ORIGINAL ARTICLE

Autoantibody profile and clinical patterns in 619 Italian patients with cutaneous lupus erythematosus

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Abstract

Background Anti-nuclear antibodies (ANA), anti-extractable nuclear antigens (ENA) and anti-dsDNA antibodies are often associated with cutaneous lupus erythematosus (CLE), with variable frequency depending on skin subtype. However, specific data based on large case-series on the pathogenetic, diagnostic and prognostic meaning of such autoantibodies are still lacking.

Objective To characterize the correlations between CLE subtypes as well as LE-non-specific skin lesions and their autoantibody pattern.

Methods Epidemiological, clinical and immunopathological data of 619 Italian patients with CLE and LE-non-specific skin lesions were analysed. Differences in age, sex, clinical features and autoantibody profile were evaluated in each LE subgroup.

Results Anti-nuclear antibodies ($P < 0.0001$), anti-dsDNA ($P < 0.0001$), ENA ($P = 0.001$), anti-Sm ($P = 0.001$), anti-RNP ($P = 0.004$) and anti-histone ($P = 0.005$) antibodies were associated with SLE. A strong association between ANA ($P < 0.0001$) and anti-dsDNA ($P < 0.0001$) and female gender was also found: positive ANA and positive anti-dsDNA had a higher prevalence among females. Chronic CLE resulted to be negatively associated with ENA (OR = 0.51, $P < 0.0001$), anti-Ro/SSA (OR = 0.49, $P < 0.0001$) and anti-dsDNA (OR = 0.37, $P < 0.0001$). Intermittent CLE resulted to be negatively associated with ENA (OR = 0.50, $P = 0.007$) and ANA (OR = 0.61, $P = 0.025$). Subacute CLE resulted to be associated with ENA (OR = 5.19, $P < 0.0001$), anti-Ro/SSA (OR = 3.83, $P < 0.0001$), anti-Smith (OR = 2.95, $P = 0.004$) and anti-RNP (OR = 3.18, $P = 0.007$). Acute CLE resulted to be strongly associated with anti-dsDNA (OR = 6.0, $P < 0.0001$) and ANA (OR = 18.1, $P < 0.0001$). LE-non-specific skin lesions resulted to be significantly associated with systemic involvement. Livedo reticularis was significantly associated with ENA ($P = 0.007$) and anti-Ro/SSA ($P = 0.036$). Palpable purpura and periungual telangiectasia were significantly associated with ANA.

Conclusion According to our findings, some well-known associations between CLE subtypes and autoantibody profile were confirmed; moreover, specific association between autoantibodies and LE-non-specific skin lesions was highlighted. A strict association between anti-ENA and anti-Ro/SSA antibodies and livedo reticularis, ANA and palpable purpura, and ANA and periungual telangiectasia was evidenced.

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Conflict of interest

None of the authors has any potential financial conflict of interest related to this manuscript.

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Introduction

Cutaneous lupus erythematosus (CLE) is a chronic, relapsing autoimmune inflammatory disease with heterogeneous manifestations according to skin morphology, site, evolution and prognosis.[1,2] Cutaneous lesions can represent the only sign of LE and, in 23–28% of cases, can be associated with systemic involvement.[3]

Based on Sontheimer and Gilliam's classification,[4] cutaneous manifestations were divided into 'specific and diagnostic', subclassified as chronic CLE (CCLE), subacute CLE (SCLE) and acute CLE (ACLE). Recently, the intermittent CLE (ICLE) subtype has also been introduced.[5] Among LE-non-specific lesions of CLE, vascular lesions, diffuse non-scarring alopecia, pigmentation changes, sclerodactyly and calcinosis were included.[4]

Regarding serology, anti-nuclear antibodies (ANA), anti-extractable nuclear antigens (ENA) and anti-dsDNA antibodies are often associated with several CLE subtypes.[6,7]

To date, few studies have investigated the epidemiologic characteristic of CLE.

In this study, we analysed the epidemiological, clinical and immunological data of LE in an Italian cross-sectional study involving patients enrolled by the Italian Group of Cutaneous Immunopathology (GIIP) during the period 2012–2015. We aimed to better characterize the specific CLE subtypes as well as LE-non-specific skin lesions, evaluating the correlation between the clinical variants of CLE and LE-non-specific skin lesions with their autoantibody pattern. We also considered associated diseases.

Materials and methods

Patients

Consecutive patients with CLE were recruited from eight Lupus Clinics throughout Italy as part of a multicenter study. Demographic, clinical and laboratory data were collected at diagnosis and input into a clinical database.

The diagnosis and classification of CLE were based on clinical and histological characteristics as well as on serological parameters.[8] Four subtypes of CLE were included as follows: CCLE [localized or generalized discoid LE (DLE), hypertrophic lupus, LE profundus/panniculitis (LEP), and chilblain LE], SCLE (papulosquamous or annular-polycyclic variants), ACLE (localized or generalized ACLE), and ICLE. In patients with more than one CLE subtype, the form with the highest risk of developing systemic involvement was declared as the main diagnosis.

We also included SLE patients with LE-specific or LE-non-specific skin lesions, diagnosed by the presence of four or more *American College of Rheumatology* (ACR) diagnostic criteria (1982), revised in 1997.[8,9]

Serological data included ANA as well as anti-dsDNA and ENA antibodies, the latter comprising anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP and anti-histone antibodies.

Data were compared separately between male and female patients. In the female group, a possible association between pregnancy or estrogens treatment with clinical features of CLE or LE-non-specific skin lesions and autoantibody profile was also evaluated.

Finally, for each patient, comorbidities were also reported.

Statistical analysis

At baseline, differences in demographic (age and gender) clinical features (systemic/non-systemic lupus) and autoantibody profile were evaluated in each subgroup using *Fisher's exact test* for categorical variables and the *nonparametric unpaired Wilcoxon test* for continuous variables. For continuous variables, mean values with confidence interval 95% (CI95) were reported in the text.

