

# Clusters of Clinical and Immunologic Features in Systemic Lupus Erythematosus: Analysis of 600 Patients From a Single Center

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**Objective:** To analyze the prevalence and characteristics of the main clinical, hematologic, and immunologic manifestations of systemic lupus erythematosus (SLE) in a cohort of 600 consecutive patients from a single center, and to determine the specific characteristics of organ involvement in a homogeneous SLE population.

**Methods:** Patients were consecutively seen in our department either as inpatients or outpatients between 1980 and 2001. All had documented medical histories and underwent a medical interview as well as a routine general physical examination. Clinical and serologic characteristics of all patients were consecutively collected in a protocol form.

**Results:** The final cohort (survival cohort) consisted of 533 (89%) women and 67 (11%) men (female to male ratio, 8:1), with an average of 29 new patients per year. Mean age at onset of symptoms attributable to the disease was 31 years (range, 5 to 84 years) and mean age at the time of diagnosis of SLE was 33 years (range, 6 to 85 years). The most frequent SLE involvement was articular involvement, found in 498 patients (83%), followed by hematologic involvement in 451 patients (75%), specific SLE cutaneous involvement in 354 patients (59%), constitutional features in 252 patients (42%), and nephropathy in 203 patients (34%). Patients enrolled in the protocol before 1991 had a higher frequency of central nervous system (CNS) involvement (27% vs 10%,  $P < .001$ ), thrombotic events (17% vs 9%,  $P = .003$ ), and abnormal hematologic parameters (85% vs 66%,  $P < .01$ ), but a lower frequency of articular involvement (79% vs 86%,  $P = .038$ ) than those enrolled after 1991. The following were observed associations: specific SLE cutaneous involvement was associated

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0049-0172/04/3304-0001\$30.00/0

doi:10.1053/S0049-0172(03)00133-1

with anti-Sm antibodies; renal involvement with hemolytic anemia and anti-double-stranded DNA antibodies; CNS involvement with thrombocytopenia and immunoglobulin G-anticardiolipin; thrombotic events with low total hemolytic complement, immunoglobulin G-anticardiolipin, and lupus anticoagulant; and myositis with anemia and anti-ribonucleoprotein antibodies.

**Conclusion:** This large study, performed in a single center, has shown cluster associations between certain clinical, hematologic, and immunologic features of SLE, reflecting specific patterns of disease expression. The accurate evaluation of clinical features and laboratory markers at disease diagnosis and during evolution may improve the clinical treatment of SLE patients.

*Semin Arthritis Rheum 33:217-230. © 2004 Elsevier Inc. All rights reserved.*

**INDEX WORDS:** Systemic lupus erythematosus; clinical manifestations; immunologic features; autoantibodies.

**S**YSTEMIC LUPUS erythematosus (SLE) is considered the most clinically and serologically diverse autoimmune disease because it may affect any organ and display a broad spectrum of clinical manifestations (1). In addition, SLE is defined by the almost-invariable presence in the blood of antibodies directed against 1 or more cell components. Certain clinical features are associated with the presence of specific antinuclear antibodies (ANA) and genetic markers, and contribute to the heterogeneity of the clinical patterns of SLE expression.

It is now thought that SLE can be divided into more homogeneous subsets with pathogenic, therapeutic, or prognostic significance (2-6). However, the characterization of the different patterns of SLE expression is complex, especially when small series of patients or cohorts from different ethnicities are analyzed. The aim of this study was to analyze the prevalence and characteristics of the main clinical, hematologic, and immunologic manifestations of SLE in a cohort of 600 consecutive patients from a single center, to determine the specific characteristics of organ/system involvement in a homogeneous SLE population.

## METHODS

### *Patient Selection*

Patients were consecutively seen in our unit either as inpatients or outpatients between 1980 and 2001. All had documented medical histories and underwent a medical interview as well as a general physical examination. Clinical and serologic characteristics of all patients were consecutively collected in a protocol form. Salient features

included were 1) age at onset of the disease, defined as the initial manifestation clearly attributable to SLE; 2) age at diagnosis, defined as the age when the patient fulfilled 4 or more of the 1997 revised American College of Rheumatology criteria for the classification of SLE (7); 3) age at protocol entry; 4) clinical manifestations at disease onset; and 5) cumulative clinical, hematologic, and immunologic manifestations (from disease onset until protocol entry).

### *Definition of Organ/System Involvement*

1. Specific cutaneous SLE involvement: presence of malar rash (fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds), cutaneous discoid lesions (raised erythematosus patches with adherent keratotic scaling and follicular plugging), subacute cutaneous lesions (photosensitive, nonscarring dermatitis appearing as either papulosquamous or annular lesions), and/or lupus panniculitis. Other cutaneous features were considered nonspecific findings of SLE.
2. Articular involvement: presence of nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion.
3. Renal involvement: 1) persistent proteinuria  $>0.5$  g/d; 2) microhematuria and/or cellular casts (red cell, hemoglobin, granular, tubular, or mixed); or 3) otherwise-unexplained elevation of serum creatinine  $>75$   $\mu\text{mol/L}$ . Renal biopsies were reviewed by 2 pathologists and categorized according to the modified classification proposed by the World Health

