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LUPUS: Trends of the disease in Northwest Punjab

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ABSTRACT

Objectives: The aim of this study was to study the clinical profile of systemic lupus erythematosus (SLE) patients from a tertiary care center in Northwest Punjab.

Materials and Methods: It was an observational cross-sectional study conducted at the Rheumatology Clinic, Adesh Hospital, Bathinda. Twenty-five patients classified to be suffering from SLE as per standard classification criteria (Systemic Lupus International Collaborating Clinics [SLICC]) were enrolled after obtaining consent for the same. Socio-demographic data, disease duration, disease activity, and treatment received were recorded. Analysis was performed for the various parameters.

Results: The majority of patients (88%) were females with a female to male ratio of 7.3:1 with mean age of 30.5 years. Mucocutaneous involvement (92%) followed by musculoskeletal (84%). Nephritis was seen in 36%, deforming arthritis in 8%, and pleural involvement in 36% while ILD in 12%. Pericarditis was seen in 16%, and myocarditis was seen in 12%. Neurological involvement was seen in 36% patients with two cases of thrombotic CVA, one case of SAH and three cases of seizure disorder. Psychiatric symptoms were observed in 16% cases. AIHA was seen in 12%, leukopenia in 44%, and thrombocytopenia in 68%. Most common antibody was anti-dsDNA being present in 48% cases, followed by Anti Ro-60, Ro-52, Anti Sm, and Anti U1RNP antibody.

Conclusion: We found a striking difference in the prevalence of pleuropulmonary features, neuropsychiatric features, Leukopenia, and thrombocytopenia in our subgroup of population as compared to the earlier studies from central and southern parts of India thus further emphasizing the fact that ethnic backgrounds predispose a patient for different phenotype.

Keywords: Lupus nephritis, Neuropsychiatric systemic lupus erythematosus, Antinuclear antibodies, Thrombocytopenia, Anti-dsDNA LUPUS: Trends of the disease in Northwest Punjab

INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disorder with multisystemic involvement. It has a broad spectrum of clinical manifestations encompassing various organs and tissues. The disease starts with a preclinical phase which is characterized by various autoantibodies and it proceeds with a more disease-specific clinically overt autoimmunity phase.

Women are affected up to 12 times more frequently than men.[1,2] About 65% of patients with SLE have disease onset between the ages of 16 and 55, 20% present before the age of 16 and 15% after the age of 55 years.[3] Genetic, epigenetic, environmental, and hormonal factors have been implicated in the pathogenesis of SLE.

Production of autoantigens during apoptosis, decreased disposal, deregulated handling, and presentation, is important for initiation of the autoimmune response.[4] The classification criteria (ACR and SLICC) are as follows [Table 1].[5,6]

Table 1: The revised ACR and the SLICC classification criteria for SLE Criteria.

	ACR criteria (1997 update) (Tan *et al*, 1982; Hochberg, 1997*)	SLICC criteria (2012) (Petri *et al*., 2012a*)
Skin	1. Malar rash. Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. 2. Discoid rash. Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occur in older lesions 3. Photosensitivity. Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.	1. Acute cutaneous lupus (lupus malar rash [do not count if malar discoid], bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash), or subacute cutaneous lupus (non-indurated psoriasiform and/or annular polycyclic lesions that resolve without scarring) 2. Chronic cutaneous lupus (classic discoid rash: localized or generalized, hypertrophic [verrucous] lupus, lupus panniculitis [profundus], mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap 3. Non-scarring alopecia
Ulcers	4. Oral or nasopharyngeal ulceration	4. Oral or nasal ulcers
Synovitis	5. Non-erosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling or effusion	5. Inflammatory synovitis in ≥2 joints: a. Characterized by swelling or effusion, or b. Tenderness and ≥30 min of morning stiffness
Serositis	6. Any of: a. Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion b. Pericarditis: Documented by ECG or rub or evidence of pericardial effusion	6. Serositis: Any of a. Typical pleurisy lasting >1 day, or pleural effusions, or pleural rub b. Typical pericardial pain (pain with recumbency improved by sitting forward) for >1 day, or pericardial effusion, or pericardial rub or pericarditis by electrocardiography
Renal disorder	7. Any of: a. Persistent proteinuria >0.5 g/day or >3+ if measurement is not performed b. b. Cellular casts: red cell, hemoglobin, granular tubular or mixed	7. Any of: a. Urine protein/creatinine (or 24 h urine protein) representing ≥500 mg of protein/24 h, or b. b. Red blood cell casts
Neurological disorder	8.Any of: a.Seizures in the absence of offending drugs or known metabolic derangements b. b. Psychosis in the absence of offending drugs or known metabolic derangements	8.Any of: a.Seizures b. Psychosis c. Mononeuritis multiplex d. Myelitis e. Peripheral or cranial neuropathy f. Cerebritis (acute confusional state)
Hematological disorder	9. Any of: a. Hemolytic anemia with reticulocytosis b. Lymphopenia: <1500/mm3 c. Thrombocytopenia: <100,000/mm3	9. Hemolytic anemia 10. Leucopenia (<4000/mm3), or lymphopenia (<1000/mm3) at least once 11. Thrombocytopenia (<100,000/mm3) at least once