A multivariate analysis by logistic regression was performed when covariates, such as age, sex or systemic/non-systemic lupus, resulted to be significantly associated with both the autoantibodies and the investigated subtypes of CLE and LE-non-specific skin lesions.

Differences in demographic (age and gender) and clinical features (systemic/non-systemic LE, CLE subgroups) were investigated in seven associated diseases (endocrine, respiratory, cardiovascular, gastrointestinal, oncological, rheumatic diseases and Sjögren syndrome) using *Fisher's exact test*.

In all analyses, a two-sided P value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA software.[10]

Results

Patients

A total of 619 patients were recruited. Of them, 589 patients (95.1%) had specific and diagnostic manifestations of CLE at diagnosis, 30 patients (4.8%) presented with LE-non-specific skin lesions only, and 130 patients (21.1%) featured both specific and diagnostic and LE-non-specific lesions. A total of 160 patients (25.8%) had SLE.

The total mean age at diagnosis in all CLE patients was 45.2 ± 1.2 years. The percentage of females was 79.6% ($n = 493$) vs. 20.4% of males ($n = 126$).

Results were reported in Table 1.

Autoantibodies analysis

The autoantibodies most frequently detected as positive were ANA (64.3%), followed by ENA (37.2%) and anti-dsDNA (17.9%) antibodies. Among ENA antibodies, we found the following positivity: anti-Ro/SSA (30.9%), anti-La/SSB (9.4%), anti-Sm (6.6%), anti-RNP (4.8%) and anti-histone (1%).

Concerning the associations between demographic, clinical characteristics and autoantibodies, ANA ($P < 0.0001$), anti-dsDNA ($P < 0.0001$), ENA ($P = 0.001$), anti-Sm ($P = 0.001$), anti-RNP ($P = 0.004$) and anti-histone ($P = 0.005$) were

Table 1 Associations between demographic and clinical characteristics and autoantibodies

Variable	ENA			anti-Ro/SSA		
	Yes (*n* = 230)	No (*n* = 389)	*P*	Yes (*n* = 191)	No (*n* = 428)	*P*
Sex (F), *n* (%)	186 (80.9)	307 (78.9)	0.606	153 (80.1)	340 (79.4)	0.914
Age at onset, mean ± years	46.1 ± 2.1	44.6 ± 1.6	0.295	45.7 ± 2.2	45.0 ± 1.5	0.589
Systemic (YES), *n* (%)	78 (33.9)	82 (21.1)	0.001	59 (30.9)	101 (23.6)	0.059
Variable	**anti-RNP**			**anti-histone**		
	Yes (*n* = 30)	No (*n* = 589)	*P*	Yes (*n* = 6)	No (*n* = 613)	*P*
Sex (F), *n* (%)	24 (80.0)	469 (79.6)	1.000	5 (83.3)	488 (79.6)	1.000
Age at onset, mean ± SE	44.2 ± 7.0	45.2 ± 1.3	0.384	39.7 ± 17.2	45.2 ± 1.3	0.320
Systemic (YES), *n* (%)	15 (50.0)	145 (24.6)	0.004	5 (83.3)	155 (25.3)	0.005
Variable	**anti-La/SSB**			**anti-Sm**		
	Yes (*n* = 58)	No (*n* = 561)	*P*	Yes (*n* = 41)	No (*n* = 578)	*P*
Sex (F), *n* (%)	51 (87.9)	442 (78.8)	0.123	36 (87.8)	457 (79.1)	0.229
Age at onset, mean ± years	44.3 ± 4.2	45.3 ± 1.3	0.724	45.4 ± 6.0	45.2 ± 1.3	0.722
Systemic (YES), *n* (%)	19 (32.8)	141 (25.1)	0.210	20 (48.8)	140 (24.2)	0.001
Variable	**Anti-dsDNA**			**ANA**		
	Yes (*n* = 111)	No (*n* = 508)	*P*	Yes (*n* = 398)	No (*n* = 221)	*P*
Sex (F), *n* (%)	99 (89.2)	394 (77.6)	0.006	333 (83.7)	160 (72.4)	0.001
Age at onset, mean ± SE	43.0 ± 3.2	45.6 ± 1.4	0.076	45.2 ± 1.6	45.1 ± 2.1	0.941
Systemic (YES), *n* (%)	87 (78.4)	73 (14.4)	<0.0001	151 (37.9)	9 (4.1)	<0.0001

associated with SLE. We found a strong association between ANA ($P < 0.0001$) and anti-dsDNA ($P < 0.0001$) and gender: positive ANA and positive anti-dsDNA had a higher prevalence among females (78.4% vs. 14.4% and 37.9% vs. 4.1%, respectively).

CLE subtypes analysis

CCLE was diagnosed in 48.9% ($n = 303$) patients, divided as follows: 35.2% ($n = 218$) localized DLE, 10.7% ($n = 66$) generalized DLE, 2.4% ($n = 15$) LEP, 0.6% ($n = 4$) chilblain lupus and 0.3% ($n = 2$) hypertrophic lupus.

SCLE was demonstrated in 18.6% ($n = 115$) patients: 15.7% ($n = 97$) had an annular-polycyclic SCLE and 2.9% ($n = 18$) had a papulo-squamous SCLE.

ACLE was shown in 10.1% cases ($n = 63$); particularly 7.9% ($n = 47$) had a localized form of ACLE and 2.6% ($n = 16$) had a generalized ACLE. Finally, ICLE was reported in 17.4% ($n = 108$) patients.

Associations between autoantibodies and CLE subgroups were reported in Table 2.

A systemic involvement was found in 98.4% ($n = 62$) ACLE patients, followed by CCLE (18.5%, $n = 56$) and SCLE (12.2%, $n = 14$) patients. None of ICLE patients had a concomitant SLE.