- Organization (8): type I, normal kidney; type II, mesangial glomerulonephritis (presence of mesangial deposits with mesangial hypercellularity); type III, focal proliferative glomerulonephritis (inflammatory changes affecting some glomeruli but leaving other uninvolved); type IV, diffuse proliferative glomerulonephritis (virtually all glomeruli show inflammation); type V, membranous nephropathy (diffuse generalized thickening of the capillary wall and predominant intramembranous and/or subepithelial electro-dense deposits, without inflammatory changes).
4. Central nervous system (CNS) involvement, seizures, psychosis, chorea, transverse myelitis, cranial neuritis or migraine, in the absence of drugs or known metabolic disturbances, (eg, uremia, ketoacidosis, or electrolyte imbalance). Peripheral neuropathies were excluded.
  5. Thrombotic events: 1) clinically diagnosed venous and/or arterial thrombosis, confirmed by complementary tests; or 2) cardiac valvulopathy.
  6. Lung involvement: 1) persistent cough and/or dyspnea, with chronic diffuse interstitial infiltrates on radiographs, altered pattern on pulmonary function studies, and/or evidence of pulmonary alveolitis/fibrosis in computed tomography scan; or 2) pulmonary hypertension. Pulmonary edema, adult respiratory distress syndrome, infectious pneumonia, malignancy, and granulomatous disease must be excluded.
  7. Muscle involvement: muscle weakness accompanied by elevation of muscle enzymes, with electromyography or biopsy findings characteristic of myositis.
  8. Other features:
    - Constitutional manifestations: 1) fever (temperature >38°C or 100°F in the absence of infection); or 2) adenopathy (enlarged nodes >0.5 cm in the cervical region, axilla, or inguinal area in the absence of infection or malignancy).
    - Cutaneous/vascular features: 1) Raynaud phenomenon (blanching of the fingers, toes, ears, nose, tongue, induced by exposure to cold, stress, or both); 2) livedo reticularis (reddish or cyanotic discoloration of the skin with a reticular pattern); or 3) cutaneous vasculitis.

- Hematologic features: 1) hemolytic anemia (decrease  $\geq 3\text{g/dL}$  in blood hemoglobin, coincident with a rise in conjugated bilirubin and a reticulocyte count >5% at the time of the hemolytic episode); 2) thrombocytopenia— $<150,000/\mu\text{L}$  in the absence of offending drugs; c) leukopenia  $< 4,000/\mu\text{L}$ ; 4) elevated erythrocyte sedimentation rate (ESR) ( $>50$  mm/h); and 5) anemia (hemoglobin  $<10$  g/dL).

*Laboratory Studies*

ANA were determined by indirect immunofluorescence by using mouse liver and Hep-2 cells as substrate. Anti-double-stranded DNA (dsDNA) antibodies were determined by Farr ammonium sulfate precipitation technique and indirect immu-

**Table 1: Cumulative Clinical Features Since the SLE Onset Until the Entry to the Protocol in 600 Patients with SLE**

Cumulative Clinical Manifestations	Number of Patients Affected	%
Arthritis	498	83
Malar rash	326	54
Fever	249	42
Photosensitivity	246	41
Nephropathy	203	34
Oral ulcers	179	30
Serositis	167	28
Raynaud phenomenon	134	22
Alopecia	107	18
Cutaneous vasculitis	77	13
Seizures/psychosis	74	12
Hemolytic anemia	50	8
Migraine	50	8
Subacute cutaneous lesions	48	8
Valvulopathy	45	8
Thrombosis	42	7
Myositis	39	7
Discoid lesions	33	6
Livedo reticularis	27	5
Lung involvement	21	4
Myocardium	6	2
Lymphadenopathy	8	1
Chorea	3	0.5
Liver involvement	2	0.3

**Table 2: Hematologic and Immunologic Findings in Patients With SLE**

Parameter	Positive*	Tested	%
Elevated ESR	131	592	22
Anemia	112	550	20
Leukopenia	396	600	66
Lymphopenia	492	600	82
Thrombocytopenia	183	600	31
ANA	596	600	99
High anti-dsDNA	537	600	90
Ro/SS-A	128	564	23
La/SS-B	44	567	8
Sm	75	600	13
U1-sn RNP	75	540	14
RF	69	565	12
Hypocomplementemia	279	583	48
Low complement C3	182	583	31
Low complement C4	222	583	38
Low total CH50	251	583	43
Antiphospholipid antibodies	137	561	24
IgG aCL	82	561	15
IgM aCL	51	561	9
LA	84	561	15

\*Present or positive in some determination since SLE onset until entry into the protocol.

nofluorescence with *Crithidia Lucilia* as substrate. Precipitating antibodies to extractable nuclear antigens, including Ro/SS-A, La/SS-B, U1-sn ribonucleoprotein (RNP), and Sm, were detected by counterimmunoelectrophoresis using calf and rabbit thymus and human spleen extracts. Rheumatoid

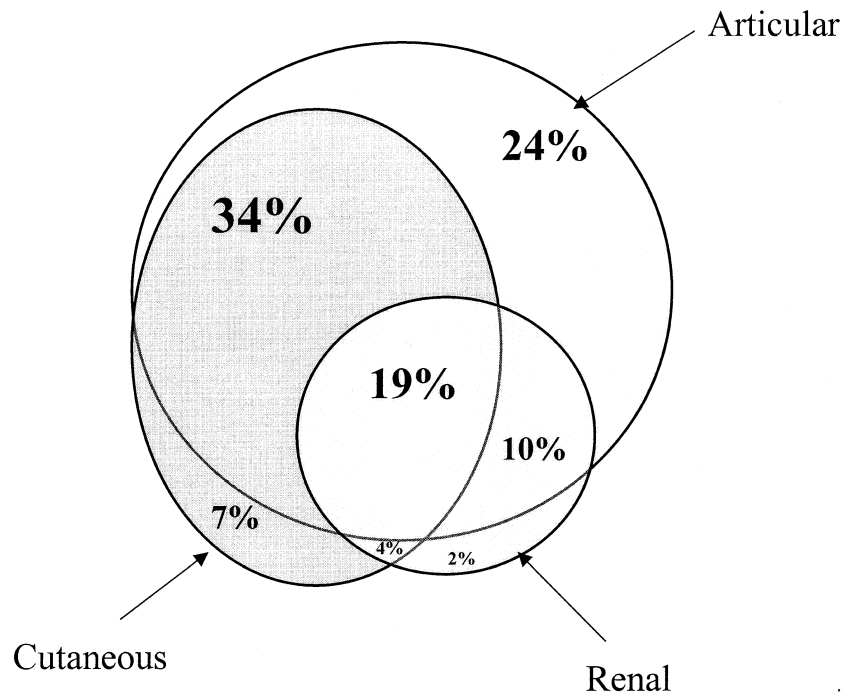
factor (RF) was detected by latex test. Anticardiolipin (aCL) antibodies of the immunoglobulin (Ig) G and IgM isotypes were measured by an enzyme-linked immunosorbent assay method as previously described (9,10). Lupus anticoagulant (LA) activity was detected by coagulation assays (11).

