SLE patients was 2 (IQR: 0-20); 9 of them (9/92, 9.8%) showed high disease activity, defined for a SLEDAI-2k >4. No differences were found in median SLEDAI-2k values among anti-HBc positive and negative SLE patients [2 (IQR: 0-14) *vs* 2; IQR: 0- 20) (p-value=0.54). A total of 22% of the anti-HBc positive SLE patients showed SLEDAI-2k>4 compared to 78% in anti-HBc negative SLE patients. However, high disease activity (SLEDAI 2k >4) was not significantly associated (p-value=0.213) with anti-HBc positivity. Thirty-five SLE patients (38.0%) showed SDI ≥1. When anti-HBc status was considered, 4 of 9 (44.4%) anti HBc-positive SLE patients were found with SDI ≥1 compared with 31 of 83 (37.3%) anti-HBc negative (p=0.727).

Factors associated with HBV infection (anti-HBc positive) among SLE and CLE patients

In SLE patients, hemodialysis was the only factor significantly associated with anti-HBc positivity [OR=11.57 (95% CI: 1.408-95.13, p-value=0.023). Among CLE patients, a strong association was found between anti-HBc positivity and cohabitation with a chronic HBV carrier [OR=0.03 (95% CI: 0.01 - 0.42), p-value=0.001]. The two anti-HCV positive SLE patients resulted positive both for anti-HBc and anti-HBs. Regarding risk factors, one of them reported intravenous and inhalation drug use, tattoo, dental treatments, and surgery; the other reported past hospitalization, endoscopy, dental treatments, surgery, and manicure.

DISCUSSION

In the present study, we aimed to assess the prevalence of hepatitis B and C infection in a cohort of patients affected by systemic and cutaneous lupus.

We found HBsAg positivity in CLE patients but not in systemic lupus group, and a similar prevalence of anti–HBc antibodies; conversely, a higher frequency of HCV infection was observed in the SLE compared to the CLE group. Even if these data did not reach significance, they can still provide preliminary indications and can be compared to results in the literature.

As widely demonstrated, infections are one of the most important environmental factors involved in SLE pathogenesis: in particular, viral infections have been implicated in disease development and exacerbation (Rigante *et al*., 2014; Rigante *et al*., 2015). Al-

though HBV and HCV infections pose a major public-health problem worldwide and represent the principal cause leading to chronic liver disease, scarce data is available in the literature concerning the possible role of these infections in Lupus patients. Furthermore, most of the studies published so far included Asian cohorts (i.e., China, Japan, Taiwan) (Wang *et al*., 2017; Watanabe *et al*., 2014; Chen *et al*., 2005; Chen *et al*., 2015; Sui *et al*., 2014; Furer *et al*., 2019) and focused mainly on SLE patients. Nonetheless, literature data suggest a higher prevalence of HCV in SLE cohorts in comparison with healthy subjects (Ahmed *et al*., 2006; Costa CDE *et al*., 2002). Conversely, HBV infection prevalence has previously been reported to be lower in SLE patients than in healthy controls, suggesting a putative protective role (Wang *et al*., 2017; Gupta *et al*., 2015). Thus, in our study we enrolled a large Italian lupus cohort, including patients affected by SLE and CLE.

In particular, the patients with CLE characterized by an exclusively cutaneous condition were considered as a comparison group ("internal control") in our cohort, versus the SLE group.

Only one patient (2.2%) affected by CLE resulted HBsAg positive.

Furthermore, we focused on the estimation of HBV infection status in SLE patients by using the anti-HBc positive rate. Here, the prevalence of anti-HBc antibodies was similar in SLE and CLE populations, even when adjusting for age and gender. Moreover, the prevalence of chronic HBV infection (i.e. patients testing HBsAg positive) was 2.2% in the CLE group, while no HBsAg positive patients were identified in the SLE group. Previous studies showed a lower prevalence of HBV infection in patients with SLE than in healthy controls (Wang *et al*., 2017; Watanabe *et al*., 2014; Chen *et al*., 2015; Zhao *et al*., 2010). In particular, taking into account previous studies performed in other cohorts, the prevalence of HBV antibodies in the SLE population was similar to that observed in the blood donor population (controls) (Mercado *et al*., 2005). This result could suggest a possible protective role exerted by SLE in HBV infection that could be related to higher levels of IFN and IL6, widely demonstrated in SLE patients. As previously reported, these cytokines could play a role in HBV infection control (Liu *et al*., 2016). This hypothesis was supported by the results of the study conducted by Tžnžsescu in 1999, observing a significant association between the presence of HBV and a lower disease activity, as assessed by SLEDAI (Tžnžsescu *et al*., 1999).

Regarding HCV infection, this virus has most often been associated with the presence of autoimmune disorders and positivity for various autoantibodies, and has been described in patients with HCV infection (Mcmurray *et al*., 1997; Pawlotsky *et al*., 1995). Nonetheless, the association between HCV infection and autoimmune disease development has been investigated without conclusive results, except for cryoglobulinemia (Pascual *et al*., 1990; Ramos-Casals *et al*., 2000).

In the present study, we found a higher frequency of HCV infection in SLE patients than in those affected by cutaneous phenotype. Moreover, the above-mentioned study published by Tžnžsescu (Tžnžsescu *et al*., 1999) observed the association between HCV infection and renal involvement; furthermore, another study enrolling a Chinese population identified an association with hepatic involvement, hypocomplementemia and cryoglobulinemia (Tžnžsescu *et al*., 1999; Qin *et al*., 2002). Although the pathogenic role of HCV infection in SLE patients is still unclear, some studies have proposed that HCV could play a role only in specific geographic areas, suggesting the involvement of genetic background (Ramos-Casals *et al*., 2000).

Concerning risk factors associated with hepatitis infection, in our cohort we found an association between anti-HBc positivity and hemodialysis and cohabitation with a chronic HBV carrier (for CLE); this result is in line with that observed in the general population. Similarly, the most important risk factor for the anti-HCV positive SLE patients was intravenous drug use (Bollettino Sistema Epidemiologico Integrato dell'Epatite Virale Acuta SEIEVA). We did not find a significant association between HCV infection and clinical/laboratory disease features and treatments. This lack of association could be due to the low number of infected patients at the time of enrollment in the study.

The possible limits of this study should be highlighted: first, the number of patients enrolled in our cohort, which consisted of 138 patients; second, the low number of patients found with evidence of viral hepatitis infection; third, the patients were enrolled at a single hospital center. For these reasons, our study can certainly be considered a preliminary study, and future in-depth multicenter projects must be carried out with larger cohorts.

CONCLUSIONS

In conclusion, we found a lower prevalence of HBV infection and a higher prevalence of HCV infection in SLE patients than in CLE patients, updating the currently available literature.

Further studies should be conducted in SLE populations to understand the pathogenic mechanisms linking viral hepatitis and SLE phenotype.

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Conflicts of interest

The authors declare no conflicts of interest.

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