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# Clinico-Pathological Study of Renal Involvement in Lupus Nephritis - Our Experience from North East India

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**Abstract** **Original Research Article**

Despite the great improvement in the diagnosis and treatment of systemic lupus erythrometus (SLE) in recent years, lupus nephritis (LN) remained the leading cause of death among SLE patients. So this study was carried out at Department of Nephrology during January 2018 to December 2018 to see the histopathological class of renal involvement in respect to clinical parameters in lupus nephritis and to find any correlation between different clinical parameters and pathological findings. SLE was diagnosed as per American Rheumatism Association criteria. Forty-four patients of SLE having evidence of renal involvement in urine (persistent protienuria with or without urinary cellular casts) were included in the study. Kidney biopsy was done in all cases and histopathological examination (HPE) and Immunofluorescence (IF) examination was done. Staging was done as per world health organization (WHO) classification. The most common age group of LN was 21-30 years. Out of 44 kidney biopsy adequate tissue was found in 38(86.3%) cases. Of 38 HPE done 94.73% had advanced classes of renal involvement. 7.9%, 52.6%, 26.3% and 7.9% were having Class III, Class IV, Class V and class VI-LN respectively. There was significant relationship between age of the patients and musculoskeletal manifestations with histopathological classes. Presence of musculoskeletal manifestation is likely to have proliferative class and more severe illness are likely to have in mature adult. Definite pattern in relation to the severity of the disease when correlated with WHO class was not found in respect of parameters like hypertension, serum creatinine, glomerular filtration rate and 24 hour urinary protein.

**Keywords:** Systemic Lupus Erythrometus, Lupus Nephritis, Immunofluorescence, Histopathological examination, Proteinuria.



## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs, tissues and cells undergo damage mediated by tissue binding auto antibodies and immune –complexes mediated injuries. Ninety percent of cases are women of childbearing age. It is caused by interactions between susceptibility genes and environmental factors resulting in abnormal immune responses [1]. SLE can occur at any age but has its onset primarily between ages 16 and 55 years. It is more common in female in comparison to male counterpart and varies with ethnicity [2]. The disease is more common among African Americans, Asians and Hispanics. The disease affects 1 of 2000 Caucasians, whereas the prevalence among African, Asian, and Hispanic persons is approximately 1 in 250[3].

In 1900 Sir William Osler first described renal disease in patients with SLE. Despite the great improvement in the diagnosis and treatment of SLE in the past 50 years, lupus nephritis (LN) remained the leading cause of death among SLE patients and it is responsible for growing percentages of cases with end-stage renal failure (ESRD) requiring renal replacement therapy (RRT), shortening the life expectancy of the patients[4]. Clinical presentations and pathological kidney lesions are diverse in SLE. Renal manifestations may range from–asymptomatic hematuria or proteinuria to overt nephritic or nephrotic syndromes, rapidly progressive glomerulonephritis (RPGN) and chronic kidney disease (CKD) [5].

The incidence of SLE is quite high in Manipur and its adjoining states and renal involvement is also common in them. So this study was conducted to see the pattern of renal involvement in SLE in this region and to find any correlation between different clinical parameters and pathological findings.

## MATERIALS AND METHODS

This study was carried out in the Department of Nephrology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur during the period January 2018 to December 2018. Patients of SLE with evidence of renal involvement were selected from nephrology clinic and indoor wards that referred for nephrology consultation. Those who fulfill the American Rheumatism Association (ARA) criteria for the diagnosis of SLE [6] and those patients having evidences of renal involvement in the form of- persistent proteinuria ≥ 0.5g per day or active urinary sediments like cellular casts , red blood cell, RBC cast etc. were included in the study [5]. Those patients who were suffering from chronic liver diseases, critically ill patients, congestive cardiac failure (CCF), carcinoma, diabetes mellitus, other previous renal disease and pregnancy were excluded from the study.

All the necessary laboratory investigations including serum antinuclear antibody (ANA) and serum anti double stranded DNA (ds-DNA) antibody were done. Per-cutaneous kidney biopsy was done under local anesthesia with 18 G needle by using bard kidney biopsy gun under ultrasonography guidance. Histo-pathological examination (HPE) and Immunofluorescence (IF) was done for every patients and classification of LN was done as per World health organization (WHO) guideline [7]. Written informed consent from the patient and institutional ethical committee approval was taken.

Data were processed through SPSS 15 version. Pearson's Chi Square test, independent t-test and ANOVA test were applied whenever found suitable and necessary interpretation was done accordingly. P-value less than 0.05 were considered statistically significant.