**Table 3: Prevalence and Epidemiologic Data of 600 Patients With SLE, According to the Different Organ/System Involvements**

Organ/System Involvement*	Patients (%)	Sex, Female (%)	Mean Age at SLE Diagnosis	Evolution (mo)
Articular	498 (83)	91	32.0 ± 0.7†	75.0 ± 4.0
Hematologic	451 (75)	84	32.4 ± 0.7	72.6 ± 3.9
Specific SLE cutaneous	354 (59)	91	29.9 ± 0.7	76.9 ± 6.0
Constitutional	252 (42)	91	32.9 ± 1.0	81.0 ± 5.7
Renal	203 (34)	87	28.7 ± 0.9	65.9 ± 5.2
Cutaneous/vascular	193 (32)	89	30.5 ± 0.9‡	62.5 ± 5.1§
CNS	107 (18)	94†	30.1 ± 1†	97.1 ± 8.7§
Thrombotic	77 (13)	84	30.8 ± 1.7	92.5 ± 11.4†
Muscular	39 (6)	90	36.2 ± 2.9	66.2 ± 10.2
Pulmonary	21 (3)	81	34.3 ± 3.4	49.0 ± 16.4

\*See definitions in the Methods section.

Statistical significance in the multivariate analysis † $P < .05$ , ‡ $P < .01$ , § $P < .005$ , || $P < .001$ , in comparison with the entire cohort.

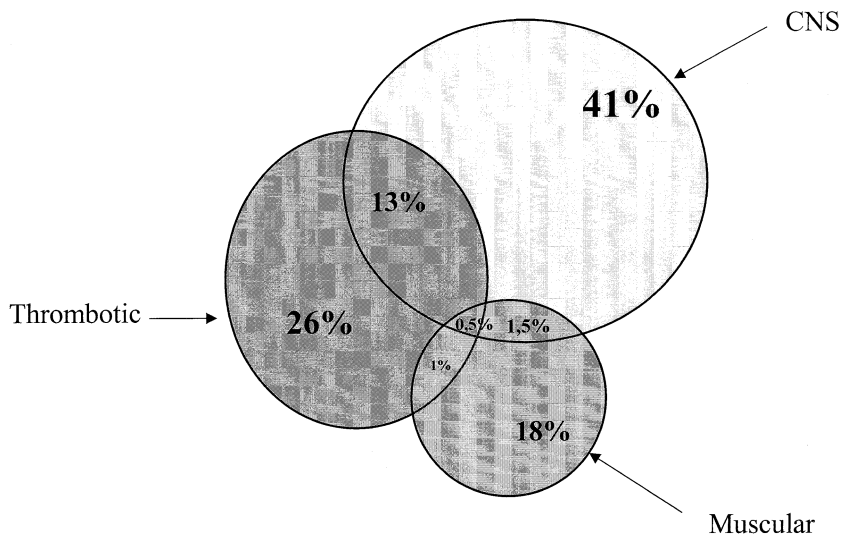


**Fig 1. Overlap between articular, cutaneous, and renal involvement in 600 patients with SLE.**

*Statistical Analysis*

Conventional chi-square and Fisher exact tests were used for analyzing qualitative differences, and the Student *t* test was used for comparison of means in large, independent samples of similar variance; *P* < .05 indicated statistical significance. When several independent variables appeared to

have statistical significance in the univariate analysis, a logistic regression test was performed to rule out possible competing correlations of variables. Results of the analysis of continuous variables are indicated as mean ± SEM. The statistical analysis was performed with the SPSS program (SPSS, Chicago, IL).



**Fig 2. Overlap between CNS, thrombotic, and muscular events in 600 patients with SLE.**

**Table 4: Prevalence of the Different Organ/System Involvement of Patients Entered into the Protocol Before and After 1991**

Organ/System Involvement†	Data at Protocol Entry		P Value
	1980-1990, n (%)	1991-2001, n (%)	
Articular	221 (79)	277 (86)	.038*
Specific SLE cutaneous	163 (59)	191 (59)	1.000
Renal	104 (37)	99 (31)	.100
CNS	74 (27)	33 (10)	<.001*
Thrombotic	48 (17)	29 (9)	.003*
Muscular	24 (9)	15 (5)	.067
Pulmonary	14 (5)	7 (2)	.074
Other cutaneous-vascular	96 (35)	97 (30)	.256
Constitutional	128 (46)	124 (38)	.068
Hematologic	237 (85)	214 (66)	<.001*

\*Statistical significance in the multivariate analysis, in comparison with the entire cohort.

†See definitions in the Methods section.

## RESULTS

### General Characteristics

The final cohort (survival cohort) consisted of 533 (89%) women and 67 (11%) men (female to male ratio, 8:1) enrolled in a 22-year period (average, 29 new patients per year). Mean age at onset of symptoms attributable to the disease was  $31.1 \pm 0.6$  years (range, 5 to 84 years); mean age at the time of diagnosis of SLE was  $32.7 \pm 0.6$  years (range, 6 to 85 years). Mean age at protocol entry was  $37.2 \pm 0.6$  years (range, 8 to 85 years). Evolution of the disease from the onset of symptoms to protocol entry ranged from 6 to 648 months (mean,  $73.9 \pm 3.6$  months).