CCLE CCLE was diagnosed in 48.9% ($n = 303$) patients. We found ANA positivity in 60.4% ($n = 183$) CCLE patients; among them, 50.5% ($n = 110$) of the patients with localized DLE and 81.8% ($n = 54$) of the patients with generalized DLE were ANA positive. All patients with LEP ($n = 15$) demonstrated positive ANA vs. 63.4% of patients without LEP. All patients with chilblain LE had positive ANA as well as systemic involvement. Only two patients had hypertrophic CLE, both with positive ANA.

CCLE was negatively associated with SLE ($P < 0.0001$), ENA ($P < 0.0001$), anti-Ro/SSA ($P < 0.0001$), anti-La/SSB ($P = 0.027$) and anti-dsDNA ($P < 0.0001$). Even after the multivariate logistic regression analysis, adjusting for covariates, this negative association was confirmed. CCLE resulted to be negatively associated with ENA (OR = 0.51, $P < 0.0001$), anti-Ro/SSA (OR = 0.49, $P < 0.0001$) and anti-dsDNA (OR = 0.37, $P < 0.0001$). Patients with CCLE had a lower prevalence of systemic involvement (18.5% vs. 32.9%), ENA (28.4% vs. 45.6%), anti-Ro/SSA (22.8% vs. 38.6%), anti-La/SSB (6.6% vs. 12.0%) and anti-dsDNA (9.6% vs. 26.0%) antibodies positivity than those without a CCLE. Analogous evidence was observed for the localized DLE while no similar associations were observed for the generalized form.

ICLE ICLE was reported in 17.4% ($n = 108$) patients. Patients with ICLE were negatively associated with ENA ($P < 0.0001$) and ANA ($P < 0.0001$). Even after the multivariate logistic regression analysis, adjusting for covariates significantly associated with ICLE and autoantibodies, ICLE resulted to be negatively associated with ENA (OR = 0.50, $P = 0.007$) and

Table 2 Associations between autoantibodies and CLE subgroups. Multivariate logistic regression was performed when covariates, such as age, sex or systemic/non-systemic lupus, resulted to be significantly associated with both the autoantibodies and subtypes of CLE; adjusted OR and *P* value were reported

Variable	Sample (*n* = 619)	CCLE				Localized CCLE				Generalized CCLE		
		Yes (*n* = 303)	No (*n* = 316)	*P*	adjOR, *P*	Yes (*n* = 218)	No (*n* = 401)	*P*	adjOR, *P*	Yes (*n* = 66)	No (*n* = 553)	*P*
Sex (F), *n* (%)	493 (79.6)	239 (78.9)	254 (80.4)	0.690		167 (76.6)	326 (81.3)	0.175		55 (83.3)	438 (79.2)	0.519
Age at onset, (mean ± years)	45.2 ± 1.2	44.5 ± 1.8	45.8 ± 1.8	0.349		44.2 ± 2.0	45.7 ± 1.6	0.343		46.9 ± 3.9	45.0 ± 1.3	0.350
Systemic (YES), *n* (%)	160 (25.8)	56 (18.5)	104 (32.9)	<0.0001		33 (15.1)	127 (31.7)	<0.0001		18 (27.3)	142 (25.7)	0.768
ENA	230 (37.2)	86 (28.4)	144 (45.6)	<0.0001	0.51, <0.0001	56 (25.7)	174 (43.4)	<0.0001	0.49, <0.0001	24 (36.4)	206 (37.2)	1.000
anti-Ro/SSA	191 (30.9)	69 (22.8)	122 (38.6)	<0.0001	0.49, <0.0001	48 (22.0)	143 (35.7)	0.001	0.53, 0.001	16 (24.2)	175 (31.6)	0.260
anti-La/SSB	58 (9.4)	20 (6.6)	38 (12.0)	0.027		15 (6.9)	43 (10.7)	0.148		4 (6.1)	54 (9.8)	0.500
anti-Sm	41 (6.6)	13 (4.3)	28 (8.9)	0.024	0.54, 0.08	7 (3.2)	34 (8.5)	0.011	0.43, 0.049	5 (7.6)	36 (6.5)	0.792
anti-RNP	30 (4.8)	11 (3.6)	19 (6.0)	0.192		4 (1.8)	26 (6.5)	0.010	0.32, 0.040	6 (9.1)	24 (4.3)	0.119
anti-histone	6 (1.0)	2 (0.7)	4 (1.3)	0.686		1 (0.5)	5 (1.2)	0.671		0 (0.0)	6 (1.1)	1.000
anti-dsDNA	111 (17.9)	29 (9.6)	82 (26.0)	<0.0001	0.37, <0.0001	15 (6.9)	96 (23.9)	<0.0001	0.31, <0.0001	11 (16.7)	100 (18.1)	0.866
ANA	398 (64.3)	183 (60.4)	215 (68.0)	0.054		110 (50.5)	288 (71.8)	<0.0001	0.49, <0.0001	54 (81.8)	344 (62.2)	0.002
Variable	**Sample (*n* = 619)**	**ACLE**				**Localized ACLE**				**Generalized ACLE**		
		Yes (*n* = 63)	**No (*n* = 557)**	***P***	**adjOR, *P***	**Yes (*n* = 47)**	**No (*n* = 570)**	***P***	**adjOR, *P***	**Yes (*n* = 16)**	**No (*n* = 603)**	***P***
Sex (F), *n* (%)	493 (79.6)	57 (91.9)	436 (78.3)	0.012		46 (93.9)	447 (78.4)	0.009		13 (81.2)	480 (79.6)	1.000
Age at onset, (mean ± years)	45.2 ± 1.2	42.5 ± 4.6	45.5 ± 1.3	0.106		41.3 ± 5.3	45.5 ± 1.3	0.057		42.4 ± 10.1	45.2 ± 1.3	0.391
Systemic (YES), *n* (%)	160 (25.8)	62 (98.4)	99 (17.8)	<0.0001		46 (98.0)	112 (19.7)	<0.0001		16 (100.0)	144 (23.9)	<0.0001
ENA	230 (37.2)	27 (43.6)	203 (36.4)	0.272		22 (44.9)	208 (36.5)	0.281		7 (43.8)	223 (37.0)	0.606
anti-Ro/SSA	191 (30.9)	22 (35.5)	169 (30.3)	0.469		19 (38.8)	172 (30.2)	0.259		5 (31.2)	186 (30.9)	1.000
anti-La/SSB	58 (9.4)	8 (12.9)	50 (9.0)	0.354		7 (14.3)	51 (9.0)	0.206		1 (6.2)	57 (94)	1.000
anti-Sm	41 (6.6)	5 (8.1)	36 (6.5)	0.591		5 (10.2)	36 (6.3)	0.361		2 (12.5)	39 (6.5)	0.287
anti-RNP	30 (4.8)	3 (4.8)	27 (4.8)	1.000		3 (6.1)	27 (4.7)	0.724		0 (0.0)	30 (5.0)	1.000
anti-histone	6 (1.0)	0 (0.0)	6 (1.1)	1.000		0 (0.0)	6 (1.1)	1.000		0 (0.0)	6 (1.0)	1.000
anti-dsDNA	111 (17.9)	32 (51.6)	79 (14.2)	<0.0001	6.0, <0.0001	23 (46.9)	88 (15.4)	<0.0001	4.4, <0.0001	10 (62.5)	101 (16.8)	<0.0001
ANA	398 (64.3)	60 (96.8)	338 (60.7)	<0.0001	18.1, <0.0001	47 (95.9)	351 (61.6)	<0.0001	13.5, <0.0001	16 (100.0)	382 (63.4)	0.001

