

ORIGINAL ARTICLES

Histopathology of lupus nephritis: A single-center, cross-sectional study from Karnataka, India

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Abstract

A cross-sectional study of SLE patients over a period of two years is reported. Renal biopsy of 32 selected patients revealed histopathological abnormalities and deposits of immune complexes, and were classified according to the WHO classification of lupus nephritis (LN). The clinical and laboratory parameters assessed were also in line with this classification, indicating the adequacy of these parameters for routine follow-up, and the biopsy was reserved for

Introduction

Systemic lupus erythematosus (SLE), a disease of unknown etiology, is characterized by excessive immune complex formation, autoantibody production, complement activation and immunologically-mediated tissue injury. The disease prevalence differs globally. The annual incidence of SLE, in relatively low- to high-risk groups, varies from 6 to 35 new cases per 100,000 population.^{1, 2} The first case of SLE was reported from India in 1965. This was followed by publishing two more case reports and a series of eight cases till 1969. The reported prevalence in the northern Indian population ranges from 14 to 60 per 100,000.³

The inflammatory involvement of SLE virtually affects every organ including the joints, skin, kidney, brain, serosa, lung, heart, and gastrointestinal tract. The renal manifestations of SLE, termed as 'lupus nephritis' (LN), are highly heterogeneous and an important cause of morbidity and mortality due to SLE. It is clinically evident in 40 to 85% of SLE patients and is an integral part of the American Rheumatoid Association (ARA) criteria for diagnosing the disease. A quarter to half of the patients with lupus has abnormalities of urinalysis or renal function early in their course, although up to 60% of adults and 80% of children may develop overt renal abnormalities later. Inpatients over 50 years of age at onset, less than 5% have had nephritis initially.⁴

Most of the SLE patients tend to be asymptomatic for renal manifestations. Urinary abnormalities and renal parameters could be indicative of renal involvement in SLE. The present analysis is a prospective observational study to evaluate the incidence of histopathological abnormalities in patients suspected to have SLE-associated nephritis through renal biopsy. We have also attempted to describe the different clinical and lab features associated with subtypes or classes of LN.

Materials and methods

The demographic, clinical, and histopathological data were collected prospectively from 34 consecutive patients diagnosed to have SLE with nephritis at St John's Medical College Hospital from Jan 2004 to Dec 2005 over a period of 2 years. The diagnosis of SLE was based on the 1997 revised American Rheumatic Association (ARA) criteria. Patients aged 16 years and above, satisfying at least four of the ARA criteria for SLE were included for the study.⁵ In-patients, out-patients, and those newly diagnosed at the time of renal biopsy were included. Patients with previous history of renal pathology, those who received nephrotoxic drug therapy in the recent past, and patients with active infection at any site were excluded. Patients with abnormal bleeding parameters, severe anemia, uncontrolled hypertension, and those in whom renal biopsy was contraindicated were also not considered for

the study. All the recruited patients were evaluated by a detailed physical examination with particular reference to features of SLE and LN, past treatment history, and other comorbid diseases. Renal investigations included complete urine analysis, 24-hour urine protein excretion, blood urea, and serum creatinine levels. Renal biopsy was considered based on the results of renal investigations. Biopsy was performed with the consent of the patient under ultrasonographic guidance and undertaken only in those who did not have any of the aforementioned contraindications. Biopsy specimens were subjected to conventional histopathology as well as immunofluorescence studies. Severity of the disease was classified according to WHO classification of LN. Activity and chronicity scores were used as an adjunct to the WHO classification.⁶

Statistical methods

Descriptive statistics, chi-square, and Fisher exact test have been used to test the significance of proportions of study parameters in the classes. Odds ratio was calculated to find the strength of relationship between study parameters and the classes of LN patients. Analysis of variance has been carried out to evaluate the significance of mean pattern across the histopathological classes. Statistical analysis was done using SPSS 11.0 and Systat 8.0 software packages.

Results

Thirty-two patients who fulfilled the ARA criteria for SLE and underwent renal biopsy were included in the study. Out of 32 subjects, 27 (84.4%) were females and five (15.6%) were males with a ratio of 5.4:1. The age of the patients ranged from 17 to 52 years, with a mean age of 28.31 ± 10.62 years. The mean age of females was 27.07 ± 9.19 , while that of males was 35 ± 16.08 years.

Demographic details of the cohort are shown in table 1.

Distribution of symptoms and signs

Symptoms and signs noted on presentation are shown in table 2 (see supplementary data). Among the comorbidities, 25% of patients presented with hypertension, while 6.3% had diabetes mellitus. There was one case each for other co-morbid illnesses namely bronchial asthma, intervertebral disc prolapse (IVDP), and tuberculosis. The most common renal symptoms presented were edema in 24 patients (75%), followed by oliguria in eight patients (25%). Arthralgia and fever were prevalent in all the four classes.