## RESULTS AND OBSERVATION

Kidney biopsy was done in 44 patients but analysis was done on 38 cases in which tissue obtained was adequate for HPE and IF interpretation. Two patients were excluded from the study as tissue sample was inadequate.

Age of the patients ranged from 16 to 58 year. Most common age group of illness was in 3$^{rd}$ decade of life followed by 4$^{th}$ decade (63.2% and 18.4% respectively) (Table-1). There were 35 (92%) females in the study group with female to male ratio of 11.7:1. Duration of disease ranges from 0.5 months to 78.2 months with a mean of 5.2 months (Table-1).

The commonest presentation was swelling of feet and puffiness of face which was seen in 78.9% (n=30) followed by reduced urine output (57.9%, n=22). Skin manifestations in the form of malar rash, discoid rash, photosensitivity, oral ulcer and Raynaud's phenomenon were also very common finding among the study population. Musculo-skeletal manifestation like headache, arthralgia or myalgia was present in 14 (36.8%) patients (Table-1).

Hypertension was present in 21(55.5%) patients of the total 38 patient (Table-1). Proteinuria ranged from 0.5 gm/ day to 9.0 gm / day with a mean of 3.1 gm / day. Nephrotic range proteinuria was found in 31.6% of the patient. Anti-ds DNA titer was raised in all patients, ranging from 41 to 508 IU / mL (Table-1). Out of the total 38 patients, 4 (10.5%) was having low positive Anti-ds DNA titer whereas 10(26.3%) it was strongly positive. The serum creatinine ranges from 0.6 – 6.4mg%. 47.4% of cases had serum creatinine of 1.5mg% or less while 53.6% had >1.5mg%. The Glomerular filtration rate (GFR) was from 10 – 101.8ml/min./1.73m² of body surface area (BSA) with a mean of 47.39ml/min/1.73m² (Table-1). In 37(97.4%) cases GFR was low (<90ml/min./1.73m² of BSA) whereas in 42.1% cases that was between 30 – 35ml/minute/1.73m$^2$ (Table-1).

Table-2 shows different HPE and IF finding of the study population. Two (5.3%) patients in the series had absence of pathologic changes by light microscopy and were diagnosed as minimal change glomerulopathy (WHO class- I). Three (7.9 %) patients revealed focal hypercellularity with proliferation of capillaries, focal fibrinoid necrosis, mild mesangial enlargement, few crescents and few glomeruli showing sclerosis with normal blood vessels. They were diagnosed as focal segmental proliferative glomerulonephritis with glomerulosclerosis-WHO class III. Diffuse hyper cellularity with endocapillary proliferation, fibrinoid necrosis, polymorphonuclear infiltration, and increased mesangial matrix, wire looping, epithelial crescents in more than 50% of glomeruli and scleroses in some glomeruli suggestive of diffuse proliferative glomerulonephritis-WHO class IV was found in 52.6%. Ten (26.3%) patients had marked uniform thickening of capillary basement membrane with mild hypercellularity with increased in mesangial matrix with variable amounts of interstitial fibrosis and tubular atrophy, but no obvious interstitial cellular infiltrate. These cases were diagnosed as diffuse membranous glomerulonephritis-WHO class V. HPE features suggestive of advanced sclerosing glomerulopathy-WHO class VI was found in three (7.9%) patients. We didn't come across any class- II LN patients in the cohort.

Table-3 shows comparison of different clinical parameters in relation to WHO class of LN and to find out their correlation. We found that age of the patients and musculoskeletal manifestations was having statistically significant correlation with WHO class of LN whereas other parameters, though clinically they are significant, were not having statistical significant relationship. Presence of musculoskeletal manifestation

are likely to have proliferative class and more severe illness are likely to have in mature adult.

## DISCUSSION

Renal disease in SLE is essentially pleomorphic with characteristic renal histology, clinical expression, clinical course and pathognomic mechanism of glomerular damage. In the present study 78.9% patient had edema at the time of presentation followed by oliguria (57.9%). Skin symptoms (44.7%) and musculoskeletal symptoms (39.5%) were also common. Our finding was in accordance with the study by Parichatikanond P *et al*. [8] where they also found edema (72.35%), proteinuria (28.4%), hematuria (14.2%), and joint symptoms (63.6%) as leading clinical features at presentation. Rajaee A *et al*. found that edema (22.3%), arthralgia (23.2%), skin rash (13.5%) as common features in patients at the time of presentation [4]. Vila LM *et al*. found arthralgia (97%), arthritis (72.3%), and photosensitivity (85%), and malar rash (78.1%) as common features at presentation [9] whereas Gan HC *et al*. found musculo-skeletal symptoms only in 20% patients [10]. But musculoskeletal involvement was much higher in study of Flower C *et al*. where 72.7 % of cases had arthritis [11]. So it seems that presentation can have wide varieties of features though edema, arthralgia, hematuria and skin rashes are common finding in most of the studies.