Table 2 *Continued*

Variable	Sample (*n* = 619)	CCLE Yes (*n* = 303)	CCLE No (*n* = 316)	*P*	adjOR, *P*	Localized CCLE Yes (*n* = 218)	Localized CCLE No (*n* = 401)	*P*	adjOR, *P*	Generalized CCLE Yes (*n* = 66)	Generalized CCLE No (*n* = 553)	*P*
Sex (F), *n* (%)	493 (79.6)	97 (84.3)	396 (78.6)	0.199		83 (85.6)	410 (78.5)	0.131		14 (77.8)	479 (79.7)	0.771
Age at onset, (mean ± years)	45.2 ± 1.2	51.5 ± 3.1	43.7 ± 1.3	<0.0001		50.5 ± 3.4	44.2 ± 1.3	0.001		56.9 ± 7.3	44.8 ± 1.3	0.002
Systemic (YES), *n* (%)	160 (25.8)	14 (12.2)	146 (29.0)	<0.0001		13 (13.4)	147 (28.2)	0.002		1 (5.6)	159 (26.5)	0.054
ENA	230 (37.2)	75 (65.2)	155 (30.8)	<0.0001	5.19, <0.0001	63 (65.0)	167 (32.0)	<0.0001	4.65, <0.0001	12 (66.7)	218 (36.3)	0.012
anti-Ro/SSA	191 (30.9)	62 (53.9)	129 (25.6)	<0.0001	3.83, <0.0001	51 (52.6)	140 (26.8)	<0.0001	3.31, <0.0001	11 (61.1)	180 (30.0)	0.008
anti-La/SSB	58 (9.4)	21 (18.3)	37 (7.3)	<0.0001		19 (19.6)	39 (7.5)	0.001		2 (11.1)	56 (9.3)	0.682
anti-Sm	41 (6.6)	13 (11.3)	28 (5.6)	0.036	2.95, 0.004	11 (11.3)	30 (5.8)	0.071		2 (11.1)	39 (6.5)	0.338
anti-RNP	30 (4.8)	10 (8.7)	20 (4.0)	0.050	3.18, 0.007	9 (9.3)	21 (4.0)	0.037	3.21, <0.0001	1 (5.6)	29 (4.8)	0.596
antiistoni	6 (1.0)	1 (0.9)	5 (1.0)	1.000		1 (1.0)	5 (1.0)	1.000		0 (0.0)	6 (1.0)	1.000
anti-dsDNA	111 (17.9)	22 (19.1)	89 (17.7)	0.688		17 (17.5)	94 (18.0)	1.000		5 (27.8)	106 (17.6)	0.343
ANA	398 (64.3)	82 (71.3)	316 (62.7)	0.085		67 (69.1)	331 (63.4)	0.301		15 (83.3)	383 (63.7)	0.132

Variable	Sample (*n* = 619)	ICLE Yes (*n* = 108)	ICLE No (*n* = 511)	*P*	adjOR, *P*
Sex (F), *n* (%)	493 (79.6)	72 (66.7)	421 (2.4)	0.001	
Age at onset, mean ± years	45.2 ± 0.6	43.1 ± 2.4	45.6 ± 1.4	0.206	
Systemic (YES), *n* (%)	160 (25.8)	0 (0.0)	160 (31.3)	<0.0001	
ENA	230 (37.2)	24 (22.2)	206 (40.3)	<0.0001	0.50, 0.007
anti-Ro/SSA	191 (30.9)	24 (22.2)	167 (32.7)	0.039	0.64, 0.088
anti-La/SSB	58 (9.4)	5 (4.6)	53 (10.4)	0.069	
anti-Sm	41 (6.6)	4 (3.7)	37 (7.2)	0.208	
anti-RNP	30 (4.8)	3 (2.8)	27 (5.3)	0.333	
anti-dsDNA	111 (17.9)	4 (3.7)	107 (20.9)	<0.0001	0.69, 0.505
ANA	398 (64.3)	47 (43.5)	351 (68.7)	<0.0001	0.61, 0.025