The prevalence of the main clinical manifestations accumulated from the onset of symptoms to protocol entry is summarized in Table 1. The frequency of the clinical features included in the current SLE classification criteria were arthritis in 498 (83%) patients, malar rash in 326 (54%) patients, photosensitivity in 246 (41%) patients, nephropathy in 203 (34%) patients, oral ulcers in 179 (30%) patients, serositis in 167 (28%) patients, seizures/psychosis in 74 (12%) patients, hemolytic anemia in 50 (8%) patients, and discoid lesions in 33 (6%) patients. Clinical features not included in the SLE criteria were detected in a substantial number of patients: fever in 249 (42%) patients,

**Table 5: Hematologic Features (Present in Some Determination Since SLE Onset Until Entry into the Protocol) in Patients With SLE According to the Main Organ/System Involvement**

	Organ/System Involvement						
	Articular (N = 498)	Specific Cutaneous SLE (N = 354)	Renal (N = 203)	CNS (N = 107)	Thrombotic (N = 77)	Muscular (N = 39)	Pulmonary (N = 21)
ESR >50 mm/h	110/492 (22)	69/350 (20)	55/201 (29)	20 (19)	19 (25)	14 (36)	4 (19)
Anemia (Hb <10 g/dL)	93/489 (19)	61/349 (18)	62/200 (31)§	14 (13)	19 (25)	15 (39)*	10 (48)‡
Hemolytic anemia	39 (8)	29 (8)	30 (15)†	10 (9)	14 (18)‡	2 (5)	2 (10)
Leukopenia	333 (66.9)	225 (64)	143 (70)	76 (71)	54 (70)	31 (80)	13 (62)
Lymphopenia	409 (82)	284 (80)	178 (88)	91 (85)	68 (88)	34 (87)	19 (91)
Thrombocytopenia	149 (30)	98 (28)	66 (33)	46 (43)‡	35 (46)	11 (28)	8 (38)

NOTE. All values in parentheses are percentages.

Statistical significance in the multivariate analysis: \* $P < .05$ , † $P < .01$ , ‡ $P < .005$ , § $P < .001$  in comparison with the entire cohort.

**Table 6: Immunologic Features (Positive Result in Some Determination Since SLE Onset Until Entry into the Protocol) in Patients With SLE According to the Main Organ/System Involvement**

	Articular Involvement (N = 498)	Specific SLE Cutaneous Involvement (N = 354)	Renal Involvement (N = 203)	CNS Involvement (N = 107)	Thrombotic Involvement (N = 77)	Muscular Involvement (N = 39)	Pulmonary Involvement (N = 21)
ANA	496 (100)	350 (99)	203 (100)	106 (99)	77 (100)	38 (97)	21 (100)
High dsDNA	446 (90)	309 (88)	197 (97)†	97 (99)	-72 (94)	37 (95)	20 (95)
Ro/SS-A	105/471 (21)	87/338 (26)	35/194 (18)	21/104 (20)	19 (25)	6 (15)	7 (35)
La/SS-B	39/471 (8)	35/338 (10)	13/194 (7)	9/104 (9)	4 (5)	3 (8)	4 (19)
Sm	64 (13)	55 (16)*	30 (15)	16 (15)	11 (15)	8 (21)	2 (10)
RNP	66/471 (14)	50/338 (15)	25/193 (13)	16/103 (16)	13 (17)	11 (28)†	2 (10)
RF	62/470 (13)	34/333 (10)	25/194 (13)	9/104 (9)	11 (15)	9 (23)	2 (10)
Low C3	155/485 (32)	120/344 (35)*	94/199 (47)	27 (26)	31 (40)	11 (28)	4 (19)
Low C4	192/485 (40)	139/344 (40)	109/199 (55)	33 (31)	37 (48)	17 (44)	7 (35)
Low CH50	214/485 (44)	153/344 (5)	120/199 (60)	44 (42)	45 (58)*	20 (51)	7 (35)
IgG aCL	72/465 (16)	48/335 (14)	35/194 (18)	22/104 (21)*	35 (46)§	4 (10)	3/19 (16)
IgM aCL	43/465 (9)	27/335 (8)	19/194 (10)	11/104 (11)	18 (23)	2 (5)	1/19 (5)
LA	68/467 (15)	47/336 (14)	32/193 (17)	22/105 (21)*	40 (53)§	1 (3)	5/20 (25)

NOTE. All values in parentheses are percentages.

Statistical significance in the multivariate analysis: \* $P < .05$ , † $P < .01$ , ‡ $P < .005$ , § $P < .001$  in comparison with the entire cohort.

Raynaud phenomenon in 134 (22%) patients, alopecia in 107 (18%) patients, and cutaneous vasculitis in 77 (13%) patients.

#### *Hematologic and Immunologic Profile*

The main hematologic and immunologic features are summarized in Table 2. Elevated ESR, arbitrarily defined as  $>50$  mm/h, was detected in 131 of 592 (22%) patients, anemia (arbitrarily defined as hemoglobin  $<10$  g/dL) in 112 of 550 (19%) patients, leukopenia ( $<4000/\mu\text{L}$ ) in 396 (66%) patients, lymphopenia ( $<1000/\mu\text{L}$ ) in 492 (82%) patients, and thrombocytopenia (platelet count  $<150/\mu\text{L}$ ) in 183 (31%) patients.

