Clinicopathological and Immunological Profile of Patients with Cutaneous Manifestations and their Relationship with Organ Involvement in Systemic Lupus Erythematosus Attending a Tertiary Care Center of Eastern India

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Abstract

Background: Lupus erythematosus (LE) is an autoimmune disorder with diverse clinical manifestations ranging from mild cutaneous disorder to life-threatening systemic illness and associated with varying immunological parameters. Aim: We conducted a study in a tertiary care center of eastern India to determine the clinical pattern, immunological profile of patients with cutaneous manifestations of systemic LE (SLE) and their relationship with organ involvement. Materials and Methods: Fifty-five consecutive patients attending dermatology OPD having features consistent with cutaneous LE and fulfilling the criteria of SLE were included. After proper history taking and clinical examination, routine blood and antinuclear antibody (ANA) profile, histopathological examination, and direct immunofluorescence test were undertaken. Results: Among 55 patients, 49 were female. ANA positivity was the most common association, followed by photosensitivity, malar rash, arthritis, oral ulcer, immunological markers, renal system involvement, discoid rash, serositis, central nervous system (CNS) involvement, and least common being the hematological involvement. Vascular basal cell degeneration was the commonest epidermal change and upper dermal periappendageal and perivascular lymphocytic infiltration was the commonest dermal change observed on histopathological examination. On direct immunofluorescence (DIF) granular pattern was seen in majority of patients. Statistically significant risk of kidney involvement was present both when patient had bullous lesions and DIF positivity of unexposed (DIF-UE) skin. CNS involvement was seen in five patients and it was found to be significantly associated with purpuric lesions. Conclusion: This study reveals cutaneous lesions and DIF testing could be reliable predictors of systemic involvement and strongly suggests DIF testing, routinely in all patients of SLE.

Key Words: Antinuclear antibody profile, cutaneous changes, direct immunofluorescence, systemic lupus erythematosus, systemic involvement

Introduction

Lupus erythematosus (LE) is an autoimmune disorder with diverse clinical manifestations ranging from mild cutaneous disorder to life-threatening systemic illness. Skin including mucous membrane is the second most commonly affected organ after joint involvement.[1] Skin and mucous membrane are symptomatically involved at some point in over 80% of patients with SLE.[2] Moreover, lupus-specific skin lesions[1] (e.g., malar rash and discoid rash) serve primarily as important diagnostic clue, whereas lupus nonspecific skin lesions (e.g., alopecia and purpura) are associated with more active disease, and thus require more aggressive therapy and disease monitoring.[6] A thorough understanding of cutaneous lesions in SLE is crucial for efficient diagnosis and management.

SLE, as we understand, presents with variety of clinical manifestations and immunological and pathological characteristics. However, there is very little data from eastern India to know the demographics, clinical, immunological, and histopathological features of SLE. So, we studied American Rheumatology Association (ARA) criteria positive consecutive cases of documented SLE patients to determine the demographic

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profile, the prevalence, and clinical types of cutaneous manifestations and also to compare, if any, clinical, and/or immunological parameters with the underlying systemic disease process.

Materials and Methods

Study population

This was an institution based, cross-sectional study where consecutive patients attending Outpatient Department of Dermatology of a tertiary care center in eastern India, Kolkata, between May 2011 to April 2012 and who were suspected of SLE were subjected to screening for diagnosis. All the patients who fulfilled the ARA criteria for SLE were included in the study provided some form of cutaneous lesion(s) that were present at the time of presentation and were willing to participate in the study through a written informed consent.

Study tools

Patients were subjected to extensive history taking and thorough clinical examination and findings were recorded in a prestructured case data sheet. A complete hemogram and routine examination and antinuclear antibody (ANA) testing were done in all patients. Histopathological examination was done where deemed necessary. Direct immunofluorescence (DIF) of skin biopsy samples obtained from both sun exposed and unexposed (UE) skin of all patients and performed from Kasturba Medical College, Manipal, due to institutional unavailability.

Analysis of data

At the end of the study, the data were compiled, tabulated, and analyzed with appropriate statistical tests using medical statistical software, Statistica version 10 [Tulsa, Oklahoma: Stat Soft Inc., 2001].