Variable	Sample (*n* = 619)	LEP Yes (*n* = 15)	LEP No (*n* = 604)	*P*
Sex (F), *n* (%)	493 (79.6)	12 (80.0)	481 (79.6)	1.000
Age at onset, (mean ± years)	45.2 ± 1.2	40.0 ± 9.3	45.3 ± 1.3	0.218
Systemic (YES), *n* (%)	160 (25.8)	2 (13.3)	158 (26.2)	0.376
ENA	230 (37.2)	4 (26.7)	226 (37.4)	0.590
anti-Ro/SSA	191 (30.9)	3 (20.0)	188 (31.1)	0.572
anti-La/SSB	58 (9.4)	1 (6.7)	57 (9.4)	1.000
anti-Sm	41 (6.6)	1 (6.7)	40 (6.6)	1.000
anti-RNP	30 (4.8)	1 (6.7)	29 (4.8)	0.530
anti-dsDNA	111 (17.9)	3 (20.0)	108 (17.9)	0.740
ANA	398 (64.3)	15 (100.0)	383 (63.4)	0.002

ANA (OR = 0.61, $P = 0.025$). Patients with vs. those without ICLE had a lower prevalence of ENA (22.2% vs. 40.3%) and ANA (43.5% vs. 68.7%). None of the patients with ICLE fulfilled ACR criteria for SLE.

SCLE SCLE was demonstrated in 18.6% ($n = 115$) patients. SCLE was significantly associated with ENA ($P < 0.0001$), anti-Ro/SSA ($P < 0.0001$), anti-La/SSB ($P < 0.0001$), anti-Sm ($P = 0.036$) and anti-RNP ($P = 0.050$). Even after the multivariate logistic regression analysis, adjusting for covariates significantly associated with SCLE and autoantibodies, SCLE resulted to be strongly associated with ENA (OR = 5.19, $P < 0.0001$), anti-Ro/SSA (OR = 3.83, $P < 0.0001$), anti-Sm (OR = 2.95, $P = 0.004$) and anti-RNP (OR = 3.18, $P = 0.007$).

Patients with vs. those without SCLE had a lower prevalence of SLE (12.2% vs. 29.0%) and had a higher prevalence of ENA (65.2 vs. 30.8), anti-Ro/SSA (53.9% vs. 25.6%), anti-La/SSB (18.3% vs. 7.3%), anti-Sm (11.3% vs. 5.6%) and anti-RNP (8.7% vs. 4.0%). Analogous evidences emerged for the polycyclic-annular variant of SCLE. Concerning the papulo-squamous variant of SCLE, it was significantly associated with ENA ($P = 0.012$) and anti-Ro/SSA ($P = 0.008$). Patients with vs. those without the papulo-squamous variant had a higher prevalence of positive ENA (66.7% vs. 36.3%) and anti-Ro/SSA (61.6% vs. 30.0%).

ACLE ACLE was diagnosed in 10.1% of cases ($n = 63$). ACLE was significantly associated with-SLE ($P < 0.0001$), anti-dsDNA ($P < 0.0001$) and ANA ($P < 0.0001$). Even after the multivariate logistic regression analysis, and adjusting for sex, ACLE resulted to be strongly associated with anti-dsDNA (OR = 6.0, $P < 0.0001$) and ANA (OR = 18.1, $P < 0.0001$). ACLE had a higher prevalence of systemic involvement (98.4% vs. 17.8%). All patients with ACLE but one had SLE. Analogous evidences emerged for both the localized and generalized forms of ACLE.

LE-non-specific skin lesions analyses

The most frequently reported LE-non-specific skin lesions were Raynaud's phenomenon ($n = 50$, 8.1%), diffuse alopecia ($n = 38$, 6.1%), livedo reticularis ($n = 23$, 3.7%), urticarial vasculitis ($n = 19$, 3.1%), palpable purpura ($n = 18$, 2.9%) and periungual telangiectasia ($n = 15$, 2.4%). Other LE-non-specific skin lesions such as thrombophlebitis, anetoderma, erythema multiforme, rheumatoid nodules, sclerodactyly, calcinosis cutis and mucinosis occurred in less than 2% of the 619 patients. Associations between autoantibodies and CLE subgroups were reported in Table 3.

A systemic involvement was found in 64% of patients with LE-non-specific skin lesions. Particularly, SLE was found in 80% ($n = 12$) patients with periungual telangiectasia, followed by patients with urticarial vasculitis (79%, $n = 15$), Raynaud's phenomenon (68%, $n = 34$), livedo reticularis (56.5%, $n = 13$), diffuse alopecia (50%, $n = 19$) and palpable purpura (50%, $n = 9$).

Raynaud's phenomenon Raynaud's phenomenon was found in 8.1% of patients ($n = 50$). Raynaud's phenomenon was significantly associated with SLE ($P < 0.0001$). Patients with vs. those without Raynaud's phenomenon had a higher prevalence of systemic involvement (68.0% vs. 22.1%).

Diffuse non-scarring alopecia Diffuse non-scarring alopecia was found in 6.1% of patients ($n = 38$). Diffuse non-scarring alopecia was significantly associated with SLE ($P = 0.001$): patients with vs. those without diffuse alopecia had a higher prevalence of systemic involvement (50.0% vs. 24.3%).

Livedo reticularis Livedo reticularis was found in 3.7% ($n = 23$) of patients. Livedo reticularis was significantly associated with SLE ($P = 0.007$), ENA ($P = 0.007$) and anti-Ro/SSA ($P = 0.036$). Even after the multivariate logistic regression, adjusting for systemic/non-systemic form, livedo reticularis resulted to be associated with ENA (OR = 2.80, $P = 0.023$) and anti-Ro/SSA, even if at the limit of significance (OR = 2.31, $P = 0.053$). Patients with vs. those without livedo reticularis had a higher prevalence of systemic involvement (56.5% vs. 24.7%), positive ENA (65.2% vs. 36.1%) and positive anti-Ro/SSA (52.2% vs. 30.0%).

