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Clinico-Immunological Profile of Systemic Lupus Erythematosus Patients of Pakistan and Their Correlation

Zafar Ayub Khan, Samina Mushtaq, Saba Samreen, Babur Salim, Syed Nazir Ahmed, Pir Muhammad Zahid, Haris Gul

Fauji Foundation Hospital, Rawalpindi Pakistan

ABSTRACT

***Objective*:** To see the clinical and immunological profile of systemic lupus erythematosus (SLE) patients and their correlation with the central nervous system and renal involvement.

***Study Design*:** Cross-sectional study.

Place and Duration of Study: Fauji Foundation Hospital Rawalpindi from Sep 2019 to Sep 2020.

Methodology: One hundred forty patients were selected according to SLE ACR (American College of Rheumatology) criteria. Detailed history and examination, including dermatological examination, were done, and blood samples were taken for baseline investigations and SLE-related autoimmune profile. Statistical analysis was done using SPSS 23 to determine the correlation between skin, central nervous system and renal involvement.

***Results*:** In our study, among the lupus-specific lesions, photosensitivity was most frequent 119 (85%) finding followed by oral ulcers 114 (81.4%), alopecia 112 (80%) and malar rash 81 (57.9%). Among the immunological profile, antinuclear antibody (ANA) was the most frequent 116 (82.9%) finding, followed by anti-double stranded antibody 71 (51.7%). Hypocomplementemia and anti-Sm antibody was significantly associated with lupus nephritis (p-value <0.05). There was no correlation between skin and neuropsychiatric involvement and skin and nephritis.

***Conclusion*:** This study depicts the clinical immune profile of SLE patients in Pakistan. In our patients, autoimmune profile and complement levels could predict renal involvement.

Keywords: Auto-antibodies, Autoimmune, Systemic lupus erythematosus (SLE), Skin rash.

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INTRODUCTION

Systemic lupus erythematous (SLE) is an autoimmune disease. The spectrum includes autoantibody formation, inflammation, and tissue injury in several body parts due to the triggering of various pro-inflammatory processes.[1] It influences young women in their 20s to 30s, mostly in their reproductive age, but it can also occur in children and the elderly.[2] Cutaneous lupus erythematous (CLE) is a disease that affects the value of well-being and quality of life. CLE may manifest as a cutaneous disease only or in the background of systemic lupus erythematous (SLE). Moreover, patients initially detected with solitary CLE may subsequently evolve to SLE. CLE is subdivided into acute, sub-acute, or chronic cutaneous lupus erythematous (ACLE, SCLE, or CCLE, respectively) based on the rash, physical appearance and histopathology. CCLE manifests in about 80%of CLE,[2] and discoid lupus erythematous. (DLE) is the main presentation of CCLE.[3] The physical appearance of DLE mostly is round and results in alopecia and scar formation.[3] Skin appearance of SLE can also be categorized into Lupus erythematosus (LE)-specific and LE-nonspecific lesions. LE-specific cutaneous lesions mostly emerge in patients with SLE and thus can be picked up as a disease (e.g. "malar rash", discoid lupus lesions), while LE-nonspecific skin lesions are not characteristic of LE as they can also be seen in other autoimmune diseases. The presence of LE-nonspecific skin changes often implies systemic involvement in LE patients. The most common LE-nonspecific skin lesions are livedo reticularis and thrombophlebitis due to LE-related coagulopathy or secondary cutaneous vasculitis.[4] Exposure to ultraviolet (UV) rays is one of the main causes of flares in SLE patients. Based on Mak *et al.* study, contact of UV rays, particularly UV-B, is, determined by dose. SLE patients with higher UV light will have greater damage to keratinocytes and more inflammation.[5]

The skin and mucous membranes are affected on most occasions in over 80% of patients with systemic lupus erythematosus (SLE). Cutaneous manifestations of systemic lupus erythematosus can present as epidermal, vascular, and mucous membrane lesions. Cutaneous illness may come earlier than systemic involvement, so the dermatologist can pick the disease before the systemic symptoms are evident. This will give the advantage of helping in properly managing patients

Correspondence: Dr Zafar Ayub Khan, House No. 118, Sector-D, Street No. 5, Alharam Model Town, Ring Road Hayatabad Peshawar, Pakistan