Results and Analysis

Fifty-five patients were included after matching inclusion criteria. Age ranged from 9 years to 50 years with more than half of the patients being young adults between 21 and 30 years (30, 54.54%). Of the 55 patients, 49 were female (89.09%) and 6 were male (10.91%) with an M:F ratio of about 1:8.

Almost equal numbers of patients were found to be residents of urban (29, 52.72%) and rural areas (26, 47.28%) coming from a medium socioeconomic status (29, 52.72%). Majority of them were housewives.

Onset of the disease in most (48, 87.27%) was insidious. Rest (7, 12.73%) had acute onset. Face was the most common site involved (48, 87.27%) with photosensitivity being the most common complaint, followed by upper limbs (25, 45.45%), trunk (23, 41.81%), and lower limbs (7, 12.72%). Patients were also having multiple sites involvement.

Among the lupus specific lesions, malar rash [Figure 1], discoid rash [Figure 2], generalized and photosensitive lupus rash, annular, and papulosquamous rash [Figure 3] were commonly found. Among the nonspecific
manifestations, alopecia (58.18%) was the most common of which nonscarring predominated (65.62%).

Other nonspecific lesions included purpura (14.54%), vesiculobullous lesions (10.90%) [Figure 4], and Raynaud’s phenomenon (10.90%) [Table 1].

Mucosal ulcers were seen in 44 (80%) patients most of them being painless (39, 88.63%). Hard palate was involved in all these cases. The other sites involved in addition were lips, buccal, and nasal mucosa.

Among systemic disorders, musculoskeletal system was most frequently involved [Table 2].

Nonerosive arthritis in the peripheral joints was the most common presentation of musculoskeletal involvement. Asymmetrical joint involvement was more common [Table 3].

The other systemic involvements in this study were kidney (in the form of proteinuria, casts etc.), CNS (seizure, psychosis), lung (pleuritis, effusion), heart (pericarditis, effusion), and hematology (anemia, leucopenia, thrombocytopenia).

Among ARA criteria, ANA (54, 98.18%) positivity was the most common association, followed by photosensitivity (50, 90.90%), malar rash (46, 83.63%), arthritis (45, 81.81%), oral ulcer (42, 76.76%), other immunological markers (42, 76.36%), renal system involvement (24, 43.63%), discoid rash (9, 16.36%), serositis (6, 10.90%), CNS involvement (5, 9.09%), and least common being the hematological system involvement (4, 7.27%) [Table 4].

Complete blood count yielded leucopenia (1 patient), and thrombocytopenia (3 patients) in only 4 out of the 55 patients in this study.

Routine microscopic urine examination, and 24-h urinary protein excretion were done in all patients. Out of the 55 patients, 24 (43.63%) showed changes suggestive of kidney involvement, which included significant quantitative proteinuria (24-h protein >0.5 gm/day in all 24 patients), renal casts (4 patients), and qualitative proteinuria (18 patients).

Complement factor (C3 and C4) estimation was done in our study to determine the prognosis of the disease. Hypocomplementemia was found in nine (16.36%) out of the 55 patients of whom one suffered from urticarial vasculitis.

We preformed ANA with titer, and complete the ANA profile in all our patients [Table 5].

High ANA (in Hep 2 cell line) titer of >1:160, significant for the disease was seen in 50 (92.59%) patients.

Histopathological examination was undertaken for both specific and nonspecific LE lesions, which were doubtful, for confirmation. Basal vacular degeneration with perivascular and periappendageal lymphocytic infiltration was the most common finding.

DIF was done to determine the prognosis of the disease. Tissues were taken from lesional skin and also from nonlesional sun exposed and unexposed areas in all patients [Table 6].

Granular pattern was seen in majority of patients (43, 78.18%). Homogeneous and linear patterns were seen in 5 (9.09%) patients each [Figure 5]. DIF positivity was considered when one or more immunoreactants (IgG, IgA, IgM, C3) were found at the dermoeipidermal junction (DEJ).