Urticarial vasculitis Urticarial vasculitis was found in 3.1% of patients ($n = 19$). Urticarial vasculitis was associated with SLE ($P < 0.0001$): patients with vs. those without urticarial vasculitis had a higher prevalence of systemic involvement (79.0% vs. 24.2%).

Palpable purpura Palpable purpura was found in 2.9% of patients ($n = 18$). Palpable purpura was significantly associated with SLE ($P = 0.026$) and ANA ($P = 0.001$): patients with vs. those without palpable purpura had a higher prevalence of systemic involvement (50.0% vs. 25.1%). All patients with palpable purpura had a positive ANA.

Periungual telangiectasia Periungual telangiectasia was found in 2.4% of patients ($n = 15$). Periungual telangiectasia was significantly associated with SLE ($P < 0.0001$) and ANA ($P = 0.002$): patients with vs. those without periungual telangiectasia had a higher prevalence of systemic involvement (80.0% vs. 24.5%). All patients with periungual telangiectasia had a positive ANA.

Drug-induced CLE

Drug-induced (DI) LE was found in 3.2% patients, of whom, 60% had CCLE, 30% SCLE and 10% LE-non-specific

Table 3 Associations between autoantibodies and LE-non-specific skin lesions. Multivariate logistic regression was performed when covariates, such as age, sex or systemic/non-systemic lupus, resulted to be significantly associated with both the autoantibodies and LE-non-specific skin lesions; adjusted OR and *P* value were reported

Variable	Sample (*n* = 619)	Palpable purpura				Urticarial leukocytoclastic vasculitis				Raynaud's phenomenon			
		Yes (*n* = 18)	No (*n* = 601)	*P*	adjOR, *P*	Yes (*n* = 19)	No (*n* = 600)	*P*	adjOR, *P*	Yes (*n* = 50)	No (*n* = 569)	*P*	adjOR, *P*
Sex (F), *n* (%)	493 (79.6)	13 (72.2)	480 (79.9)	0.385		17 (89.5)	476 (79.3)	0.391		47 (94.0)	446 (78.4)	0.006	
Age at onset, (mean ± years)	45.2 ± 1.2	45.2 ± 10.4	45.2 ± 1.3	0.944		46.4 ± 6.7	45.1 ± 1.3	0.076		39.3 ± 4.0	45.7 ± 1.3	0.005	
Systemic (YES), *n* (%)	160 (25.8)	9 (50.0)	151 (25.1)	0.026		15 (79.0)	145 (24.2)	<0.0001		34 (68.0)	126 (22.1)	<0.0001	
ENA	230 (37.2)	6 (33.3)	224 (37.3)	0.809		5 (26.3)	225 (37.5)	0.470		25 (50.0)	205 (36.0)	0.066	
anti-Ro/SSA	191 (30.9)	3 (16.7)	188 (31.3)	0.299		3 (15.8)	188 (31.3)	0.208		21 (42.0)	170 (29.9)	0.081	
anti-La/SSB	58 (9.4)	1 (5.5)	57 (9.5)	1.000		1 (5.3)	57 (9.5)	1.000		8 (16.0)	50 (8.8)	0.122	
anti-Sm	41 (6.6)	1 (5.5)	40 (6.7)	1.000		1 (5.3)	40 (6.7)	1.000		5 (10.0)	36 (6.3)	0.365	
anti-RNP	30 (4.8)	0 (0.0)	30 (5.0)	1.000		0 (0.0)	30 (5.0)	1.000		5 (10.0)	25 (4.4)	0.085	
anti-dsDNA	111 (17.9)	7 (38.9)	104 (17.3)	0.028	1.89, 0.308	12 (63.2)	99 (16.5)	<0.0001	2.96, 0.061	18 (36.0)	93 (16.3)	0.002	0.85, 0.655
ANA	398 (64.3)	18 (100.0)	380 (62.2)	0.001		16 (84.2)	382 (63.7)	0.087		43 (86.0)	355 (62.4)	0.001	1.54, 0.349

Variable	Sample (*n* = 619)	Periungual telangiectasia			Livedo reticularis				Diffuse non-scarring alopecia		
		Yes (*n* = 15)	No (*n* = 604)	*P*	Yes (*n* = 23)	No (*n* = 472)	*P*	adjOR, *P*	Yes (*n* = 38)	No (*n* = 581)	*P*
Sex (F), *n* (%)	493 (79.6)	14 (93.3)	479 (79.3)	0.327	21 (91.3)	472 (79.2)	0.194		35 (92.1)	458 (78.8)	0.059
Age at onset, (mean ± years)	45.2 ± 1.2	34.6 ± 5.4	45.4 ± 1.3	0.008	41.5 ± 6.9	45.3 ± 1.3	0.330		38.5 ± 4.5	45.6 ± 1.3	0.008
Systemic (YES), *n* (%)	160 (25.8)	12 (80.0)	148 (24.5)	<0.0001	13 (56.5)	147 (24.7)	0.002		19 (50.0)	141 (24.3)	0.001
ENA	230 (37.2)	4 (26.7)	226 (37.4)	0.590	15 (65.2)	215 (36.1)	0.007	2.80, 0.023	16 (42.1)	214 (36.8)	0.604
anti-Ro/SSA	191 (30.9)	3 (20.0)	188 (31.1)	0.572	12 (52.2)	179 (30.0)	0.036	2.31, 0.053	12 (31.6)	179 (30.8)	1.000
anti-La/SSB	58 (9.4)	3 (20.0)	55 (9.1)	0.158	0 (0.0)	58 (9.7)	0.154		2 (5.3)	56 (9.6)	0.566
anti-Sm	41 (6.6)	0 (0.0)	41 (6.8)	0.615	4 (17.4)	37 (6.2)	0.058		3 (7.9)	38 (6.5)	0.733
anti-RNP	30 (4.8)	1 (6.7)	29 (4.8)	0.530	2 (8.7)	28 (4.7)	0.308		3 (7.9)	27 (4.6)	0.420
anti-dsDNA	111 (17.9)	5 (33.3)	106 (17.6)	0.162	11 (47.8)	100 (16.8)	0.001	2.70, 0.070	8 (21.1)	103 (17.7)	0.662
ANA	398 (64.3)	15 (100.0)	383 (63.4)	0.002	18 (78.3)	380 (63.8)	0.187		30 (79.0)	368 (63.3)	0.055

skin lesions. DI-LE was significantly associated with anti-histone antibodies ($P = 0.014$), while a negative association between DI-LE and anti-Ro/SSA antibodies ($P = 0.047$) was demonstrated.