Clinical features

1. Mucocutaneous features: Mucocutaneous involvement is very common in lupus patients with both lupus-specific and non-specific lesions [Table 2].[7]
2. Musculoskeletal features: Arthritis/arthropathy, myositis, and avascular bone necrosis.

Renal features:

3. Renal involvement is seen in up to 40–50% of patients and is an important cause of morbidity, recurrent hospital admissions, and mortality. Immune complex formation and deposition in the kidney results in intraglomerular inflammation. This further causes influx of leukocytes and activation and proliferation of resident renal cells along with compliment pathway activation. Proteinuria of different grades (nephritic and nephrotic) is the predominant feature of lupus nephritis.[8]
4. Nervous system features: Lupus can involve both the CNS and the peripheral nervous system.[9]

Central nervous system aseptic meningitis, cerebrovascular disease, demyelinating syndrome, movement disorder (chorea), myelopathy, seizure disorder, acute confusional state, cognitive dysfunction, mood disorder, psychosis peripheral nervous system acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome), autonomic disorder, mononeuropathy, single/multiplex, neuropathy, cranial, and polyneuropathy.

5. Pleura and lungs: Pleuritis is the most common pleuropulmonary manifestation of SLE.[10] Pleuritic

Table 2: Classification of lupus-associated skin lesions.

LE specific skin lesions	LE non-specific skin lesions
Acute cutaneous LE	Cutaneous vascular disease
Localized	Vasculitis
Generalized	Leukocytoclastic
	Palpable purpura
Subacute cutaneous LE	Urticarial vasculitis
Annular	Polyarteritis nodosa-like
Papulosquamous (psoriasiform)	Papulonodular mucinosis
	Dego's disease-like
Chronic cutaneous LE	Atrophy blanche-like
"Classic" DLE	Livedo reticularis
Localized	Thrombophlebitis
Generalized	Raynaud's phenomenon
Hypertrophic (verrucous) DLE	Erythromelalgia
Lupus panniculitis (profundus)	LE non-specific bullous lesions
Mucosal LE	Epidermolysis bullosa acquisita
Lupus tumidus	Dermatitis herpetiformis-like bullous LE
Chilblains lupus	Pemphigus erythematosus
	Porphyria cutanea tarda
	Urticaria
	Vasculopathy
	Anetoderma/cutis laxa
	Acanthosis nigricans (type B insulin resistance)
	Periungual telangiectasia
	Erythema multiforme
	Leg ulcers
	Lichen planus
	Alopecia (non-scarring)
	"Lupus hair"
	Telogen effluvium
	Alopecia areata
	Sclerodactyly
	Rheumatoid nodules
	Calcinosis cutis

chest pain is seen in 45–60% of patients and may occur with or without a pleural effusion. Clinically, apparent pleural effusions have been reported in up to 50% cases. Effusions are usually bilateral. The effusion is invariably exudative with higher glucose and lower lactate dehydrogenase levels in comparison to what is seen in patients of rheumatoid arthritis.

6. Cardiovascular features: Pericarditis occurs in 15–25% of patients with SLE.

Pericardial effusions are usually mild to moderate. They can have varied presentations ranging from an asymptomatic occurrence to cardiac tamponade.

Myocardial involvement is rare and it occurs usually in the presence of generalized lupus activity.

7. Hematological features: Anemia, leucopenia, lymphopenia, thrombocytopenia, lymphadenopathy, and splenomegaly.
8. Others liver, gastrointestinal tract, and ophthalmological involvement.

Diagnosis serological

TESTS Antinuclear antibodies (ANAs): The ANA (immunofluorescence) assay is frequently used as screening test for possible connective tissue disease because of its very good sensitivity (>90% when using human cultured cells as the substrate) and simplicity.

