Salinas et al. J Dermatol Res Ther 2016, 2:034
Volume 2 | Issue 5
ISSN: 2469-5750
DOI: 10.23937/2469-5750/1510034

Journal of
Dermatology Research and Therapy

Original Research: Open Access

Cutaneous Manifestations in Patients with Systemic Lupus Erythematosus: Data from a Multiethnic Latin American Cohort (GLADEL)

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Abstract

Objective: The aim of this study was to assess the prevalence and associated features of cutaneous manifestations in patients with systemic lupus erythematosus (SLE) as well as to evaluate whether cutaneous manifestations are predictors of the occurrence of other clinical manifestations.

Material and Methods: SLE patients from 34 centers in nine Latin American countries with a recent diagnosis (≤ 2 years) were studied. Socioeconomic-demographic characteristics and clinical features according to the presence of cutaneous manifestations were examined by univariable and multivariable logistic regression analyses. Their predictive value for the occurrence of other clinical manifestations was also examined.

Results: Of the 1480 patients included, 93.7% had cutaneous manifestations, 91.0% of them occurred before the diagnosis of SLE. Cutaneous manifestations occurred more frequently in women (90.5% vs. 80.6%, p = 0.002), and in those with systemic

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Citation: Salinas MJH, Saurit V, Alvarellos A, Caeiro F, Wojdyla D, et al. (2016) Cutaneous Manifestations in Patients with Systemic Lupus Erythematosus: Data from a Multiethnic Latin American Cohort (GLADEL). J Dermatol Res Ther 2:034

Received: August 25, 2016: **Accepted:** October 10, 2016: **Published:** October 12, 2016

(83.1% vs 69.9%, p = 0.002) and musculoskeletal manifestations (93.5% vs. 83.9%, p = 0.002) and anti-Ro antibody positivity (52.5% vs. 31.7%, p = 0.015) but less frequently in those with pleuropulmonary involvement (27.5% vs. 43.0%, p = 0.002). Cutaneous manifestations were protective of the subsequent occurrence of pleuropulmonary (OR 0.519, 95% CI 0.372-0.724) and hematological (OR 0.621, 95% CI 0.440-0.876) manifestations.

Conclusions: Cutaneous manifestations occur frequently and early in SLE. They were associated with female gender, the presence of systemic and musculoskeletal manifestations and anti-Ro antibody positivity. They were protective of the development pleuropulmonary and hematologic manifestations.

Keywords

Systemic lupus erythematosus, Clinical manifestations, Epidemiology

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disease which is quite heterogeneous in its clinical manifestations. Cutaneous manifestations occur in 50% to 85% [1-8] of SLE patients making the skin the most commonly affected organ and the most frequent target of initial clinical manifestations following joint involvement [9,10].

Cutaneous manifestations are indeed important features of SLE and have always been included in the classification criteria of this disease. For example, in the revised and updated American College of Rheumatology (ACR) classification criteria lesions such as malar rash, discoid rash, photosensitivity, and oral ulcers had a high specificity for SLE [11,12]. In the recently published SLICC (Systemic Lupus Erythematosus International Collaborating Clinics) criteria, mucocutaneous manifestations otherwise not considered in these previous ACR criteria, such as subacute cutaneous lupus, bullous lupus, lupus panniculitis, scarring alopecia and others were included [13].

In spite of their overall benign appearance, skin lesions may significantly affect the patients' self-esteem, quality of life and job performance [14]. Regardless of gender, skin lesions do affect the patients' self-esteem and may be accompanied by variable degrees of emotional distress [15].

The purpose of the present study was to assess the prevalence of cutaneous manifestations occurring over the course of SLE and their associated features, as well as to evaluate whether cutaneous manifestations are predictive of the occurrence of other clinical manifestations in a Latin American Lupus cohort.