ACR criteria

Photosensitivity was found in 47.8% of patients. It was associated with ENA ($P = 0.027$), anti-Ro/SSA ($P = 0.001$) and anti-dsDNA ($P = 0.014$) antibodies.

Arthritis was found in 18.9% of patients. It was associated with anti-dsDNA (OR = 4.2; $P = <0.0001$), ENA ($P = 0.003$) and anti-Ro/SSA ($P = 0.005$).

Oral ulcers were present in 8.2% ($n = 51$) of patients: 33.3% had CCLE, 22% ACLE, 15.6% SCLE and 29.1% had LE-non-specific skin lesions); 84.3% had a systemic involvement. Oral ulcers were associated with female sex ($P = 0.018$), and anti-dsDNA (OR = 4.2; $P < 0.0001$).

Renal disorder was found in 3.5% of patients. It was associated with SLE and anti-dsDNA ($P < 0.0001$).

Serositis was found in 3.4% of patients. They were associated with SLE and anti-RNP ($P = 0.015$).

Neurologic disorder was found in 2.1% of patients. It was associated with SLE anti-dsDNA ($P < 0.0001$).

Smoking, pregnancy and estrogens treatments

A total of 180 patients (29.6%) were smokers. A strong association between smoking and ICLE was demonstrated ($P = 0.002$). ICLE had the highest percentage of smokers ($n = 46$, 42.6%) in comparison with the other subtypes (CCLE 29.7%, ACLE 27.4%, SCLE 20.9%). On the contrary, a negative association between SCLE and smoking was found ($P = 0.024$). SCLE had the lowest percentage of smokers in comparison with the other subtypes (31.6% vs. 20.9%).

A strong association between smoking and CCLE patients with systemic involvement was also shown ($P = 0.013$). Patients with CCLE and systemic involvement were smokers more often than patients with CCLE without SLE (44.6% vs. 29.7%). LE-non-specific skin lesion, followed by cutaneous small vessel leukocytoclastic vasculitis and non-scarring alopecia. All these lesions appeared in the active phases of the disease. Similar data were found in a recent study on 260 patients with SLE.[11] On the contrary, Biazar *et al.* showed a higher incidence of diffuse alopecia followed by Raynaud's phenomenon. ACLE was the subtype which showed LE-non-specific lesions more often than SCLE, but the incidence of LE-non-specific skin lesions in ACLE was not significantly different from CCLE.[12]

Smoking is considered a risk factor for CLE,[13] especially for ICLE patients. In comparison with the literature data, our study showed a lower percentage of CLE smokers (29.6% vs. 47.2%). We confirmed the negative influence of smoking on ICLE patients, but we added some relevant details, such as the association between smoking and CCLE patients with systemic involvement and between smoking and SLE patients with LE-non-specific skin lesions. Thus, smoking represents a risk factor for CLE and SLE patients and smoking cessation programmes should be encouraged, especially in these subgroups of patients.

Previous epidemiologic studies have shown that patients with LE have an increased risk of comorbidity.[14–21] In our study, we found an increased risk of Sjögren syndrome, as well as endocrine and respiratory diseases in SLE patients, regardless the CLE subtypes. An association among cardiovascular and gastrointestinal diseases and age was shown; accordingly, patients with vs. those without such diseases were older.

Concerning oncological diseases, it has recently been shown that patients with SCLE[22] and, in few cases, with DLE[23] have a significantly increased cancer risk, especially for oral cancer, lymphomas, respiratory cancer and non-melanoma skin cancer.[23] In our study, we did not find any correlation among CLE and cancers. The only significant association was with age: elderly had a higher risk of cancers as it is shown in general population.[24]

Finally, no significant associations were demonstrated among rheumatic diseases and demographic and clinical characteristics of CLE patients. However, as our study was not prospective, we collected data just at LE diagnosis and data on long-term risk about associated diseases are not available.

Discussion

This paper represented the first Italian multicentre cross-sectional study on CLE.

According to previous studies,[12,25,26] we showed a prevalence of CCLE that was the most common CLE subtype and represented the 49% of all skin forms, followed by SCLE, ACLE and ICLE.

Concerning demographic features, our study confirmed some well-known associations.[27,28] Particularly, we found a clear predominance of female sex, as a whole and in the different skin subtypes. There was also a significant association between Raynaud's phenomenon and female gender. The female/male ratio was 3.9: 1 (range 2 : 1–5.8 : 1), in accordance with the literature data which indicates an overall female: male ratio between 1 : 1–6: 1.[29,30]

There was a statistically significant correlation between female sex and ANA antibodies ($P = 0.001$) and female sex and anti-dsDNA antibodies ($P = 0.006$). These data agree with those reported in the literature. A recent study on 308 Spanish patients with CLE,[30] stratified by gender, showed a prevalence of the female sex and a higher incidence of ANA positivity with higher values in females. Moreover, a study on 1002 patients with CLE showed a significant difference in gender, with a highest percentage of female sex in ACLE, followed by SCLE, CCLE and ICLE.[12]

The average age at diagnosis was 45.2 ± 1.2 years, similar to previously reported data (mean age 43.0 ± 15.9 years)[31–34]: confirming other studies, SCLE patients were older than the ones with the other subtypes of CLE (SCLE > CCLE > ICLE > ACLE).[12,27]

In our study, patients with SLE and cutaneous lesions were younger than those without a systemic involvement (42.0 ± 1.3 vs. 46.3 ± 0.7). These data agree with those of the literature as SLE is most common in patients below 50 years.[35] Particularly, early-SLE (age <50 years) seems to have cutaneous manifestations more often than late-SLE (age > 50 years). These differences seem to be associated with many factors including age, immunosenescence, environment and immunogenetics.[36]

Concerning autoantibodies, we focused on ANA, ENA (including anti-Ro/SSA, La-SSB, anti-Sm, anti-RNP, anti-histone) and anti-dsDNA antibodies.

