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Clinical Patterns of Cutaneous and Mucosal Lesions in Patients with Systemic Lupus Erythematosus

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Abstract
Introduction: *SLE is an auto-immune disease with diverse patterns of auto-antibody production with multi-organ involvement. Cutaneous illness often precedes the systemic involvement, giving the opportunity to recognize the disease process much before the systemic complaints are expressed.*
Objective: *To evaluate the clinical pattern of cutaneous and mucosal lesions in patients with SLE using the Gilliam's system of classification and to look for the various immunological markers of SLE in them.*
Methodology: *A hospital-based cross-sectional descriptive study in which Forty five consecutive patients of SLE who fulfilled the revised American college of rheumatology (ACR) criteria for the classification of SLE were included.*
Results: *Among the LE-specific skin lesions, ACLE lesions were exclusively seen in 28 patients, SCLE lesions were seen exclusively in 3 patients, CCLE lesions were exclusively seen in 2 patients, whereas a combination of ACLE lesions along with CCLE lesions were seen in 12 patients. ACLE was found to be the most common LE-specific skin lesion (40/45, 88.89%), followed by CCLE (14/45, 31.11%). Among the LE-non-specific skin lesions, oral ulceration was the most common, seen in 84% of patients, followed by telogen effluvium (76%). Raynaud's phenomenon was the most common (20%) LE- nonspecific vasculopathy.*
Conclusions: *Cutaneous manifestations are some of the commonest and earliest manifestations of SLE. Various LE-specific skin lesions and LE-non-specific skin lesions, as described by Gilliam, aid in the diagnosis and management of SLE. Immunological markers like Anti-ds DNA antibody might act as a predictive marker for renal involvement in SLE.*
Keywords: *SLE, Gilliam's classification, Antinuclear antibodies, ACR criteria.*

Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease that has a broad range of clinical manifestations. SLE is a heterogeneous disease marked by diverse patterns of auto-antibody production with multi-organ involvement. The spectrum of disease ranges from minor organ

involvement (e.g., cutaneous lesions) to life-threatening major organ involvement (e.g., renal, nervous system, etc). The diversity of expression of the diseases is determined by genetic, demographic and environmental factors.[1,2] Cutaneous illness often precedes the systemic involvement, giving the opportunity to the dermatologist to recognize the disease process much before the systemic complaints are expressed.

Lupus erythematosus (LE) patients may develop various types of clinically distinctive skin lesions. The involvement of skin in patients with SLE ranged from 55% to 100% .[3] Dermatological presentation of SLE has been used by physicians as a conceptual framework to manage the disease[4]

Gilliam classified the cutaneous manifestations of LE according to:

1) Those which show the characteristic histopathology of lupus erythematosus (LE-specific) and
2) Those that are associated phenomena without any characteristic histopathologic changes of LE (LE-nonspecific).

The LE-specific lesions were further subclassified into acute, subacute and chronic forms.[5,6]

The aim of our study was to evaluate the clinical pattern of cutaneous and mucosal lesions in patients with SLE in our locality using the Gilliam's system of classification and also to look for the various immunological markers of SLE in them.

Materials & Methods

The study was initiated after obtaining clearance from Institute research committee and institute ethics committee.

This study was a hospital-based cross-sectional descriptive study, conducted in department of dermatology venereology and leprology of a tertiary care institution.

Forty five consecutive patients of SLE who presented to the outpatient department or were inpatients or were referred from other departments and fulfilled the revised American college of rheumatology (ACR) criteria for the classification of SLE were included in the study irrespective of their age or gender.

Patients with overlap diseases, mixed connective tissue diseases, those taking drugs other than the specific drugs for SLE, those with skin lesions only (that is, cutaneous lupus erythematosus without systemic involvement) and patients who were unable to give accurate data were excluded from the study.