In the present study, we found commonest age group affected to be 20-30 years age group with 63.2% patients. Significant number of cases was in 31-40 years age group (18.4%) but there was no definite pattern in relation to disease severity. Baldwin DS *et al*. found 20-40 years age group as having the highest incidence of LN [12]. Mahajan SK *et al*. found mean age of patients as 28 ± 12.2 year in their study [13]. Other studies by Parichatikanond P *et al*. [8] and Esdaile JM *et al*. [14] also found the same age group as that of our study. Rajaee A *et al*. also found mean age of patients to be 24.35 ± 9.2year in their study which was quite comparable with our study [4]. This preponderance for younger age group may be due to the fact that estrogen hormone which is one of the trigger for lupus activity is highest during the younger age group.

As in other studies our study also showed female dominance in nature. Estrogen hormone is one of the triggering factors of SLE and lupus is more common in women during their childbearing years when estrogen levels are highest. This may be the explanation for female preponderance. Mean duration of onset of LN was 5.2 ± 12.97 months. Our finding is similar with that of Nossent HC et al but differs from finding of Esdaile JM et al where it was 11.6 months [14, 15]. This variation in the duration of illness may be due difference in socio-economic and educational status of the population, the institutional criteria for kidney biopsy and availability of expertise hand.

In this study we found that 47.3% of patients had hypertension which is comparable with findings of other studies where the incidence of hypertension ranges from 33% to 68% [8, 10, 16-18]. This wide range of incidence may be because of the variation in the composition of cohort of study population, clinical status of the patients, racial and geographical difference etc.

Nephrotic range proteinuria was found in 31.6% cases as in other studies [8, 16]. It was observed that the class-I LN had highest mean 24 hr. protein excretion followed by Class-V while lowest value was found in class-VI. In a study by Parichatikanond P *et al*. [8] found that 24hr protein excretion showed increasing trend according to the severity of renal disease in contrast to our study. Proteinuria depends on many factors like presence or absence of comorbidities like hypertension, fever, physical exercise, etc. and this may be the explanation for this difference. We didn't come across any class- II LN patients in the cohort and this may be because of short duration of study and less number of patient.

In our study all the patients had positive value of Anti ds DNA but there was no significant correlation with WHO LN class. In other studies this was positive in 46.3% to 92% of the study population [8-11]. Our finding is much higher as it was considered as one of the diagnostic as well as inclusion criteria for the study whereas others studies included patients with clinical diagnosis also. Highest creatinine level was seen among the patients having Class III and IV and lowest in Class I. GFR in our study ranged from 10-101.8ml/min/1.73m$^2$ of body surface area with mean of 47.39ml/min/1.73m$^2$. Parichaikanond P. *et al.* [8] and Esdiale JM *et al*. [14] also found highest creatinine level in class IV. Thus we conclude that patients with high serum creatinine levels were more likely to be in WHO class III or IV. In our study we did not find any correlation between GFR and severity of histopathological lesions.

## CONCLUSION

Constellation of clinical features like edema, skin manifestations, hypertension, should prompt further investigation for proteinuria and markers of SLE. Definite pattern in relation to the severity of the disease when correlated with WHO class was not found in respect of parameters like hypertension, serum creatinine, GFR and 24 hours urinary protein. But these parameters could throw some light as what is to be expected when these parameters are correlated to WHO classes of lupus nephritis. Keeping in view the relatively small number of patients and short period of the study further study involving larger number of patient may help in further evaluation.

**Table-1: Clinical characteristic of Lupus nephritis patients**

| Age group in years | No. of cases | Percentage (%) |
|---|---|---|
| 11-20 | 3 | 7.9 |
| 21-30 | 24 | 63.2 |
| 31-40 | 7 | 18.4 |
| 41-50 | 3 | 7.9 |
| 51-60 | 1 | 2.6 |
| Sex distribution | | |
| Female | 35 | 92.1 |
| Male | 3 | 7.1 |
| Clinical Signs at presentation | | |
| Hypertension | 21 | 55.3 |
| Edema | 33 | 86.8 |
| Skin Manifestations | 21 | 55.3 |
| Musculoskeletal Manifestations | 14 | 36.8 |
| GFR(ml/min./1.73m² of BSA | | |
| 90 or above | 1 | 2.6 |
| 60 - 89 | 11 | 28.9 |
| 30 - 59 | 16 | 42.1 |
| 15 - 29 | 7 | 18.4 |
| <15 | 3 | 7.9 |
| Anti-dsDNA Antibody IU/ml | | |
| 30 - 60 | 4 | 10.5 |
| 61 - 200 | 24 | 63.1 |
| >200 | 10 | 26.3 |
| Total | 38 | 100.0 |