Material and Methods

GLADEL *(Grupo Latino Americano De Estudio del Lupus)* was established in 1997 as an observational inception lupus cohort constituted by 34 centers distributed among nine Latin American countries. Patients were included with a recent SLE diagnosis (less than two years); fulfillment of four ACR 1982 SLE criteria was not mandatory at enrollment [11], however, 96.0% of patients fulfilled these criteria during their follow-up. In order to have a balanced representation of centers in the initial cohort, each center was asked to incorporate a minimum of 20 and a maximum of 30 randomly selected patients. Randomization was done locally at each center. The first patients were entered in October 1997, and to insure their recent onset they could only be included if the diagnosis of SLE had been made after January 1st 1996 by a rheumatologist or a qualified internist with experience in SLE. After incorporating the initial 30 patients, each group continued to include one new randomly selected patient per month diagnosed within the previous two years. Patients were invited to participate by their treating physician and an informed consent was signed and saved at each participating center. Each patient was interviewed and her or his medical record's information was validated. All researchers followed local regulations according to their institutional review boards.

During each visit, patient data were collected in a common database (ARTHROS) by a clinician trained in the program. At the coordinating center, strict control and supervision of the data received was undertaken, with permanent communication with the submitting center for any queries arising and/or missing data.

History, physical examination and laboratory tests were performed at entry and at all subsequent visits, which took place every six months after the initial visit. Medications taken were also noted; however, the precise data on their average and cumulative dose were not obtained. The average follow-up time was 4.3 years. Ethnicity was defined according to the parents' and all four grandparents' self-reported ethnicity. The following ethnic groups were considered: Caucasian (individuals with all white European ancestors), Mestizo (individuals born in Latin America who had both Amerindian and white ancestors), African-Latin American (ALA) (individuals born in Latin America with at least one African ancestor whether other ancestors were white or not) and other. In short, we used self-reported ethnic definitions rather than ancestry-informative markers (AIMs) to define the different ethnic groups. Socioeconomic status was evaluated using the Graffar index [16]. Disease activity was ascertained with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [17] at all visits. Damage was assessed at yearly intervals with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [18].

The local ethics committee of each participating center approved the protocol.

Statistical analysis

The socioeconomic, demographic, clinical and laboratory features of patients with and without cutaneous manifestations at any time during the disease course were compared with Pearson Chi squared or Fisher's exact tests for proportions, and the Students t-test for continuous data. The odds ratio (OR) and the 95% confidence interval (CI) were calculated using univariable logistic regression. A p value equal or less than 0.05 was considered statistically significant; variables significant in these analyses were included in a multivariable logistic regression adjusting for gender, age, the average SLEDAI score and the last SDI score excluding cutaneous manifestations. Univariable and multivariable analyses to assess whether cutaneous manifestations are predictors of subsequent occurrence of other clinical manifestations were also performed. For these analyses, only the cutaneous manifestations present before fulfillment of diagnostic criteria were included but not the ones that appeared after the fulfillment of these criteria; recurrences were also excluded.

The different immunological laboratory tests had not been obtained in all patients. Antinuclear antibodies (ANA), anti-DNA antibodies and complement had not been performed in about 15% of the patients; however, the proportion of patients with missing data was comparable in those with and without cutaneous manifestations, so that, the original data were used. The anti-RNP, anti-Sm, anti-La, anti-Ro and anti-cardiolipin antibodies had not performed in about 30% of the patients; however, no significant difference was observed in the proportion of patients with missing data between patients with and without all cutaneous manifestations so again the original data were used. However, the lupus anticoagulant and anti-β2 glycoprotein 1 test had been performed in less than 50% of the patients and thus both tests were excluded from the analyses.

All analyses were carried out using SPSS, version 19 (Chicago Illinois).

Results

Of the 1480 patients included in this study, 89.9% (n = 1330) were women and 10.1% (n = 150) were men; patients had a mean (SD) age at SLE onset of 27.7 (11.7) years; 93.7% (n = 1387) have had at least one cutaneous manifestation during their follow up and most patients (91.0%, n = 1264) showed cutaneous manifestations before

fulfilling the four SLE classification criteria. Most patients had more than one type of skin lesion; the most common manifestations were malar rash 65.0%, alopecia 63.0%, photosensitivity 59.5% and oral ulcers 44.7%. The frequency of each type of cutaneous manifestation is shown in figure 1.