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and will decrease the consequent morbidity and mortality. Cutaneous lesions in patients with SLE are the main disease manifestations which give information that may be of diagnostic as well as prognostic significance. The cutaneous lupus erythematosus disease area and severity index (CLASI) is used as a medical device that gauges the disease activity, measures the disease-related skin involvement, and specifies guidelines for identifying a clinical alteration; this medical tool measures disease damage in cutaneous lupus erythematosus.[6] Predictable frequency rates in the USA and Europe range from 1-23 per 100,000 per year. The occurrence in adults is as high as 150 per 100,000 in the United States and 20-50 per 100,000 in Europe. Prevalence rates generally fall within 30-50 per 100,000 populations. Incidence rates vary from 0.9 per 100,000 to 3.1% annually.[7]

A complete analysis of the existing SLE epidemiologic data in Pakistan has not been performed so far. Therefore, various abnormalities in the skin, kidney, haematological, musculoskeletal, pulmonary, cardiovascular and neurological systems and their frequency and prevalence in our region remain largely unknown.

Skin involvement in SLE correlates to disease flare and internal organ involvement, but there have been no such studies in Pakistan that include the correlation of skin rashes with internal organ pathology. Hence our study will help to assess and predict patients' clinical and immunological correlation with renal involvement.

METHODOLOGY

This was a cross-sectional study conducted at the Rheumatology Outpatient Department (OPD), Fauji Foundation Hospital (FFH), Rawalpindi Pakistan. After taking approval from the Ethical Committee of the hospital, the study was carried out from September 2019 to September 2020. Informed consent was taken from all patients included in the study.

By using the WHO calculator, sample size was calculated. Following were the calculations: Confidence level=95%, anticipated population proportion= 36.3%,[8] absolute precision required=8%, Sample size (n) approximately=140 patients.

Inclusion Criteria: Patients diagnosed with SLE according to ACR criteria9 were included.

Exclusion Criteria: Patients with a history of drug-induced lupus, overlap syndrome and mixed connective tissue disease were excluded from the study.

All patients of SLE meeting the inclusion criteria who presented to Rheumatology OPD of FFH were assessed with detailed history and physical examination. The detailed history of the patients included duration of disease, number of miscarriages or thrombotic events, symptoms of SLE and any examination or laboratory parameter suggestive of disease flare. A dermatologist evaluated the patients for diagnosis of specific cutaneous manifestations of SLE. A blood sample was taken from all patients and sent for routine investigations, including blood complete picture (CP), renal function tests (RFTs), Urine routine analysis (for casts and proteins), and muscle enzyme levels. Immune profile included ANA (antinuclear antibody), anti-dsDNA (anti-double stranded antibody), extractable nuclear antigen (ENA profile),antiphospholipid antibody (APL) profile and complement levels.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Mean and standard deviation was calculated for numeric variables, and frequencies with percentages were calculated for categorical data. Paired t-test was used to compare means of continuous data. In addition, a Chi-square test was used to compare the skin manifestations and CNS and renal involvement, and the *p*-value ≤0.05 was considered significant.

RESULTS

A total of 140 patients were included in the study, and 138 (98%) were female. The mean disease duration was 42.0±45.0 months (Table-I).

Photosensitivity was found in 119 (85.0%) of the patients, followed by oral ulcers 114 (81.4%), alopecia 112 (80.0%) and malar rash 81 (57.9%). 28 (20.0%) of the patients had urticaria and 15 (10.7%) had SCLE and discoid rash. Panniculitis was present in 9 (6.4%) of the patients and lupus profundus in 2 (1.4%). Raynaud phenomena was present in 93 (66.4%), arthritis in 92 (65.7%), fever in 65 (46.4%), sicca symptoms in 55 (39.3%), lupus nephritis in 41 (29.3)% and CNS involvement in 15 (10.7%) (Table-II).

Of the laboratory parameters, 116 (82.9%) had positive ANA, 71 (50.7%) positive dsDNA, 80 (57.1%) had anemia, 65 (46.4%) had hypocomplementemia, 45 (32.1%) leucopenia, 45 (32.1%) positive anti Ro, 27 (19.3%) anti La, 21 (15%) anti Sm, 29 (20.7%) anti-RNP. Anti-cardiolipin antibody was present in 37 (26.4%), lupus anticoagulant in 2.1% (3) and beta 2 glycoprotein in 1 (0.7%) (Table-III).