Pattern and end titers are very important as far as interpretation of ANA is concerned. ANA is positive in up to 98% cases of lupus.[11]

Anti-double stranded DNA, Anti-Smith, Ant U1RNP, Anti Ro, Anti La, and antiphospholipid antibodies are other frequently encountered antibodies.

Histopathological test skin biopsy, renal biopsy.

Management

It depends on the (1) organ involvement, (2) nature of involvement (organ/life threatening vs. non-organ/life threatening), (3) disease activity, (4) age and sex of the patient, and (5) comorbidities.

Drugs includes: (1) NSAIDS (Nonsteroidal anti-inflammatory drugs), (2) GLUCOCORTICOIDS, (3) DMARDS (hydroxychloroquin, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, etc.), (4) cyclophosphamide, and (5) BIOLOGICALS—Anti CD20 (Rituximab) Anti BAFF (belimumab) interferon alpha therapies.

MATERIALS AND METHODS

After approval from our Institutional Review Board and Ethics Committee, a total of 25 SLE patients fulfilling the inclusion and exclusion criteria were enrolled at Rheumatology Clinic, Adesh Hospital from June 2019 to November 2019, after obtaining consent. Socio-demographic data, organ system involvement, disease duration, disease activity, and treatment received were recorded according to a pro forma. Patients underwent full physical examination. Blood samples were taken from patients to determine the complete blood count with other routine biochemistries. ANA and other relevant investigations were done.

RESULTS

Results from the study are depicted in [Table 3].

EPIDEMIOLOGY 25 patients of lupus were enrolled over a period of 6 months. The majority of patients (88%) were

Table 3: Depicting the various patient characteristics, and organ system involvement.

Name	Age	Sex	Mucocut	Arthritis	Myositis	Pleural	Pulmonary	Pericard	MYOCARD	Renal	Neuro	Psych	Others	ANA	Other antibodies	Anemia	Leucopenia	Lymphopenia	Thrombocytopenia	Disease duration
1	22	F	Yes	Yes	No	No	No	No	No	No	Yes	No	No	Positive	No	Yes	No	No	No	2 yrs
2	34	F	Yes	Yes	No	Yes	No	No	No	Yes	No	No	No	Positive	Anti-ds DNA	Yes	Yes	Yes	Yes	1 yr
3	25	F	Yes	No	No	No	No	Yes	No	No	No	No	No	Positive	Ant Ro 60,52	No	No	No	Yes	4 yrs
4	19	F	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Positive	Anti-ds DNA	Yes	Yes	Yes	Yes	1 yr
5	17	F	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No	Positive	Anti-ds DNA	Yes	Yes	Yes	Yes	3 yrs
6	48	F	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No	Positive	Anti-ds DNA	Yes	Yes	No	Yes	5 yrs
7	33	F	No	No	No	No	No	No	No	No	No	No	No	Positive	No	Yes	Yes	Yes	Yes	1 yr
8	44	F	Yes	Yes	No	Yes	Yes	No	No	No	No	Yes	No	Positive	Anti-ds DNA	Yes	No	No	No	2 yrs
9	17	F	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No	Positive	Anti-ds DNA	Yes	No	No	No	1 yr
10	27	F	No	Yes	No	No	No	No	No	No	No	No	No	Positive	No	Yes	Yes	Yes	Yes	5 yrs
11	23	F	Yes	Yes	N/O	Yes	No	Yes	No	No	Yes	Yes	No	Positive	No	No	Yes	Yes	Yes	3 yrs
12	28	F	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No	Positive	Anti RO 52,U1RNP	Yes	No	No	No	2 yrs
13	36	F	Yes	Yes	Yes	No	No	No	Yes	Yes	No	No	No	Positive	Anti-ds DNA	Yes	N/O	Yes	Yes	6 yrs
14	19	F	Yes	Yes	No	No	No	No	No	No	Yes	No	Yes(Hep)	Positive	Anti-ds DNA	Yes	Yes	No	No	2 yrs
15	27	F	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Positive	Anti-ds DNA	Yes	No	No	No	4 yrs
16	25	F	Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	Positive	Anti RO 52,U1RNP,Sm	Yes	Yes	Yes	No	2 yrs
17	33	F	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No	Positive	No	No	No	No	No	4 yrs
18	30	F	Yes	Yes	No	No	No	No	No	No	No	No	No	Positive	No	No	No	No	Yes	1 yr
19	21	F	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	Positive	Anti-ds DNA	Yes	No	No	Yes	6 yrs
20	24	F	Yes	No	No	No	No	No	No	No	Yes	Yes	No	Positive	Anti ds DNA	Yes	No	No	Yes	2 yrs
21	52	F	Yes	Yes	No	Yes	No	No	No	No	No	No	No	Positive	No	No	No	No	Yes	4 yrs
22	47	F	Yes	Yes	No	No	No	No	No	No	No	No	No	Positive	No	Yes	Yes	Yes	Yes	2 yrs
23	28	M	Yes	Yes	No	No	No	No	No	Yes	No	No	No	Positive	Anti-ds DNA	Yes	No	Yes	Yes	5 yrs
24	44	M	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	Positive	Anti Sm	Yes	No	No	Yes	2 yrs
25	38	M	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	No	Positive	Anti Sm	No	Yes	No	Yes	6 yrs