A positive result of ANA was found in 596 (99.5%) patients before enrollment in the protocol. High anti-dsDNA levels were found in 537 (90%) patients. Anti-Ro/SS-A antibodies were found in 128 of 569 (23%) patients, anti-La/SS-B antibodies were found in 44 of 567 (8%) patients, anti-U1-snRNP antibodies were found in 75 of 540 (14%) patients, and anti-Sm antibodies were found in 75 (13%) patients. RF was found in 69 of 565 (12%) patients. Hypocomplementemia was detected in 279 of 583 (48%) patients: low complement C3 levels were found in 182 (31%) patients, low complement C4 levels in 222 (38%) patients, and low total hemolytic complement (CH50) levels in 251 (43%) patients. Antiphospholipid antibodies

were analyzed in 561 patients: positive titers of IgG-aCL were detected in 82 (15%) patients, IgM-aCL in 51 (9%) patients, and LA activity in 84 (15%) patients.

#### *Characterization of the Organ/Systems Involvement*

The prevalence of organ/system involvement is summarized in Table 3. The most frequent involvement was arthritis in 498 (83%) patients, followed by hematologic involvement in 451 (75%) patients, specific SLE cutaneous features in 354 (59%) patients, constitutional features in 252 (42%) patients, and nephropathy in 203 (34%) patients. Most patients had more than 1 organ/system involved. Using a visual approach with Ven diagrams, we found a great overlap among cutaneous, articular, and renal involvement (Fig 1). In contrast, we found less overlap among CNS, thrombotic, and muscular events (Fig 2). We also analyzed the prevalence of various organ/system involvement by date of entry into the protocol (before and after 1991) (Table 4). Patients entered in the 1980s had a higher frequency of CNS involvement (27% vs 10% in those entered before 1991,  $P < .001$ ), thrombotic events (17% vs 9%,  $P = .003$ ), and abnormal hematologic parameters (85% vs 66%,  $P < .01$ ), but a lower frequency of articular involvement (79% vs 86%,  $P = .038$ ).

**Table 7: Cumulative Prevalence of the Main Clinical SLE Manifestations in Previous Series**

Author	Year	Patients		Fever	Articular Involvement	Myocarditis
		(n)	Country			
Harvey et al (12)	1954	105	USA	90 (86)	94 (90)	42 (40)
Dubois et al (13)	1964	520	USA	437 (84)	478 (92)	42 (8)
Estes et al (14)	1971	140	USA	NR	133 (95)	11 (8)
Fries et al (15)	1975	193	USA	106 (55)	102 (53)	NR
Tan et al (7)	1982	177	USA	NR	152 (86)	NR
Hochberg et al (16)	1985	150	USA	NR	114 (76)	NR
Pistiner et al (17)	1991	464	USA	190 (41)	422 (91)	56 (12)
Vlachoyiannopoulos et al (18)	1993	292	Greece	133 (46)	120 (41)	NR
Cervera et al (2)	1993	1000	European countries	520 (52)	840 (84)	NR
Petri et al (19)	1997	574	USA	NR	NR	NR
Wang et al (20)	1997	539	Malaysia, China, India	NR	272 (50)	NR
Alarcón et al (21)	2002	555	USA	NR	489 (88)	NR
Present series	2002	600	Spain	249 (42)	498 (83)	6 (2)
Total	—	5309	—	1725 (54)	3714 (78)	157 (9)

NOTE. All values in parentheses are percentages.

Abbreviation: NR, not registered.

**Articular involvement.** Four hundred ninety-eight (83%) patients had articular involvement. In 384 (64%) patients, this feature was an initial manifestation of the SLE. Age at SLE diagnosis in these patients was  $32 \pm 0.7$  years, and there were 454 women and 44 men (ratio, 10:1). When compared with patients without articular involvement ( $n = 102$ ), those with arthritis had a higher prevalence of female sex (91% vs 78%,  $P < .001$ ), fever (44% vs 28%,  $P < .005$ ), oral ulcers (32% vs 21%,  $P < .05$ ), alopecia (20% vs 8%,  $P < .005$ ), and Raynaud phenomenon (24% vs 14%,  $P < .05$ ) in univariate analysis. However, only fever and alopecia were significant independent variables on multivariate analysis (Tables 5 and 6).

**Specific SLE cutaneous involvement.** Three hundred fifty-four (59%) patients had specific SLE cutaneous features. In 342 (57%) patients, these features were an initial manifestation of SLE. Age at SLE diagnosis in these patients was  $29.9 \pm 0.7$  years, and there were 321 women and 33 men (ratio, 10:1). When compared with patients without specific SLE cutaneous involvement ( $n = 246$ ), those with cutaneous involvement had a higher prevalence of oral ulcers (36% vs 21%,  $P < .001$ ), alopecia (23% vs 10%,  $P < .01$ ), anti-Sm (16% vs

8%,  $P < .01$ ), and low complement C3 (35% vs 26%,  $P < .05$ ) in univariate analysis. However, only oral ulcers, alopecia, and anti-Sm were significant independent variables on multivariate analysis (Tables 5 and 6).

**Renal involvement.** Two hundred three (34%) patients had renal involvement. In 72 (12%) patients, this feature was an initial manifestation of SLE. Age at SLE diagnosis in these patients was  $28.7 \pm 0.9$  years, and there were 177 women and 26 men (ratio, 7:1). Renal biopsy was performed in 171 patients. Type I nephropathy was diagnosed in 13 patients (8%), type II in 31 (18%) patients, type III in 33 (19%) patients, type IV in 68 (40%) patients, and type V in 26 (15%) patients.