Table-I: Patients' Demographics (n=140)

Patients Demographics	n (%)
Age (Mean±SD) years	33.8±12.6
Gender	
Female	98 (98.6)
Male	2 (1.4)
Marital Status	
Married	69 (49.3)
Single	69 (49.3)
Miscarriages within 10 weeks	13 (9.2)
Miscarriages after 10 weeks	10 (7.1)
Disease duration in months (Mean±SD)	42.0±45.0
Malar rash	81 (57.9)
Discoid rash	15 (10.7)
Photosensitivity	119 (85.0)
Alopecia	112 (80.0)
Oral ulcers	114 (81.4)
SCLE (Subacute Cutaneous Lupus Erythematosus)	15 (10.7)
Panniculitis	9 (6.4)
Livedo reticularis	4 (2.9)
Bullous lesions	3 (2.1)
Lupus profundus	2 (1.4)
Lupus tumidus	2 (1.4)
Urticaria	28 (20.0)
Telangiectasia	2 (1.4)
Purpura	1 (0.7)

Table-II: Extra-Cutaneous Manifestations (n=140)

Extra-Cutaneous Manifestations	n (%)
Arthritis	92 (65.7)
Vasculitis	10 (7.1)
Raynauds	93 (66.4)
Dry mouth	55 (39.3)
Dry eyes	44 (31.4)
Fever	65 (46.4)
Nephritis	41 (29.3)
Neurologic involvement	15 (10.7)
Serositis	10 (7.1)
Myositis	9 (6.4)

No significant association of dermatological manifestations was seen with either renal or CNS disease. Of the antibodies, anti-Sm and hypocomplemtia were correlated with lupus nephritis (*p*-value<.5) (Table-IV).

DISCUSSION

Systemic lupus erythematosus is an immune-mediated multisystem disease which ranges in manifestations from mild mucocutaneous involvement to severe internal organ insults, endangering the function and survival of the individual and impairing quality of life and both physical and social well-being.

In our study, age analysis revealed a wide range of patients from 12-69 years, which was consistent with the previous studies by Lewis *et al*.[10] However, despite this wide range of patients, predominant incidence occurs in the third and fourth decade, as shown by 75%of the patients in this study.

Table-III: Laboratory Parameters and Serology (n=140)

Laboratory Parameters and Serology	n (%)
Anemia	80 (57.4) (Mean Hbg/dl (8.80±2.56)
Leucopenia	45 (32.6%) (Mean wbc count = 3.5×10^9±1.1)
Thrombocytopenia	47 (33.3%) (Mean Platelet count = 88×10^9±13)
Anti Nuclear Antibody (ANA)	116 (82.9)
Antids DNA	71 (50.7)
low C3,C4	65 (46.4)
Anti Ro	45 (32.1)
Anti La	27 (19.3)
Anti Sm	21 (15.0)
Anti RNP	29 (20.7)
Lupus anticoagulant	3 (2.1)
Anticardiolipin antibody	37 (26.4)
Beta2 glycoprotein antibody	1 (0.7)

Table-IV: Association of dermatological manifestations with nephritis and neuropsychiatric involvement (n=140)

Dermatological Manifestations	Renal Involvement Present		Renal Involvement. Absent		*p*-value	Central Nervous System Involvement Present		Central Nervous System involvement Absent		*p*-value
	Positive n (%)	Negative n (%)	Positive n (%)	Negative n (%)		Positive n (%)	Negativ n (%)	Positive n (%)	Negative n (%)	
Malar Rash	24 (17)	16 (11)	57 (40.7)	43 (30.7)	0.85	10 (7.1)	5 (3.5)	71 (50.7)	55 (39.2)	0.58
SCLE (Subacute Cutaneous Lupus Erythematosus)	4 (2.8)	36 (25.7)	10 (7.1)	90 (64.2)	1.00	2 (1.4)	13 (9.2)	13 (9.2)	113 (80.7)	0.662
Discoid Rash	2 (1.4)	37 (26.4)	13 (9.2)	87 (62.1)	0.23	2 (1.4)	12 (8.5)	13 (9.2)	113 (80.7)	0.647
Panniculitis	3 (2.14)	37 (26.4)	5 (3.5)	95 (67.8)	0.68	2 (1.4)	13 (9.2)	7 (5)	119 (85)	0.245
Urticaria	6 (4.2)	34 (24.2)	21 (15)	79 (56.4)	0.48	3 (2.1)	12 (8.5)	25 (17.8)	101 (72.1)	1.000
Livedo Reticularis	1 (0.7)	39 (27.8)	3 (2.1)	97 (69.2)	1.00	-	15 (10.7)	4 (2.8)	122 (87.1)	0.484
Bullous	-	40 (28.5)	3 (2.1)	97 (69.2)	0.55	-	15 (10.7)	3 (2.1)	123 (87.8)	0.546
Alopecia	33 (23.5)	7 (5)	79 (56.4)	21 (15)	0.81	11 (7.8)	4 (2.8)	102 (72.8)	24 (17.1)	0.484

The gender involvement was predominantly female as 98% were female patients, somewhat more in comparison with previous research was done by Rider *et al*. in 2018.[11] It may be due to institutional affiliation since our institution caters for female family members of war veterans. Drug-induced lupus (DILE) is also an important subset of SLE, which mostly presents with mucocutaneous involvement and sparing severe internal organ derangement.[12] Pakistan is an endemic region for tuberculosis; hence anti tuberculous therapy used in the treatment can be considered an important cause of DILE. This subset was not included in our study.