The study subjects were interviewed using a pre-tested, semi-structured questionnaire. This questionnaire comprised of three parts. Part-A collected information regarding socio-demographic characteristics like age, gender, and systemic symptoms related to SLE. Part-B recorded information on the clinical presentation of skin and mucosal lesions as per the Gilliam's classification at the time of presentation and the ANA status.

Results

Of the total 45 subjects four were men and 41 were women. Most of the study subjects (37.8%) belonged to the age group of 21-30 years. Six patients were in pediatric age group.

The disease seem to affect the residents of both urban and rural areas equally in our study and most (29, 52%) of the subjects were from medium socio-economic status and majority were engaged in household work (34, 76%). The onset in maximum number of patients was insidious (89%) over an average duration of 4-6 month. This emphasized the chronic and variable course of the disease described earlier.

LE-specific skin lesions

Table 1 shows the details of LE-specific skin lesions in the study population according to Gilliam's classification:

Among the LE-specific skin lesions, ACLE lesions were exclusively seen in 28 patients, SCLE lesions were seen exclusively in 3 patients, CCLE lesions were exclusively seen in 2 patients, whereas a combination of ACLE lesions along with CCLE lesions were seen in 12 patients. Hence, the total number of subjects who had ACLE lesions were 40,

and the total number of subjects who had CCLE were 14.

ACLE was found to be the most common LE-specific skin lesion (40/45, 88.89%) in form of active lesions or healed post-inflammatory hyperpigmentation followed by CCLE (14/45, 31.11%) in SLE patients.

LE-nonspecific skin lesions

Table 2 shows the details of LE-nonspecific skin lesions in the study population according to Gilliam's classification:

We found that oral ulceration was the most common LE-nonspecific lesion in patients with SLE, occurring in around 84% of patients, followed by telogen effluvium, occurring in 76% of patients. We also found that Raynaud's phenomenon was the most common LE- nonspecific vasculopathy, occurring in 20% of patients.

Systemic involvement

Figure 1 depicts the systemic involvement among the study subjects. In our study we found that constitutional symptoms was seen in 100% of patients of SLE average duration being 2months to 6months prior to skin lesions. Next most common systemic involvement was musculoskeletal (36/45), followed by renal involvement (24/45).

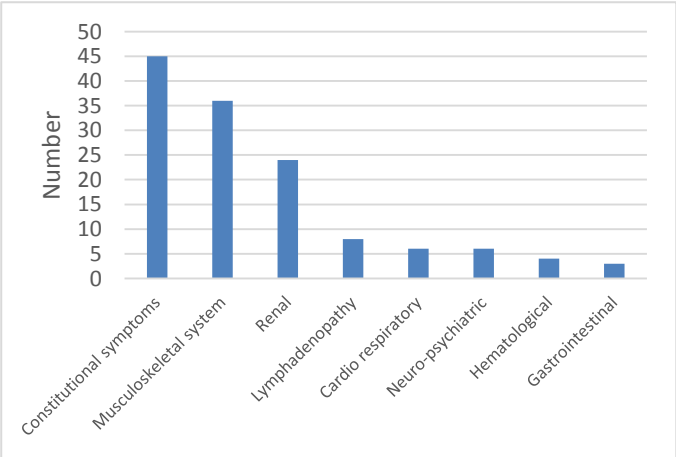

Fig. 1: Systemic involvement among the study subjects.

ANA positivity

Among the immunological parameters, we did ANA test by EIA, and Hep-2 method and ANA -ENA profiles which included anti ds-DNA, anti-Sm and others. ANA were found positive in 98% of cases. Most (92%) of the ANA positive patients also had a high titre (>1:160). Anti ds-DNA antibody were positive in 85% of cases in those cases where kidney was involved suggesting it is a predictive marker for kidney involvement.

Antinuclear antibody positivity was seen in 97.8% of the study population while using the HEp-2 method and in 91% when done by EIA method.

Table-3 shows frequency of positivity of various relevant auto-antibodies in patients of SLE done by using ANA profile 3, euroline. We found that anti-ds DNA antibodies was positive in highest percentage begin 84%, followed by anti-nucleosome antibodies, positive in 53% of patients.