The frequency of the different cutaneous manifestations as a function of ethinicity is shown in table 1. Alopecia was less frequently observed in Caucasians than in the other ethnic groups (59.7% vs 66.8% Mestizos, 64.0% African / Latin American and 72.1% other; p = 0.043) while discoid rash was more frequent in African / Latin American than in the other ethnic groups (19.9% vs 13.2% Caucasians, 11.3% Mestizos, and 4.7% other; p = 0.007).

Table 2 shows the relationship between cutaneous and other clinical manifestations. Patients with cutaneous manifestations had a significantly higher frequency of systemic (fever, prolonged febrile syndrome, asthenia, fatigue, anorexia, weight loss, adenopathy) (83.1% vs. 69.9%; p = 0.002) and musculoskeletal manifestations (93.5% vs. 83.9%; p = 0.002) as well as a higher proportion of patients with a SLEDAI ≥ 4 (58.8% vs. 46.2%; p = 0.022); they were also more frequent users of antimalarials (83.2% vs. 64.5%; p < 0.001) at some point during the course of their disease. They also exhibited anti-RNP (55.3% vs. 33.3%; p = 0.006), anti-Ro (52.5% vs. 31.7%; p = 0.015) and anti-Sm (47.0% vs. 32.6%; p = 0.015) antibodies positivity more frequently than those without cutaneous manifestations. On the other hand, patients with cutaneous manifestations exhibited a lower frequency of pleuropulmonary manifestations (27.5% vs. 43.0%; p = 0.002) and cardiac involvement (20.1% vs. 34.4%; p = 0.002) than those without them.

Multivariable analysis

The results of the multivariable analysis are also shown in table 2. Variables retained in this analysis were female gender (OR 3.052, 95% CI 1.132 to 8.233), the presence of systemic (OR 2.865, 95% CI 1.290 to 6.364) and musculoskeletal manifestations (OR 5.542, 95% CI 2.071 to 14.836) and anti-Ro antibody positivity (OR 2.485, 95% CI 1.131 to 5.461); on the other hand, cutaneous manifestations were negatively associated with the occurrence of pleuropulmonary manifestations (OR 0.443, 95% CI 0.207 to 0.950).

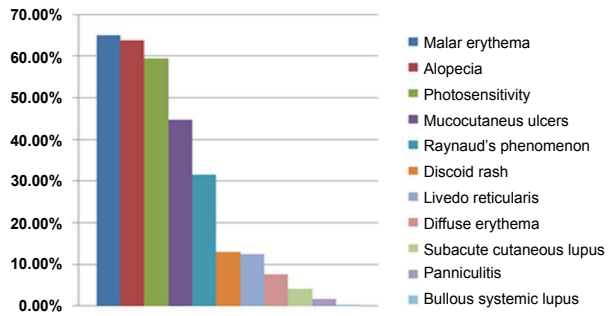

Figure 1: Frequency of type of Cutaneous Manifestation.

Cutaneous manifestations: predictor of clinical manifestations

As shown in table 3, the presence of cutaneous manifestations was protective of the subsequent occurrence of pleuropulmonary (OR 0.519, 95% CI 0.372 to 0.724) and hematological (OR 0.621, 95% CI 0.440 to 0.876) manifestations.

Discussion

This is the first report on a large number of Latin American SLE patients that describes the cutaneous manifestations of the disease and reflects the reality of daily clinical practice among them. A very high frequency of cutaneous manifestations (93.7%) was observed in this GLADEL cohort; this is even higher than the frequencies described by Dubois, et al. and Harvey, et al. in US patients [3,4], and those found in studies of European (59%), Iranian and Pakistani (82%) populations [2,6,7]. However, the frequency found in our cohort is similar to that found in Brazilians where cutaneous manifestations occurred in over 90% of the patients being the most common malar rash and photosensitivity [19]. A sustained exposure to ultraviolet light among our Latin American patients could be the explanation for these findings. The most frequent manifestations we observed were malar rash, alopecia, photosensitivity and Raynaud phenomenon, similar to what has been described in many other previous studies [6,8,20-24].