| **Table 1: Types of skin lesions (n=55)** |
|-----------------------------------------|
| **Lupus specific**                      | **No. of patients** | **Lupus nonspecific** | **No. of patients** |
|-----------------------------------------|---------------------|-----------------------|---------------------|
| Malar rash                              | 45 (81.81%)         | Alopecia              | 32 (58.18%)         |
| Photosensitive lupus rash               | 25 (45.45%)         | Purpura               | 8 (14.54%)          |
| Papulosquamous lesion                   | 15 (27.27%)         | Raynaud’s phenomenon  | 6 (10.90%)          |
| Discoid rash                            | 9 (16.36%)          | Vasculobullous lesions| 6 (10.90%)          |
| Annular lesion                          | 4 (7.27%)           | EM like               | 4 (7.27%)           |
| Generalized lupus rash                  | 4 (7.27%)           | Calcinosis cutis      | 1 (1.81%)           |
| Mucosal ulcers                          | 44 (80%)            | Urticarial vasculitis | 1 (1.81%)           |
|                                         |                     | Livedo reticularis    | 1 (1.81%)           |
|                                         |                     | Others                | 35 (63.63%)         |

Figure 4: A case of SLE with bullous lesion and underlying ecchymosis
Statistically significant kidney involvement was present when patients had bullous lesions and also DIF positivity of UE (DIF-UE) skin [Table 7] when risk ratios for kidney disease were calculated amongst bulla positive and bulla negative patients, it revealed an odds ratio of 22.14 (95% confidence interval is 1.18–416.16).

Similarly, DIF-UE positive compared to DIF-UE negative patients showed an odds ratio of 108.33 (95% confidence interval is 3.84–3053.5).

CNS involvement was seen in five patients and it was found to be significantly associated with purpuric lesions [Table 8]. Risk of CNS involvement, when purpura was seen compared to when purpura was absent, revealed an odds ratio of 149.29 (95% confidence interval is 6.77–3289.6).

Discussion

SLE is an autoimmune disorder with diverse clinical manifestations ranging from mild cutaneous disorder to life-threatening systemic illness, which may terminate into death.

Analysis of age distribution of SLE patients showed that their age ranged from 9 years to 50 years, which was more or less similar to studies conducted by Masi et al.[5] and Malaviya et al.[6] The peak prevalence was seen in the third decade in both the series. In this study, also almost 64% of patients were in between second and third decades. Two patients were in pediatric age group.

The overall male-to-female ratio in our study was 1:8, which is widely mentioned in the literature.[7] History of inciting drugs is important in case of SLE, the most common drugs implicated being isoniazid, hydralazine, and procainamide.[8,9] In this study, however, no patient was found to be exposed to the offending drugs.

The most common site of LE lesion in this study was face (87%) followed by others. Both lupus specific and nonspecific lesions were detected among which malar rash (lupus specific) was predominant (83%). It is comparable with other studies.[10] Frequency of discoid and other rashes was comparatively less, in comparison to other studies.[10] Among the nonspecific lesions,
nonscarring diffuse alopecia was most common (58%) and quite similar to other studies.[10] Other nonspecific lesions were less common in our patients.

Painless ulcer was the most common mucosal lesion in this study, hard palate being the predominant site. In one study,[11] about half of patients with systemic lupus had oral ulcers that were usually painful if discoid and painless if erythematous. They tend to be located on the hard palate, on the buccal mucosa, or along the vermillion border.

In a study by Zeevi et al.,[4] 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. In this study, bullous lesions were associated with kidney involvement (Fisher's exact test, two-tailed, \( P = 0.005 \)). The relationship between bullous SLE and lupus nephritis in children was demonstrated by Sirka et al.,[12] Purpuric lesions were strongly associated with CNS involvement in our study (Fisher's exact test, two-tailed, \( P < 0.001 \)) which was compatible with the study conducted by Akrekar et al.,[13] Livedo reticularis and erythromelalgia are also commonly seen in lupus patients and it is associated with flaring of cerebral vasculitis.[14] In our study, no such associations were detected.

Among the systems involved in SLE, most frequent one is the musculoskeletal system. In this study, it was involved in 82% of cases. Nonerosive oligoarthritis was more common (78%) than polyarthritis and small joint involvement predominated (98%). The study by Cervera et al.,[15] revealed that arthritis in SLE tended to have fewer erosions and fixed deformities compared with rheumatoid arthritis. Among the other systemic involvements, in this study, kidney was the second most common (44%) and heart was the least common (2%) organ affected.

Kidney involvement as per ARA criteria includes urinary parameters. In this study, significant proteinuria was detected in 24 (43.63%) patients out of 55 patients. It is of key importance that patients with lupus have routine urine analysis for protein, blood, and cellular casts; as in one study,[16] it was revealed that nephritis could occur during a flare of SLE.