When compared with patients without renal involvement ( $n = 397$ ), those with nephropathy had a higher prevalence of fever (55% vs 35%,  $P < .001$ ), cutaneous vasculitis (18% vs 10%,  $P < .01$ ), serositis (37% vs 23%,  $P < .001$ ), elevated ESR (29% vs 18%,  $P < .005$ ), anemia (31% vs 13%,  $P < .001$ ), hemolytic anemia (15% vs 5%,  $P < .001$ ), high anti-dsDNA (97% vs 86%,  $P < .001$ ), low complement C3 (47% vs 23%,  $P < .001$ ), low complement C4 (55% vs 29%,  $P < .001$ ), and low CH50 (60% vs 34%,  $P < .001$ ) in univariate

**Table 7: Cumulative Prevalence of the Main Clinical SLE Manifestations in Previous Series (Cont'd)**

Malar Rash	Oral/Nasal		Photosens	Raynaud	Discoid Lesions	CNS Damage	Renal Involvement
	Alopecia	Ulcers					
41 (39)	3 (3)	15 (14)	12 (11)	11 (10)	NR	NR	68 (65)
296 (57)	109 (21)	47 (9)	172 (33)	94 (18)	150 (29)	135 (26)	239 (46)
55 (39)	55 (39)	10 (7)	NR	29 (21)	13 (9)	83 (59)	74 (53)
19 (10)	87 (45)	35 (18)	NR	33 (17)	19 (10)	NR	90 (47)
101 (57)	46 (26)	48 (27)	76 (43)	51 (29)	32 (18)	21 (12)	106 (60)
92 (61)	68 (45)	35 (23)	68 (45)	66 (44)	23 (15)	59 (39)	NR
158 (34)	144 (31)	88 (19)	172 (37)	116 (25)	107 (23)	NR	144 (464)
120 (41)	100 (34)	76 (26)	116 (40)	92 (32)	100 (34)	36 (12)	85 (29)
580 (58)	NR	240 (24)	450 (45)	340 (34)	100 (10)	270 (27)	390 (39)
331 (58)	317 (55)	219 (38)	335 (58)	NR	162 (28)	NR	319 (56)
410 (76)	NR	185 (34)	222 (41)	NR	30 (6)	123 (23)	399 (74)
322 (58)	NR	293 (53)	334 (60)	NR	107 (19)	67 (12)	223 (40)
326 (54)	107 (18)	179 (30)	246 (41)	134 (22)	33 (6)	74 (12)	203 (34)
2851 (54)	1036 (32)	1470 (28)	2203 (44)	966 (27)	876 (17)	868 (22)	2340 (45)

analysis. Only fever, serositis, anemia, hemolytic anemia, and high anti-dsDNA were significant independent variables on multivariate analysis (Tables 5 and 6).

**CNS involvement.** One hundred seven (18%) patients had CNS involvement. In 43 (7%) patients, this feature was an initial manifestation of SLE. Age at SLE diagnosis in these patients was  $30.1 \pm 1.2$  years, and there were 101 women and 5 men (ratio, 20:1). When compared with patients without neurologic involvement ( $n = 493$ ), those with neurologic involvement had a higher prevalence of female sex (94% vs 88%,  $P < .05$ ), alopecia (25% vs 16%,  $P < .05$ ), thrombocytopenia (43% vs 28%,  $P < .005$ ), and IgG-aCL (21% vs 13%,  $P < .05$ ) in univariate analysis. However, only alopecia, thrombocytopenia, and IgG-aCL were significant independent variables on multivariate analysis (Tables 5 and 6).

**Thrombotic events.** Seventy-seven (13%) patients had thrombotic events. In 8 (1%) patients, this feature was an initial manifestation of SLE. Age at SLE diagnosis in these patients was  $30.8 \pm 1.7$  years, and there were 65 women and 12 men (ratio 5:1). When compared with patients without thrombosis ( $n = 523$ ), those with thrombotic

events had a higher prevalence of Raynaud phenomenon (33% vs 21%,  $P < .05$ ), livedo reticularis (12% vs 3%,  $P < .01$ ), hemolytic anemia (18% vs 7%,  $P < .005$ ), low CH50 (58% vs 41%,  $P < .005$ ), IgG-aCL (46% vs 10%,  $P < .001$ ), IgM aCL (23% vs 7%,  $P < .001$ ), and LA (53% vs 9%,  $P < .001$ ) in univariate analysis. However, only livedo reticularis, low CH50, IgG-aCL, and LA were significant independent variables on multivariate analysis (Tables 5 and 6).

**Muscle involvement.** Thirty-nine (6.5%) patients had myositis. In 18 (3%) patients, this feature was an initial manifestation of SLE. Age at SLE diagnosis in these patients was  $36.2 \pm 2.9$  years, and there were 35 women and 4 men (ratio, 9:1). When compared with patients without muscle involvement ( $n = 561$ ), those with myositis had a higher prevalence of Raynaud phenomenon (46% vs 21%,  $P < .001$ ), elevated ESR (36% vs 21%,  $P < .05$ ), anemia (36% vs 18%,  $P < .005$ ), anti-RNP (28% vs 13%,  $P < .05$ ), RF (23% vs 11%,  $P < .05$ ), and LA (16% vs 3%,  $P < .05$ ). However, only Raynaud phenomenon, anemia, and anti-RNP were significant independent variables on multivariate analysis (Tables 5 and 6).