Cutaneous manifestations were associated with a higher frequency of systemic manifestations and musculoskeletal manifestations, the latter being the other most common manifestation of the disease; this is, somewhat similar to a study conducted in Spain, in which patients with subacute cutaneous lesions presented arthralgia and systemic manifestations more frequently than patients with chronic cutaneous manifestations [25].

An important finding of our study was the occurrence of a lower frequency of cardiac and pleuropulmonary manifestations in patients with cutaneous involvement; these data, reinforce a previous report [26]. Furthermore, cutaneous manifestations were protective of the subsequent occurrence of hematologic and pleuropulmonary manifestations, fact which has not previously been reported. A protective effect for the occurrence of renal manifestations was not found in our study; however we have previously found discoid lupus (occurring at disease onset) to be protective of the subsequent development of lupus nephritis [27] and that patients with photosensitivity experience a longer time to the occurrence of renal disease [28]. This apparent discrepancy probably relates to the fact that we have examined all cutaneous manifestations together and not individually.

Although we found a higher frequency of patients with a SLEDAI ≥ 4 in those with cutaneous manifestations, this association is of questionable value since these manifestations were not excluded from the SLEDAI; nevertheless, we have included the SLEDAI score in the multivariable analyses as an adjustment variable.

It is widely accepted that anti-Ro antibodies, produced by the exposure of self-antigens from the cell surfaces to ultraviolet

Table 1: Cutaneous Manifestation Frequency by Ethnicity.

	Caucasian (n = 606)	Mestizo (n = 645)	African/Latin American (n = 186)	Others (n = 43)	p
Malar Erythema, n (%)	402 (62.2)	422 (65.4)	111 (59.7)	27 (62.8)	0.402
Alopecia, n (%)	362 (59.8)	431 (66.8)	119 (64.0)	31 (72.1)	0.043
Photosensitivity, n (%)	377 (62.2)	366 (56.7)	110 (59.1)	27 (62.8)	0.253
Mucocutaneous Ulcers, n (%)	263 (43.4)	303 (47.0)	75 (40.3)	21 (48.8)	0.320
Raynaud's Phenomenon, n (%)	208 (34.3)	194 (30.1)	51 (27.4)	15 (34.9)	0.213
Discoid Rash, n (%)	80 (13.2)	73 (11.3)	37 (19.9)	2 (4.7)	0.007
Livedo Reticularis, n (%)	75 (12.4)	84 (13.0)	18 (9.7)	7 (16.3)	0.554
Diffuse Erythema, n (%)	59 (9.7)	40 (6.2)	10 (5.4)	3 (7.0)	0.069
Subacute Cutaneous Lupus, n (%)	28 (4.6)	21 (3.3)	10 (5.4)	3 (7.0)	0.367
Panniculitis, n (%)	9 (1.5)	10 (1.6)	4 (2.2)	2 (4.7)	0.434
Bullous Systemic Lupus, n (%)	2 (0.3)	2 (0.3)	2 (1.1)	0	0.480

Table 2: Sociodemographic, Clinical and Serological Features According to Whether Cutaneous Manifestations Were Present or Not. Univariable and Multivariable Analyses.