Among the 55 patients, 4 patients developed hematological involvement in terms of leucopenia, lymphopenia, and thrombocytopenia as per the ARA criteria. Other systemic involvements were CNS, lung, and heart but in less number of patients.

ARA criteria are the most sensitive for classification of SLE but are of limited value in determining the course and prognosis.[17,18] Studies have revealed that it is also of no use in predicting the outcome of those cases who presents with cutaneous LE without any systemic features.[19,20] In our study, ARA criteria were utilized to fulfill the inclusion criteria only.

In this study, it was seen that among the 11 criterias, the most common was the ANA (98%), followed by photosensitivity (90%), malar rash (83%), and others. The least common was the hematological system involvement (7%). In comparison, a study[21] revealed ANA (99.1%), photosensitivity (22.3%), and malar rash (42.9%) in their series. This study showed a high titer of ANA (>1:160) in a substantial number of patients (92%). Studies had shown that higher titer of anti-ds-DNA antibody was associated with kidney involvement. However, our study did not show significant association of positive anti-ds-DNA with renal involvement. The reasons could be that we had

### Table 7: Association of renal involvement with different clinical and laboratory parameters

| Renal involvement present | Renal involvement absent | \( P \) |
|---------------------------|--------------------------|--------|
| Positive                  | Negative                 |        |
| ACLE                      | 20                       | 26     | 1.000 (Fisher's exact test, two-tailed) |
| Photosensitive rash       | 9                        | 16     | 0.414 (Fisher's exact test, two-tailed) |
| Discoid rash              | 2                        | 7      | 0.271 (Fisher's exact test, two-tailed) |
| Alopecia                  | 9                        | 12     | 1.000 (Fisher's exact test, two-tailed) |
| Bulla                     | 6                        | 0      | 0.005 (Fisher's exact test, two-tailed) |
| ds DNA                    | 20                       | 20     | 0.141 (Fisher's exact test, two-tailed) |
| DIF-UE                    | 13                       | 2      | <0.001 (Fisher's exact test, two-tailed) |

### Table 8: Association of CNS involvement with different clinical and laboratory parameters

| CNS involvement present | CNS involvement absent | \( P \) |
|-------------------------|------------------------|--------|
| Positive                | Negative               |        |
| ds DNA                  | 4                      | 36     | 1.000 (Fisher's exact test, two-tailed) |
| EM-like                 | 3                      | 3      | 0.007 (Fisher's exact test, two-tailed) |
| Purpura                 | 5                      | 3      | <0.001 (Fisher's exact test, two-tailed) |

[10,11,12,13,14,15,16,17,18,19,20,21]
not estimated anti-ds-DNA titer and correlated only positivity.

The concept of ANA-negative lupus was first mooted by Koller et al.\textsuperscript{[22]} In our study, one patient was ANA negative despite use of Hep-2 cell line, and in her, all the features suggestive of lupus were present.

DIF is considered positive when one or more immunoreactants (IgG, IgA, IgM, and C3) are found at the dermo-epidermal junction. DIF showed lesional positivity in most (84%) cases. It was demonstrated in one study that positive DIF from sun protected normal skin helped in assessing the severity of the disease and correlated positively with risk of developing nephritis.\textsuperscript{[23]} In this study, also DIF from unexposed area strongly correlated with renal involvement with 100% sensitivity.

The modified ARA criteria have subsequently been replaced by Systemic Lupus International Collaborating Clinics (SLICC) Classification criteria which takes into account at least one clinical and laboratory criteria each out of the required ≥ 4 criteria.\textsuperscript{[24]} It has been seen in particular that ARA or SLICC criteria though sensitive enough for the diagnosis of SLE are of limited value for determining its further course and prognosis.\textsuperscript{[21]} Therefore, the clinical judgment of the dermatologist along with the serology, histopathological examination, and DIF aid in the diagnosis and management of SLE.

**Conclusion and Limitation**

Our study revealed that both the cutaneous manifestations of SLE and DIF testing could be strong predictors of systemic involvement. We, therefore, recommend DIF testing, including one sample from nonlesional, sun exposed–UE site, routinely in all patients presenting with SLE.

However, our study is limited by the fact that it was a cross-sectional study with limited number of patients and we did not have the facilities to quantitate anti-ds-DNA in titer.

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**Conflicts of interest**

There are no conflicts of interest.

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