**Table 8: Prevalence of the Main Hematologic and Immunologic Features: Previous Series**

Author (Reference)	Anemia (<11 g/dL)	Hemolytic Anemia	Leukopenia (<4000)	Thrombocytopenia (<100,000)
Harvey et al (12)	82 (78)	NR	NR	27 (26)
Dubois et al (13)	296 (57)	NR	224 (43)	36 (7)
Estes et al (14)	102 (73)	17 (12)	92 (66)	27 (19)
Fries et al (15)	73 (38)	NR	68 (35)	NR
Tan et al (7)	NR	32 (18)	81 (46)	37 (21)
Hochberg et al (16)	86 (57)	NR	62 (41)	45 (30)
Pistiner et al (17)	139 (30)	37 (8)	237 (51)	74 (16)
Vlachoyiannopoulos et al (18)	142 (49)	63 (22)	31 (11)	7 (3)
Cervera et al (2)	NR	80 (8)	NR	220 (22)
Petri et al (19)	348 (60)	NR	433 (75)	NR
Wang et al (20)	NR	102 (19)	212 (39)	161 (30)
Alarcón et al (21)	NR	NR	NR	NR
Present series	112 (19)	50 (8)	396 (66)	183 (30)
Total	1380 (46)	381 (12)	1836 (50)	817 (20)

NOTE. All values in parentheses are percentages.

Abbreviation: NR, not registered.

*Lung involvement.* Twenty-one (4%) patients had lung involvement. In 5 (1%) patients, this feature was an initial manifestation of SLE. Age at SLE diagnosis in these patients was  $34.3 \pm 3.4$  years, and there were 17 women and 4 men (ratio, 4:1). When compared with patients without pulmonary involvement ( $n = 579$ ), those with lung involvement had a higher prevalence of fever (81% vs 40%,  $P < .001$ ), cutaneous vasculitis (43% vs 12%,  $P < .001$ ), and anemia (48% vs 18%,  $P < .005$ ). However, only fever and cutaneous vasculitis were significant independent variables on multivariate analysis (Tables 5 and 6).

#### DISCUSSION

This study analyzed the prevalence and characteristics of clinical and immunologic features in a large cohort of SLE patients from a single center that follows all the cases diagnosed within its referral area. Patients were derived from a variety of specialists, mainly internists, rheumatologists, nephrologists, and dermatologists. Only patients with 4 or more of the 1997 American College of Rheumatology criteria for SLE classification (7) were included in our survivor cohort, thus avoiding equivocal cases or those with a "lupus-like" syndrome. Therefore, this cohort should be representative of what is currently accepted as SLE patients.

Differences in disease expression related to clinical, hematologic, and immunologic parameters were observed. Articular, cutaneous, and renal involvement were the most common manifestations, although several other features not specified in the American College of Rheumatology criteria also were frequent, including fever in 42% of patients, Raynaud phenomenon in 22%, alopecia in 18%, and cutaneous vasculitis in 13%. The prevalence of the major clinical features in the present series is comparable with that of previous studies (2,4-7,12-21) (Table 7). The most frequent hematologic features observed in our patients were lymphopenia (82%), leukopenia (66%), and thrombocytopenia (31%). Compared with other studies in smaller series, we found a lower prevalence of anemia (16,22), leukopenia (22), and lymphopenia (22), but a similar prevalence of thrombocytopenia (16) and hemolytic anemia (22) (Table 8). These differences may be related to the various ethnic origins of the populations studied. Articular involvement was an initial manifestation of SLE in 64% of patients, and the final prevalence of this feature was 83%. Similarly, renal involvement rose from 12% to 34%, CNS involvement from 7% to 18%, and thrombosis from 1% to 13%. However, cutaneous findings were unchanged (57% at the onset to 59%). These data indicate the rate of development of manifestations during a 22-year period.

**Table 8: Prevalence of the Main Hematologic and Immunologic Features: Previous Series (Cont'd)**

ANA	Anti-dsDNA	Anti-Sm	Anti-Ro/SSA	Anti-RNP	aCL/aPL
NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR
122 (87)	NR	NR	NR	NR	NR
183 (95)	75 (39)	50 (26)	NR	NR	NR
175 (99)	119 (67)	55 (31)	NR	NR	NR
NR	42 (28)	26 (17)	48 (32)	51 (34)	NR
445 (96)	186 (40)	28 (6)	88 (19)	65 (14)	176 (38)
259 (89)	189 (65)	23 (8)	105 (36)	40 (14)	63 (22)
960 (96)	780 (78)	100 (10)	250 (25)	130 (13)	NR
538 (94)	NR	85 (15)	NR	144 (25)	188 (69)
500 (93)	366 (68)	NR	NR	NR	NR
538 (97)	NR	NR	NR	NR	NR
596 (99)	537 (90)	75 (12)	128 (22)	75 (14)	137 (24)
4316 (95)	2294 (67)	442 (13)	619 (25)	505 (17)	564 (30)

We also found that patients diagnosed in the 1980s had a higher frequency of CNS involvement, thrombotic events, and abnormal laboratory parameters, and a lower frequency of articular involvement. This pattern may relate to better management of SLE in the 1990s, with a more rational use of the main therapeutic options (corticosteroids, immunosuppressive and anticoagulant agents).

The frequency of the major immunologic features of SLE in our series also is comparable with other reports (2,7,12-21) (Table 8). ANA were detected in the great majority of patients, and a high titer of anti-dsDNA antibodies was found in 88%. Interestingly, aPL (24%) and anti-Ro/SS-A (23%) were, respectively, the third and fourth most frequently detected autoantibodies, whereas anti-RNP (14%), anti-Sm (13%), and RF (12%) were detected in lower percentages. The prevalence of anti-extractable nuclear antigens antibodies in our cohort is similar to that previously described (25-27). Anti-Ro/SS-A antibodies, often accompanied by anti-La/SS-B, are found in SLE with a prevalence varying between 20% and 30%. The prevalence of antiphospholipid antibodies in our SLE population was similar to that reported by other authors (28), although preliminary studies on this subject showed a higher prevalence (36% to 60%) of aCL in SLE (9,29,30). The differences in prevalence of aCL positivity may result from the sen-

sitivity of the technique or the cut-off point for positivity.