Both lupus-specific and lupus non-specific cutaneous lesions were found in our patients. Amongst the skin manifestations, photosensitive skin rash was most frequent, present in 85.1% of the patients, followed by non-scarring alopecia and malar rash in 80.1% and 57.4% of patients, respectively. This finding is consistent with the previous studies carried out in Pakistan.[13] Other lupus-specific lesions include discoid lupus (10.6%) and SCLE (10.6%), and lupus panniculitis (6.4%). Discoid lupus is the most common form of chronic cutaneous lupus with a gene good prognosis.[14]

Livedo reticularis was found in 2.8% and bullous lesions in 2.1% of patients in our cohort. Although livedo reticularis is more closely associated with the presence of antiphospholipid antibodies,[15] this was independent of the antiphospholipid antibody positivity in our Population.

Oral ulcers are present in 81.6% of the patients, per the previous studies.[16] The pathogenesis underlying oral ulcers has been postulated to be antigen-antibody complexes forming, causing degeneration of keratinocytes in the basement membrane of the oral mucosa. Raynaud's was manifested in 66.7% and arthritis (mostly non-erosive) in 66%. Fever was seen in 46.1% of the patients in our cohort, which in the previous studies has been shown in 36-86% of the patients; hence our results were largely consistent in this regard.[17] The causes of fever in SLE other than the disease itself include infection, malignancy and other autoimmune diseases.[18] Dry mouth was seen in 39% of the patients, followed by dry eyes in 31.9%, and sicca symptoms in 9-33% of the patients, as mentioned in the literature.[19] Nephritis was seen in 29.1% of the patients in this cohort which is almost similar to that found in the previous studies.[20] Lupus nephritis is one of the major and clinically important complications of the SLE, which is also the main determinant of its prognosis.

Neuropsychiatric involvement was seen in 10.6% of the patients, which is another important cause of morbidity and mortality in SLE. Unfortunately, neuropsychiatric involvement mostly occurs in the early disease, and despite advances in diagnosis and management, there is a lack of any gold standard investigation to confirm its presence.[21]

The frequency of anaemia, leucopenia and thrombocytopenia was 57.4%, 32.6% and 33.3%, respectively. Anaemia is a common haematological abnormality seen in patients with SLE, with common etiologies including anaemia of chronic disease, iron deficiency anaemia, autoimmune hemolytic anaemia, anaemia of renal failure and others.[22] ANA was positive in 83% of the patients and anti-ds-DNA in 51.1%. Out of 46.1% of patients had hypocomplementemia, which was significantly correlated with nephritis. A study by Sawada *et al*. has also shown similar results.[23] Anti-Ro, Anti-RNP, Anti-La and Anti-Sm were positive in 32.6%, 21.3%, 19.9% and 15.6% of the patients, respectively. Of the anti-phospholipid antibodies, anticardiolipin was found in the highest frequency (27%), followed by lupus anticoagulant (2.8%) and beta 2 glycoprotein (1.4%), which is consistent with previous studies.[24]

Neither of the lupus-specific or lupus non-specific dermatological manifestations was shown to have any significant correlation with nephritis or neuropsychiatric involvement. Its cause may be because disease activity involving internal organs may be independent of the obvious clinical features like rash and LE-specific skin lesions are T cell-mediated immune responses. LE non-specific lesions are due to immune complex-mediated damage.

LIMITATIONS OF STUDY

The main limitations of our study include the predominant female cohort of the patients and the absence of a control group resulting in a lack of comparison. In addition, tissue diagnosis of the patients for renal specimen was not performed.

The future research may include a detailed evaluation of the patients with the help of skin biopsy, including histopathologic examination and immunofluorescence and finding the correlation between various dermatological manifestations and internal organ involvement.

CONCLUSION

Our study showed that the autoimmune profile and complement level could predict renal involvement in SLE patients in the Pakistani Population.

Conflict of Interest: None.

Author's Contribution

ZAK: Introduction methods, SM: Data collection, SS: Results calculation, BS: Titte, SNA: Abstract, PMZ: Discussion, HG: Data analysis.

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