females with a female to male ratio of 7.3:1. The age at time of diagnosis varied from 17 years to 52 years with mean age of 30.5 years. The majority of patients were between 20 and 40 years of age group (64%). About 16% patients were below 20 years of age

while 20% patients were above 40 years at time of diagnosis.

Organ system involvement

Constitutional features (fatigue and weight loss) were seen in 76% patients. Mucocutaneous manifestations were seen in 92% of patients. Arthralgias and arthritis were seen in 84% patients while deformities were seen only in two patients overall. Myositis was observed in 6 (24%) patients. Pleural involvement (pleuritis/pleural effusion) was seen in 36% patients. Parenchymal lung involvement in the form of interstitial lung disease was seen in 12% patients with the majority of 66% having concomitant pleural involvement. Pericardial involvement (pericardial effusion) was evident on 2D ECHO in 4 (16%) patients. The majority of these had simultaneous pleural involvement also. Myocardial involvement was seen in three patients with all of them having concomitant myositis also. Nine (36%) patients had evidence of lupus nephritis on urine routine, urine P/C ratio, and 24 h urinary protein quantification. Renal biopsy was done only in three patients as rest did not provide consent for the same. Nine patients had neurological involvement with two out of them having thrombotic CVA, one having sub-arachnoid hemorrhage, and three having seizure disorder. Psychiatric manifestations were evident in four patients with majority (75%) of them having neurological involvement also. Only one patient had hepatic involvement inform of autoimmune hepatitis. Average duration of onset of symptoms was 3 years before diagnosis.

Lab parameters

ANA was positive in 100% cases with homogenous pattern being the most common in 80% cases. Anti-dsDNA positivity (elevated titers) was seen in 48% cases, Anti Sm antibody was positive only in two patients while Anti Ro 60, Ro 52, and U1RNP were seen in three cases. Anemia was present in 76% (19) patients while 12% (3) cases had a positive coombs test. Eleven patients had leukopenia with of them having concomitant lymphopenia suggesting active disease. Seventeen (68%) patients had thrombocytopenia. One patient presented with isolated thrombocytopenia along with sub-arachnoid hemorrhage. ESR was elevated in 18 cases while elevated CRP was seen in six patients with the majority of them having pleural involvement and arthritis.

DISCUSSION

SLE is the prototypic autoimmune disease characterized by multisystem involvement and the production of an array

of antibodies which is most commonly seen in females of childbearing age group (between puberty to menopause). The same was evident in this study with F: M ratio being 7.3:1 and average age at the time of diagnoses being 30.5 years.

Similar results were seen in study by Muzzaffar *et al*. from Medanta Hospital where they studied 305 SLE patients out of which around 85% patients were females. The various organ system involvements in different Indian studies are shown in [Tables 3 and 4]. Most common organ system involvement in our study was mucocutaneous (92%). Similar results were observed in study by Malaviya *et al*.[12] where close to 90% patients has mucocutaneous involvement. Musculoskeletal system was affected in 84% patients in our study. About 92%, 88%, and 90% affection of MSK were seen in study by Malaviya *et al*.,[12] Saigal *et al*.,[13] and Binoy *et al*.[14]