Signs observed in clinical examination were associated with the four classes of LN as shown in table 2. The most commonly presented symptom in all the 4 classes of LN was edema; 29.17%, 20.83%, 41.67%, and 8.33% in Class II, III, IV, and V respectively. Other commonly observed clinical manifestations such as alopecia and malar rash were present in Class II, III, and IV; but not in Class V. Gangrene was reported in one Class II patient.

Hypertension was noted in eight patients of LN with 11.1% in Class II, 14.3% in Class III, 38.5% in Class IV and 33.3% in Class V. It was observed that patients with Class IV were 3.3 times more likely to have hypertension. At the time of biopsy, the recorded mean systolic and diastolic blood pressure showed a higher frequency in Class IV compared to other classes. BP ranged from systolic BP 156 ± 48 mm Hg and diastolic BP 88 ± 9 mm Hg, while the other classes showed a near normal range. However, none of the clinical manifestations showed any predilection to a particular class of nephritis.

Table 1. Demographic data and distribution

Age group (years)	Male (%)	Female (%)
≤20	1 (20)	9 (33.3)
21-30	1 (20)	12 (44.4)
31-40	1 (20)	3 (11.1)
41-50	1 (20)	3 (11.1)
>50	1 (20)	-
Total	5 (100)	27 (100)
Mean ± SD (Range)	35.0 ± 16.1 (17-52)	27.1 ± 9.2 (12-46)

Table 2. Histopathological classification of LN based on symptoms and clinical examinations

Sl. No.	Symptoms / Signs	Total (%)	Class II (n=9)	Class III (n=7)	Class IV (n=13)	Class V (n=3)	P value
On presentation							
1	Fever	14 (43.8)	5	2	6	1	1.0
2	Arthralgia	19 (59.4)	5	5	7	2	1.0
3	Photosensitivity	7 (21.9)	1	1	5	-	0.39
4	Myalgia	11 (34.4)	3	2	5	1	1.0
5	Rash	8 (25.0)	2	1	5	-	0.68
6	Edema	24 (75.0)	7	5	10	2	1.0
7	Oral ulcers	5 (15.6)	-	1	2	2	0.33
8	Alopecia	6 (18.8)	1	-	4	1	0.17
9	Cough	5 (15.6)	1	2	2	-	1.0
10	Oliguria	8 (25.0)	3	-	5	-	0.68
On clinical examination							
1	Malar rash	5(15.6)	1	2	2	-	0.48
2	Discoid rash	2(6.25)	2	-	-	-	0.25
3	Edema	22 (68.7)	5	4	11	2	0.48
4	Oral ulcers	2(6.25)	-	-	1	1	1.0
5	Alopecia	5(15.6)	1	1	3	-	1.0
6	Gangrene	1 (3.12)	1	-	-	-	1.0
7	Pleuritis	5 (15.6)	1	1	3	-	1.0
8	Hepatomegaly	3 (9.37)	1	1	1	-	1.0
9	Splenomegaly	3(9.37)	1	1	1	-	1.0
10	Ascitis	2(6.25)	-	-	2	-	0.48
11	Psychosis	1(3.12)	-	-	1	-	1.0
13	Joint tenderness	4 (12.5)	-	3	1	-	0.59
14	Joint Swelling	6 (18.8)	-	3	2	1	1.0
15	Deformities	1(3.12)	1	-	-	-	1.0
16	Hypertension	8 (25.0)	1	1	5	1	0.22

Distribution of clinical and laboratory measures among classes of LN

A series of laboratory tests including hematology, biochemistry, urine analysis and immunological studies were performed on the subjects. Based on the findings, the subjects were assigned to the various classes of LN, according to the WHO criteria (Table 3). Anemia was observed mainly in Class IV and Class III. Severe anemia in Class IV (7.99 ± 3.67 gm%) was statistically significant ($P = 0.038$) when compared to other three classes. The WBC count ranged from 900 to 14,200 cells/mm³ and platelet count ranged from 66,000 to 3.6 lakh cells/mm³, but predilection to any particular class has not been noted. Blood urea, serum creatinine and serum potassium were studied as renal parameters. Abnormal blood urea and serum creatinine were seen in all the four classes. Highest incidence of elevated blood urea (130.65 ± 135.35) and serum creatinine (4.07 ± 5.49) was observed in Class IV as compared to other classes.

Albuminuria was observed in all four classes of LN, which ranged from traces to $4 \pm$ albumin by dipstick in urine. However, Class IV patients were 5.7 times more likely to have urine albumin (3 ± 4) ($P = 0.026$). Twenty-four hour urine protein excretion of >500 mg/day was noted in 62.5% patients. This, however, did not show any specific distribution for the classes of LN. The urine analysis of the study group showed some active sediment in almost all patients as detailed in table 3. Urine RBC >5 cells/HPF was present in 46.9% patients, urine WBC >5 cells/HPF was seen in 75% patients, and urine granular casts in 34.4% of the patients. Class IV LN was 2.54 times more likely to have urine WBC >5 /HPF.