	With Cutaneous Manifestations (n = 1387)[#]	Without Cutaneous Manifestations (n = 93)[#]	Univariable Analyses		Multivariable Analyses[*]	
			OR (95% CI)	p Value	OR (95%CI)	p Value
Female, n (%)	1255 (90.5)	75 (80.6)	2.281 (1.323-3.934)	0.002	3.052 (1.132-8.233)	0.028
Age at SLE onset ≤ 30 years, n (%)	878 (63.3)	41 (44.1)	0.457 (0.299-0.698)	< 0.001	0.969 (0.943-0.996)	0.023
Ethnicity, n (%)						
Caucasian	567 (40.9)	39 (41.9)	Reference	0.748		
Mestizo	606 (43.7)	39 (41.9)	1.069 (0.676-1.690)	0.882		
African/Latin American	171 (12.3)	15 (16.2)	0.784 (0.422-1.457)	0.330		
Others	43 (3.1)	0	1.000 (0.000-1.000)	0.987		
Socioeconomic status, n (%)						
High / Medium High	140 (10.1)	12 (12.9)	Reference	0.482		
Medium	398 (28.7)	29 (31.2)	1.176 (0.584-2.368)	0.703		
Medium Low / Low	849 (61.2)	52 (55.9)	1.399 (0.729-2.688)	0.305		
Clinical Manifestations, n (%)						
Systemic	1152 (83.1)	65 (69.9)	2.112 (1.327-3.361)	0.002	2.865 (1.290-6.364)	0.010
Musculoskeletal	1297 (93.5)	78 (83.9)	2.771 (1.532-5.012)	0.002	5.542 (2.071-14.836)	0.001
Ocular	242 (17.4)	17 (18.3)	0.945 (0.549-1.628)	0.780		
Pleuropulmonary	381 (27.5)	40 (43.0)	0.520 (0.313-0.796)	0.002	0.443 (0.207-0.950)	0.036
Cardiac	290 (20.1)	32 (34.4)	0.504 (0.322-0.788)	0.002		
Renal	819 (59.0)	57 (61.3)	0.911 (0.592-1.401)	0.670		
Neurologic	498 (35.9)	27 (29.0)	1.369 (0.864-2.171)	0.218		
Hematologic	1089 (78.5)	79 (84.9)	0.648 (0.362-1.160)	0.151		
SDI ≥ 1 (at last follow-up), n (%)	773 (55.7)	53 (57.0)	0.952 (0.620-1.452)	0.830		
Mean SLEDAI ≥ 4, n (%)	816 (58.8)	43 (46.2)	1.660 (1.091-2.533)	0.022		
Deceased, n (%)	82 (5.9)	8 (8.6)	0.668 (0.313-1.425)	0.292		
Treatment, n (%)						
Antimalarial use	1154 (83.2)	60 (64.5)	2.724 (1.741-4.261)	< 0.001		
Corticosteroids use	1308 (94.3)	84 (90.3)	1.774 (0.860-3.659)	0.108		
Cyclophosphamide use	47 (3.4)	1 (1.1)	3.227 (0.440-23.652)	0.361		
Methotrexate use	169 (12.2)	6 (6.5)	2.012 (0.866-4.673)	0.133		
Azathioprine use	444 (32.0)	33 (24.7)	1.433 (0.883-2.326)	0.167		
Immunological laboratory, n (%)						
Anti-ANA antibodies	1302 (98.0)	91 (100.0)	1.070 (1.055-1.085)	0.406		
Anti-DNA antibodies	829 (72.7)	62 (77.5)	0.771 (0.449-1.325)	0.434		
Anti-RNP antibodies	308 (55.3)	14 (33.3)	2.474 (1.275-4.801)	0.006		
Anti-Sm antibodies	335 (47.9)	15 (32.6)	2.177 (1.153-4.109)	0.015		
Anti-Ro antibodies	330 (52.5)	13 (31.7)	2.377 (1.209-4.674)	0.015	2.485 (1.131-5.461)	0.023
Anti-La antibodies	182 (31.2)	9 (24.3)	1.412 (0.653-3.053)	0.464		
IgG Anticardiolipin antibodies	347 (49.4)	16 (42.1)	1.344 (0.694-2.602)	0.409		
IgM Anticadiolipin antibodies	139 (38.1)	15 (44.1)	0.778 (0.388-1.561)	0.475		
Hypocomplementemia	810 (68.5)	46 (61.3)	1.369 (0.847-2.214)	0.203		

[#]Total n are different in the evaluation of immune laboratory.

[*]Gender, age, the average SLEDAI score and the last SDI score were included in the multivariable analyses as adjustemet variabels.

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index (including cutaneous manifestations).

SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (excluding cutaneous manifestations).

OR: Odd Ratio.

CI: confidence Interval.

Table 3: Presence of Cutaneous Manifestations as Predictive Factor Other Clinical Manifestations.