BSA=basal surface area, GFR=glomerular filtration rate

**Table-2: Histopathological classes of lupus nephritis among study group**

| Diagnosis | WHO Class | No. of cases | Percentage (%) |
|---|---|---|---|
| Minimal change glomerulopathy | I | 2 | 5.3 |
| Focal segmental glomerulonephritis with glomerulosclerosis | III | 3 | 7.9 |
| Diffuse proliferative glomerulonephritis | IV | 20 | 52.6 |
| Diffuse membranous glomerulonephritis | V | 10 | 26.3 |
| Advanced sclerosing glomerulopathy | VI | 3 | 5.3 |
| Total | | 38 | 100.0 |

**Table-3: Clinical features and statistical comparison of LN class.**

| Parameter | WHO Classification | | | | | $X^2$Value/ F-value | P Value |
|---|---|---|---|---|---|---|---|
| | I | III | IV | V | VI | | |
| Sex<br>Male<br>Female | -<br>2(5.7) | -<br>3(8.6) | 2(66.7)<br>18(51.4) | 1(33.3)<br>9(25.7) | -<br>3(8.6) | 0.869 | 0.929 |
| Age(year)<br>Mean ± SD | 24.00±<br>1.00 | 32.00±<br>11.35 | 28.15±<br>9.06 | 25.10±<br>4.43 | 42.66±<br>2.51 | 3.268 | 0.023* |
| Duration of Disease<br>Mean ± SD | 1.50±<br>0.50 | 11.66±<br>11.23 | 16.18±<br>40.78 | 5.22±<br>10.88 | 76.00±<br>90.06 | 2.083 | 0.105 |
| Edema<br>Present<br>Absent | 2(6.1)<br>- | 3(9.1)<br>- | 17(51.5)<br>3(60) | 9(27.3)<br>1(20) | 2(6.1)<br>1(20) | 1.973 | 0.741 |
| Skin Manifestations<br>Present<br>Absent | 1(4.8)<br>1(5.9) | 1(4.8)<br>2(11.8) | 12(57.1)<br>8(47.1) | 6(28.6)<br>4(23.5) | 1(4.8)<br>2(11.8) | 43.277 | 0.333 |
| Musculoskeletal Manifestations<br>Present<br>Absent | -<br>- | 1(7.1)<br>2(8.3) | 8(57.1)<br>12(50.0) | 1(7.1)<br>9(37.5) | 1(7.1)<br>1(4.2) | 18.972 | 0.015* |
| Blood Pressure<br>Systolic | 125.00±<br>15.00 | 140.00±<br>17.32 | 133.50±<br>20.50 | 122.40±<br>11.34 | 140.00±<br>26.45 | 1.006 | 0.419 |
| Diastolic | 80.00±<br>10.00 | 86.66±<br>15.27 | 86.70±<br>14.75 | 78.80±<br>8.75 | 86.66±<br>15.27 | 0.676 | 0.614 |
| Serum Anti dsDNA IU/ml<br>Mean ± SD | 73.79 ±<br>50.01 | 185.00 ±<br>176.70 | 217.10 ±<br>92.52 | 143.00 ±<br>61.81 | 198.33 ±<br>2.88 | 1.719 | 0.169 |
| 24 hr Urinary Protein (g)<br>Mean ± SD | 6.50 ±<br>2.50 | 3.33 ±<br>2.30 | 2.65 ±<br>1.23 | 3.70 ±<br>2.64 | 1 .90 ±<br>1.08 | 2.457 | 0.065 |
| Serum Creatinine (mg %)<br>Mean ± SD | 1.15 ±<br>0.15 | 3.26 ±<br>2.80 | 2.38 ±<br>1.43 | 1.24 ±<br>0.44 | 1.80 ±<br>1.05 | 2.212 | 0.089 |
| GFR ml/min.<br>Mean ± SD | 33.58 ±<br>33.75 | 38.81 ±<br>33.33 | 39.87±<br>22.84 | 60.26 ±<br>18.87 | 43.27 ±<br>21.45 | 2.291 | 0.080 |

LN=Lupus nephritis, GFR= glomerular filtration rate

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