Table 1 LE-specific skin lesions in the study population according to Gilliam's classification

	Type of skin lesion			N=45 (%)
A	**Acute cutaneous LE (ACLE)** 40 (88.89%)	Localised		13 (28.89)
		Generalised		27 (60.00)
B	**Subacute cutaneous LE (SCLE)** 3(6.67%)	Annular		2 (4.44)
		Papulosquamous		1 (2.22)
C	**Chronic cutaneous LE (CCLE)** 14 (31.11%)	Classic discoid LE	Localised	2 (4.44)
			Generalised	7 (15.56)
		Hypertrophic/Verrucous DLE		2 (4.44)
		Lupus profundus/ Lupus panniculitis		1 (2.22)
		Mucosal	Oral	1 (2.22)
			Conjunctival	0
		Lichenoid DLE		1 (2.22)
		Chillblains LE		0
		Lupus tumidus		0

Table 2 - LE-nonspecific skin lesions in the study population according to Gilliam's classification:

LE-nonspecific skin lesions		No. (%)
Oral ulcer		38 (84.45)
Nonscarring alopecia:	Telogen effluvium	34 (75.6)
	Lupus hair	9 (20)
Raynaud's phenomenon		9 (20)
Periungual telangiectasia		4 (8.9)
Vasculitis lesions		3 (6.7)
Livedo reticularis		2 (4.4)
Urticarial vasculitis		3 (6.7)
Erythromelalgia		1 (2.2)
LE-nonspecific bullous lesions		1 (2.2)
Erythema multiforme		3 (6.7)
Thrombophlebitis		0
Papulonodular mucinosis		0
Calcinosis cutis		0
Sclerodactyly		0
Rheumatoid nodule		0

Table 3: ANA-ENA profile Using Euroline test kit

No.	Antibodies	Number of patients N(%)
1	nRNP/Sm	19 (42.2)
2	Sm	17 (37.8)
3	SS-A	14 (31.1)
4	Ro-52	21 (46.6)
5	SS-B	6 (13.3)
6	PCNA	0 (0)
7	dsDNA	38 (84.4)
8	Nucleosomes	24 (53.3)
9	Histones	22 (48.9)
10	Ribosomal-P-Protein	4 (8.9)

Discussion

Systemic lupus erythematosus (SLE) is an autoimmune disorder with diverse clinical manifestations ranging from mild cutaneous disorder to life-threatening systemic illness which may culminate in death.

The present study included 45 patients of systemic lupus erythematosus attending Dermatology OPD of a tertiary care hospital.

The criteria for inclusion in this study were based on ACR classification which encompasses both clinical and immunological parameters. All patients fulfilling 4 of the 11 criteria were included in our study.

Analysis of age distribution of SLE patients showed that their age ranged from 8 years to 52 years, which was more or less similar to two studies conducted by Masi et al[7] and Malaviya et al.[8] The peak incidence was seen in the 3rd decade in both the series. In our study also almost 69% patients were in the 2nd and 3rd decades.

The overall male to female ratio in our study was 1:10. The study by Ward also had similar gender distribution.[9] We found gender disparity is not as prominent later age (>40 years of age).

History of drugs is important in case of SLE as drug-induced lupus is clinically and serologically different from classic lupus. The most common drugs implicated are isoniazid, hydralazine, and procainamide.[10] In our study however, no patients were found to be exposed to the said drugs.

The most common site of LE lesion in our study was face (87%) followed by others. Both lupus specific and nonspecific lesions were detected among which malar rash (lupus specific) predominant (68.9%). It is compatible with the study by Wysenbeek et al.[11] Incidence of discoid and other rashes were comparatively lower. Among the nonspecific lesions oral ulcer was most common (84.5%). Nonscarring diffuse alopecia was found in (75.6%) quite higher then, to a study by Wysenbeek et al.[11] Livedoreticularis and LE- nonspecific vesicobullous lesions, erythromelalgia were less common in our study. Sclerodactly, calcinosis cutis, papulonodular musinosis and rheumatoid nodules were not detected in our study.