Arthritis was the most frequent SLE manifestation (>80% of patients), and also was the most frequent feature at disease onset (64% of patients). As previously reported (31), our SLE patients with articular involvement were older, had a greater female to male ratio, and had a higher prevalence of fever and alopecia. Stahl et al (32) studied 160 hospitalized patients with SLE at the National Institutes of Health and found a close association among arthritis, fever, dermatitis, and pleuropericarditis.

This prevalence of SLE-specific cutaneous lesions in our patients was 59%. This was associated with other mild clinical features (oral ulcers and alopecia), and with some immunologic markers (anti-Sm and low complement C3). Skin involvement is the second most frequent manifestation of SLE, at onset or at a later stage of the disease (33-35). SLE patients with cutaneous involvement usually have a mild disease course. Zecevic et al (35) reported that the presence of subacute lesions was associated with a milder clinical expression of SLE and with disease activity as assessed by the Systemic Erythematosus Disease Activity Index. We also found an association between cutaneous SLE involvement and low C3 levels, as described previously (36).

Renal involvement was present in one third of our SLE patients, and varied from 29% to 53% in different series (14,37). We found a lower prevalence than observed by Petri (19) and Wang et al (20), probably as a result of differences in race and socioeconomic status. We found a lower mean age at SLE diagnosis and a higher prevalence of fever, anemia, hemolysis, and elevated anti-dsDNA antibodies in SLE patients with nephritis, in accord with previous studies. Wallace's group (38,39) found a mean age difference of 4 years in SLE patients with nephritis compared with those without (27 vs 31 years, respectively). A similar pattern was reported by Nossent et al (40). Wallace et al (41) also noted that the most frequent findings in SLE patients with nephritis were a family history of SLE, anemia, high titers of anti-dsDNA antibodies, and low C3 and C4 complement levels.

A clinical cluster of neurologic involvement, thrombocytopenia, and IgG-aCL was observed. Previous studies in SLE patients have described the association of neurologic involvement with clinical or laboratory features found in antiphospholipid syndrome, such as livedo reticularis or thrombocytopenia (42-44). In addition, several studies found a close association between neurologic involvement and positive aPL (44-47), with a specific association with the IgG isotype, in line with our results (43). Karassa et al (43) found that the likelihood of CNS events was higher in SLE patients with associated antiphospholipid syndrome, and that high titers of IgG-aCL was strongly associated with CNS involvement. Toubi et al (45) also reported that CNS disease is significantly associated with aPL, and that magnetic resonance imaging abnormalities correlated closely with positive aPL.

We found pulmonary involvement in only 4% of our patients, a prevalence similar to that observed in previous studies. Orens et al (48) reported clinically significant interstitial lung disease in <6% of SLE patients. The most detailed information comes from the University of Southern California Medical Center study by Eisenberg et al (49) that described 18 patients identified during a 1-year period, with radiographic evidence of interstitial lung disease. This represented <3% of the patients with SLE followed. Other studies reported chest radiography abnormalities consistent with interstitial lung disease in 9 of 150 patients with SLE (14) and pathologic evidence of pulmonary fibrosis in 4

of 120 autopsies (50). In our SLE patients with lung involvement, we found association with fever, cutaneous vasculitis, and anemia. Association with fever was described in 1 study (51), whereas anemia was reported in SLE patients with alveolar hemorrhage (53,54). In the 15 patients described by Zamora et al (55), the mean reduction in hematocrit was 7.1%. Although anemia may reflect alveolar hemorrhage, coexisting hemolytic anemia or other problems may confuse the interpretation of reduced hematocrit.

Muscle involvement was found in 7% of our patients, and was most closely associated with Raynaud phenomenon, anemia, and anti-RNP antibodies. A wide spectrum of abnormal histologic findings is described in muscle biopsies of SLE patients, with particular emphasis on the presence of myositis, which accounts 5% to 11% of muscle changes (56). The increased prevalence of anti-RNP antibodies in association with myositis has been described previously (57), as has the association with Raynaud phenomenon (58). A cross-sectional study of 49 patients with SLE determined that those with anti-U1-RNP and/or anti-Sm antibodies had a higher frequency of scleroderma-associated features, such as Raynaud phenomenon, sclerodactyly, interstitial changes on chest radiography, and nail-fold capillary abnormalities (59). However, because considerable clinical overlap between SLE and mixed connective tissue disease exists, whether mixed connective tissue disease is a distinct systemic autoimmune disease or merely a syndrome that may occur during the course of SLE or systemic sclerosis remains unclear, because some patients with mixed connective tissue disease evolve into SLE or systemic sclerosis (16).

The clinical/immunologic clusters described in this study may aid the diagnosis and treatment of SLE patients. We found several epidemiologic patterns according to the organ/system involved; for example, a higher prevalence of women with articular or CNS involvement, or a younger age at SLE diagnosis in patients with cutaneous, renal, or CNS involvement. We also found organ-specific clusters of hematologic and immunologic parameters that may identify patients likely to develop life-threatening SLE features such as renal, CNS, or pulmonary involvement. These patients require higher doses of corticosteroids and immunosuppressive agents, together with closer monitoring. In contrast, some of the clusters described (cutaneous,

articular, or constitutional) identify patients with a more benign course. In our clinical experience, the use of corticosteroids/immunosuppressive agents in these patients should be strictly limited, maintaining corticosteroid therapy at the lowest possible doses in the quiescent phases, with visits to the physician scheduled every 6 to 12 months.

## ACKNOWLEDGMENT

The authors thank Josep Vivancos, Albert Bové, Alfons López-Soto, Lucio Pallarés, Margarita Navarro, Carles Miret, Francisco José Muñoz, Gerard Espinosa, Sonia Jiménez, and Pilar Brito for their contribution to this article. They also thank David Buss for his editorial assistance.

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