		With Cutaneous manifestations	Without Cutaneous manifestations	Univariable Analyses		Multivariable Analyses*	
				OR (95% CI)	p value	OR (95%CI)	p Value
Clinical Manifestations, n (%)	Systemic	181 (44.2)	45 (54.2)	0.679 (0.423-1.091)	0.117		
	Musculoskeletal	58 (42.0)	24 (49.0)	0.755 (0.393-1.453)	0.408		
	Ocular	126 (10.7)	27 (13.5)	0.770 (0.493-1.203)	0.273		
	Pleuropulmonary	133 (12.9)	35 (22.4)	0.490 (0.322-0.744)	0.002	0.519 (0.372-0.724)	0.001
	Cardiac	116 (10.3)	22 (13.0)	0.764 (0.471-1.248)	0.283		
	Renal	299 (36.0)	46 (39.0)	0.880 (0.592-1.307)	0.540		
	Neurological	277 (25.4)	41 (22.7)	1.161 (0.799-1.687)	0.460		
	Hematologic	314 (52.0)	53 (70.7)	0.449 (0.267-0.758)	0.002	0.621 (0.440-0.876)	0.002

*Variables included in step 1: gender, age at diagnosis and clinical manifestations.

B radiation [29], play a role in the pathogenesis of skin lesions association which we have confirmed. Other authors have found these antibodies to be associated with photosensitive rashes, alopecia and subacute cutaneous lesions [8,25,30,31]. It should be noted however, that no relationship between the different skin rashes and the presence of certain antibodies, including anti-Ro has been found in patients of African descend [32].

Anti-RNP antibodies positivity has been associated with cutaneous manifestations; Grönhagen, et al. found these antibodies

to be associated with acute cutaneous lesions in a study of 260 SLE patients [7]. Anticardiolipin antibodies positivity has been associated with the occurrence of Raynaud phenomenon and livedo reticularis, among others; these manifestations are well-known components of the antiphospholipid syndrome and have also been associated with anti-Beta 2 glycoprotein 1 antibodies positivity [7]. Hypocomplementaemia was not associated with the presence of cutaneous manifestations; however, other authors have reported hypocomplementemia to be associated primarily with cutaneous vasculitis [33]. However, we have not examined these association because of the paucity of data about complement levels and the fact that we have examined all cutaneous manifestations together.

The association of cutaneous manifestations with the use of antimalarials, more than likely reflects the fact that their presence is a clear indication for therapy with these compounds as has been widely reported and recognized [1,34-36].

An important limitation of our study is that the association of skin lesions and some auto-antibodies could not be examined since they were not available in all patients, had not been obtained at a central laboratory or at the time cutaneous manifestations occurred. This prevents us from making a definitive interpretation of some of the associations we are reporting. Another limitation is that the diagnosis of cutaneous manifestations has not been carried out systematically by dermatologists; however, all patients have been evaluated by rheumatologists trained and experienced in the recognition of cutaneous manifestations of SLE. Finally, we could not examine the relationship between these manifestations and the average and cumulative doses of the drugs used since this detailed information had not been obtained. Nevertheless, we think that the data being reported is quite valuable.

In conclusion, cutaneous manifestations occur quite frequently in Latin American SLE patients and they appear to be an early manifestation of the disease. The most frequent manifestations were malar erythema, alopecia and photosensitivity. Cutaneous manifestations were associated with the presence of systemic and musculoskeletal manifestations and positive anti-Ro antibodies; they were, however, inversely associated with the presence of pleuropulmonary manifestations. Finally, they were protective of the occurrence of pleuropulmonary and hematologic manifestations.

Acknowledgments

We are grateful to Daniel Villalba and Leonardo Grasso for providing expert assistance with the ARTHROS (version 6.0) software.

Author Contributions

All authors were involved in drafting or revising this article critically for important intellectual content, and all authors approved the final version to be published. Dr. María J. Haye Salinas and Bernardo A. Pons-Estel have full access to the dataset used for the study and take responsibility for data integrity and accuracy of the analyses performed.

Financial Support

This project was supported in part by grants from The Pan American League of Associations for Rheumatology (PANLAR). Supported by grants from the Federico Wilhelm Agricola Foundation Research (to B.A.P-E).

On behalf of GLADEL

The following participants are members of GLADEL, have incorporated at least 20 patients into the database with adequate follow-up and in particular provided data related to elderly onset SLE.

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