These autoantibodies play a key role in the diagnosis of SLE as they are included both in ACR[8,9] and *Systemic Lupus International Collaborating Clinic* (SLICC) criteria.[37] They should therefore be measured in all subjects with CLE to exclude a systemic involvement. In our study, we considered only ACR criteria since some cases were diagnosed before the introduction of SLICC criteria.

ANA autoantibodies represented the criterion most frequently encountered both in CLE and SLE patients (24.4% and 39.9% of cases, respectively). These antibodies are useful and important complementary tools for the diagnosis and follow-up of patients with several autoimmune diseases.[38]

According to the literature, ANA positivity was present with varied percentage depending on the skin subtype, without any specificities but, as in our study, the distribution in the different subtypes was the same: ACLE > SCLE > CCLE > ICLE.[7,12]

Our study confirmed a higher prevalence of ENA and anti-Ro/SSA antibodies in SCLE patients and in patients with photosensitivity. Interestingly, a strong association between SCLE and anti-Sm (OR = 2.95, $P = 0.004$), as well as between SCLE and anti-RNP (OR = 3.18, $P = 0.007$) antibodies was found, regardless the presence of systemic involvement.

Moreover, patients with vs. those without SCLE had a lower prevalence of SLE (12.2 vs. 29.0%). Even if in the past SCLE was supposed to be associated with systemic involvement in a high percentage of cases (up to 50%),[39] recently it has been demonstrated that patients with SCLE are less likely to have SLE with percentage of about 20%, more similar to our results.[40]

A correlation among anti-dsDNA antibodies and SLE was also found.[41] Interestingly, a statistically significant correlation was found between anti-dsDNA antibodies and oral ulcers. Many studies have emphasized the importance of early diagnosis of oral lesions to recognize patients with SLE as a systemic disease.[42,43] In our experience, oral ulcers were associated more often with CCLE and with LE-non-specific skin lesions and with female sex. No associations with smoking were found.

In our analyses, LE non-specific skin lesions were found in 21.1% of patients. LE non-specific skin lesions usually occur with increased frequency in SLE patients and they are often useful indicators of systemic disease activity.[30] In an Italian study by Cardinali *et al.*,[29] LE-non-specific skin lesions were found in 31% of patients and always in association with systemic involvement. Raynaud's phenomenon was the most common LE-non-specific skin lesion, followed by cutaneous small vessel leukocytoclastic vasculitis and non-scarring alopecia. All these lesions appeared in the active phases of the disease. Similar data were found in a recent study on 260 patients with SLE.[11] On the contrary, Biazar *et al.* showed a higher incidence of diffuse alopecia followed by Raynaud's phenomenon. ACLE was the subtype which showed LE-non-specific lesions more often than SCLE, but the incidence of LE-non-specific skin lesions in ACLE was not significantly different from CCLE.[12]

Smoking is considered a risk factor for CLE,[13] especially for ICLE patients. In comparison with the literature data, our study showed a lower percentage of CLE smokers (29.6% vs. 47.2%). We confirmed the negative influence of smoking on ICLE patients, but we added some relevant details, such as the association between smoking and CCLE patients with systemic involvement and between smoking and SLE patients with LE-non-specific skin lesions. Thus, smoking represents a risk factor for CLE and SLE patients and smoking cessation programmes should be encouraged, especially in these subgroups of patients.

Previous epidemiologic studies have shown that patients with LE have an increased risk of comorbidity.[14–21] In our study, we found an increased risk of Sjögren syndrome, as well as endocrine and respiratory diseases in SLE patients, regardless the CLE subtypes. An association among cardiovascular and gastrointestinal diseases and age was shown; accordingly, patients with vs. those without such diseases were older.

Concerning oncological diseases, it has recently been shown that patients with SCLE[22] and, in few cases, with DLE[44] have a significantly increased cancer risk, especially for oral cancer, lymphomas, respiratory cancer and non-melanoma skin cancer.[23] In our study, we did not find any correlation among CLE and cancers. The only significant association was with age: elderly had a higher risk of cancers as it is shown in general population.[24]

Finally, no significant associations were demonstrated among rheumatic diseases and demographic and clinical characteristics of CLE patients. However, as our study was not prospective, we collected data just at LE diagnosis and data on long-term risk about associated diseases are not available.

Conclusion

The present study provides important information on epidemiologic data in a cohort of 619 CLE patients. We confirmed some known associations between autoantibodies and CLE subtypes, adding some relevant details for diagnostic purposes, such as the association between anti-dsDNA antibodies and oral ulcers, regardless a systemic involvement. As oral ulcers are often associated with SLE, we suggest to strictly monitor these patients to evaluate a possible systemic evolution. The same conclusions

can be drawn about LE-non-specific skin lesions that were significantly associated with SLE.

Moreover, as smoking has a higher prevalence among CLE patients, we suggest to discuss with CLE patients its role in inducing or worsening skin and systemic lesions, to interrupt smoking as soon as possible.

Interestingly, our results showed that patients with SCLE had a lower prevalence of SLE compared to CCLE and ACLE subtypes. None of ICLE patients showed a systemic involvement.

Finally, patients with CLE have a higher incidence of associated diseases, such as thyroid diseases, especially in cases of systemic involvement. Thus, we suggest to evaluate all the patients with CLE to check concomitant comorbidities at the time of diagnosis.

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