The prevalence of lupus nephritis in our study was 36%. Saigal *et al*.[13] and Binoy *et al*.[14] in their respective studies had a lupus nephritis prevalence of 57% and 34%, respectively. The prevalence of pleural involvement (pleuritis and pleural effusions) in our study was 36% while ILD was seen in 12% cases. The incidence of ILD was 11.7%, 8%, and 12.6% in studies by Saigal *et al*.,[13] Binoy *et al*.,[14] and Aggarval *et al*.[15] respectively. Neurological and psychiatric features were seen in 36% and 16% patients in our study while it was 38%, 13.3%, 13.3%, and 4.6% in studies by Malaviya *et al*.,[12] Saigal *et al*.,[13] Binoy *et al*.,[14] and Aggarval *et al*.,[15] respectively. Cardiovascular involvement in the form of pericardial effusion and myocarditis was seen in 16% and 12% cases in our study. About 29%, 6.7%, 5.3%, and 2.3% was the prevalence of CVS involvement in various other Indian studies,[12-15] respectively. The prevalence of autoimmune hemolytic anemia in our study was 12%, while in various other studies[12-15] were 7%, 25%, 1.3%, and 8.1%, respectively. Leukopenia was seen in 44% cases while other studies[12-15] had 16%, 43.4%, 14.7%, and 18.4% cases of leukopenia. About 68% cases in our study had thrombocytopenia whereas it was seen only in 11%, 33.3%, 12%, and 15% cases in other Indian studies, respectively.[12-15] [Table 5] depicts various studies conducted in India.

Table 4: Depicting organ system involvement in study of 305 patients at Medanta Hospital, Gurgaon.

Organ involvements	No.	% age
Constitutional	169	55.40
Musculoskeletal	226	71.10
Mucocutaneous	244	80.00
Hematological	132	43.30
Renal	88	28.90
Cardiac	91	29.80
Pulmonary	81	26.60
Neurological	68	22.30
GIT	69	22.60
Ocular	40	13.10

Anti-DNA antibodies constitute a subgroup of antinuclear antibodies that bind to either single-stranded or double stranded DNA. Both subtypes of DNA-binding antibodies may be found in SLE.

Actual prevalence described is 60–90% of patients, is highly specific to SLE: Less than 0.5 % of healthy people or patients with other autoimmune diseases have anti-dsDNA antibodies, whereas 70% of SLE patients are positive.[16]

Because of their high specificity, anti-dsDNA antibodies are universally used as a diagnostic criterion for SLE (70–98% of patients are positive for such antibodies).

Serum anti-dsDNA antibody levels have been correlated with nephritis in some cohorts with progression to end-stage renal disease.[17]

Table 5: Depicting various organ system involvement in different Indian studies in the past.

Clinical manifestation	Malaviya[12] (1988) *n*=329 (%)	Binoy[14] (2003) *n*=75(%)	Saigal[13] (2011) *n*=87 (%)	Sachin Aggrava[15] (2013) *n*=87 (%)
Malar Rash	85	40	43.3	71.3
Discoid Rash	NA	5.3	1.7	32.2
Oral ulcers	64	64	61.7	42.53
Photosensitivity	67	32	75	63.2
Arthralgia	92	89.3	86.7	52.9
Autoimmune hemolytic anemia	7	1.3	25	8.1
Leukopenia	16	14.7	43.3	18.4
Thrombocytopenia	11	12	33.3	14.9
Nephritis	73	33.3	56.7	69
Pulmonary	NA	8	11.7	12.6
Cardiovascular	29	5.3	6.7	2.3
Neuropsychiatric	38	13.3	13.3	4.6
DsDNA	55	76	65	93.9

In our study, Anti-ds DNA titers were raised in 48% patients and it correlated with the activity of the disease particularly lupus nephritis.

CONCLUSION

A total of 25 patients were studied out of which 88%

were females with the mean age of 30.5 years. The most common symptoms were related to mucocutaneous involvement (92%) followed by musculoskeletal (84%). Nephritis was seen in 36%, deforming arthritis in 8%, and pleural involvement in 36% while ILD in 12%. Pericarditis was seen in 16%, and myocarditis in 12%. Neurological involvement was seen in 36% patients with two cases of thrombotic CVA, one case of SAH, and three cases of seizure disorder. Psychiatric symptoms were observed in 16% cases. AIHA was seen in 12%, leukopenia in 44%, and thrombocytopenia in 68%. Most common antibody was Anti-dsDNA being present in 48% cases,

followed by Anti Ro-60,Ro-52, Anti Sm, and Anti U1RNP

antibody. In this study, we had significantly higher number of cases with pleuropulmonary involvement, neurological involvement, leukopenia, and thrombocytopenia as compared to various others studies from central and southern parts of India, which may be due to different ethnicity and different environmental factors thus emphasizing the heterogeneous nature of this disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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