Regarding generalised ACLE, we observed confluent erythematous, edematous macules and papules, and it was associated with increased disease activity of SLE (27, 60 %). In all cases photo-exposed parts were more severely involved compare to covered parts. All our observation findings were found to be similar to the observations in the two studies by Kuhn A et al. [12,13]

Painless ulcers were the most common oral lesions in our study (84.5%), hard palate being the predominant site (100%). In a study by Hallegua et al, about one half of patients with systemic lupus had oral ulcers that were usually painful if discoid, and painless if erythematosus.[14] They tend to be located on the hard palate, on the buccal mucosa, or along the vermilion border (lower lip> upper lips)

In one study by Zeevi et al, it was found that lupus-specific skin lesions serve primarily as an important diagnostic clue whereas lupus nonspecific skin lesions are associated with more active disease.[15] In our study bullous lesions were associated with kidney involvement. The relationship between bullous SLE and lupus nephritis in children was demonstrated by Sirka et al.[16] EM-like and purpuric lesions were strongly associated with CNS involvement in our study, which is compatible with one study conducted by Akrekar et al.[17] Livedo reticularis and erythromelalgia were also commonly seen in lupus patients and it was associated with flaring of cerebral vacuitis.[18]

In our study, no such systemic associations were detected with malar rash, photosensitive rash or discoid rash.

We got a single case of bullous SLE, patient presented with tense vesicles and bulla which is one of LE- nonspecific manifestation. Its estimated incidence is fewer than 0.5 cases per million population per year. Subepidermal blister and a predominantly neutrophilic dermal infiltrate was seen in histopathology of the lesion.

Among the systems involved in SLE, most frequent one is the musculoskeletal system. In our study it was involved in 80% of cases.

Among patients with arthritis, nonerosive oligoarthritis was most common (78%) than polyarthritis and small joint involvement predominated (98%) than large joint involvement. In one study by Cervera et al it was revealed that arthritis in SLE tends to have fewer erosions and fixed deformities compared with rheumatoid arthritis.[19] Among the other systems in our study, renal involvement was the second most common (53%) and gastrointestinal system was the least common (7%) system affected.

In our study we found constitutional symptoms in 100% of patients. Study by Kole et al also reveals similar findings.[20] Average duration of constitutional symptoms prior to appearance of skin lesions was about 2-6 month, in our study.

Renal involvement as per the ACR criteria was detected in 80% of patients in our study. It is of key importance that patients with lupus have routine urine analysis with microscopy looking for protein, blood, and cellular casts as the study by Fries et al has revealed that nephritis can occur during a flare of SLE. [21]

Among the 45 patients, four patients developed haematological involvement in terms of leucopenia, lymphopenia and thrombocytopenia as per the ACR criteria. Other systems involved in our study subjects were CNS, cardiopulmonary, gastrointestinal but in very few patients.

Among the immunological parameters, we performed ANA test by EIA, and Hep-2 method and ANA –ENA (Anti Nuclear Antibodies - Extractable Nuclear Antigens) profiles which included anti ds-DNA, anti-Sm and others. ANA were found positive in 98% of cases suggesting its high sensitivity along with high titre (>1:160) in a substantial number of patients (92%). Anti ds-DNA antibody were positive in 85% of cases in those cases where kidney was involved suggesting it is a predictive marker for kidney involvement. Studies conducted elsewhere.[22-24] also showed that higher titre of anti ds-DNA antibody was associated with kidney involvement.

Conclusion

Cutaneous manifestations are some of the commonest and earliest manifestations of SLE. Apart from the classical malar rash and discoid rash described in the ACR criteria, various other LE-specific skin lesions and LE-non-specific skin lesions, as described by Gilliam, aid in the diagnosis and management of SLE. Immunological markers like Anti-ds DNA antibody might act as a predictive marker for renal involvement in SLE.

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