Immunofluorescence findings

All the patients were subjected to conventional histopathology analysis as well as immunofluorescence. Figure 1 shows the micrographs of LN affected biopsy samples at different stages. Autoantibodies specific for LN like dsDNA were qualitatively analyzed for each of the classes by immunofluorescence staining, and 75% of patients were identified as dsDNA positive. This did not statistically associate with the classes ($P >0.05$). The complement levels (C3 & C4) were subnormal in all the four classes. C3 and C4 levels were lowest in both Class III (41.2%) and IV (37.5%). Though they did not show statistical significance, they showed a tendency to be lower in Class IV. Patients with Class IV showed 1.63 times more likely to have low C3.

Nine patients were assigned to WHO Class II LN (28.1%),

7 to Class III (21.9%), 13 to Class IV (40.6%), and 3 to Class V (9.4%) LN. None of the patients were classified as WHO Class I and Class VI LN. Figure 2 shows the frequency of distribution of the activity and chronicity indices seen on biopsy among the different classes. Most of the cases in Class IV showed a higher activity index (6/24 - 14/24). The chronicity index, however, was observed to be distributed almost equally in all the 4 classes (0/12- 9/12). Direct immunofluorescence revealed Class IV to have higher incidence of immune deposits (100%) as compared to other classes. Class V had lowest incidence of immune deposits (50%).

Correlation of activity and chronicity indices

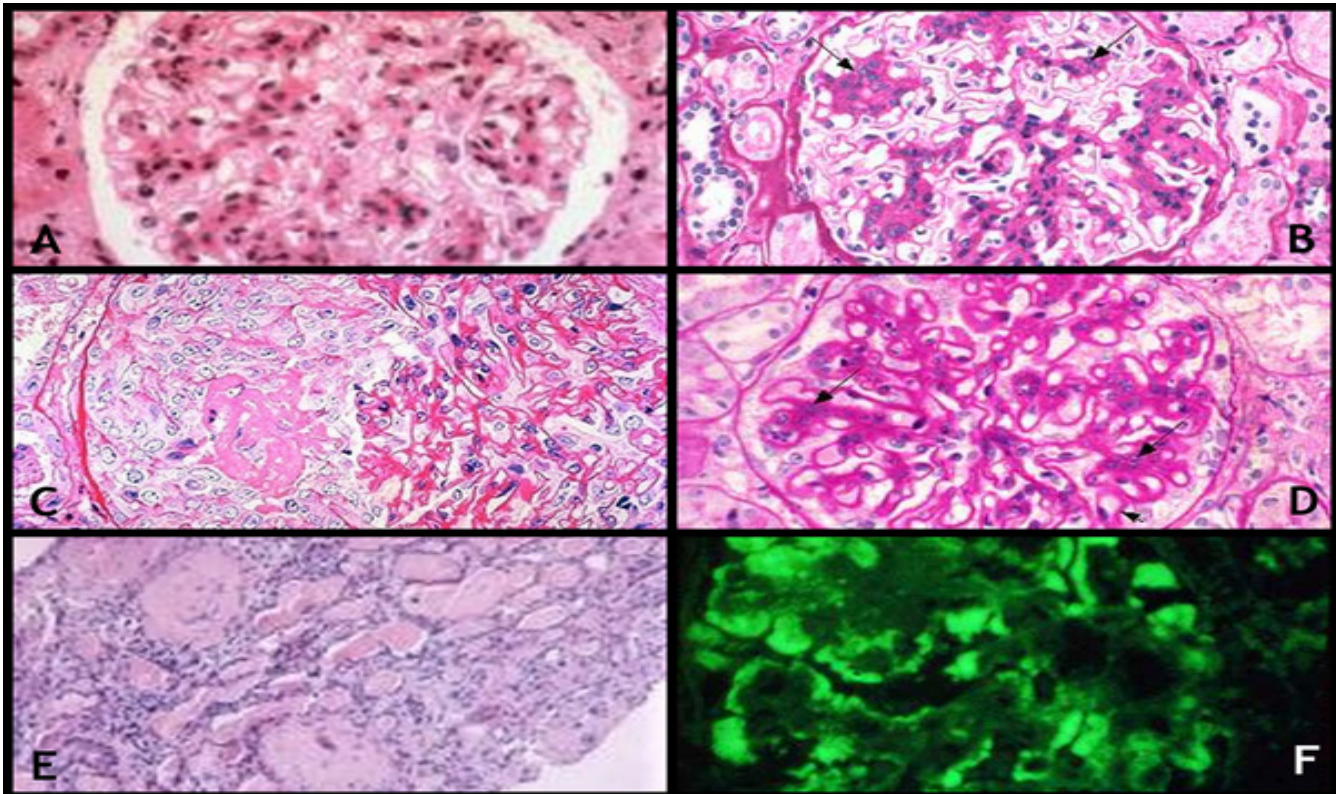
Among the parameters used to assess the severity of the disease, ESR was found to have good correlation with activity index, which was not statistically significant ($R^2 = 0.48$, $P = 0.134$). Whereas chronicity index demonstrated no correlation ($R^2 = -0.03$, $P = 0.03$). C3 was fairly correlating to both activity ($R^2 = 0.12$, $P = 0.038$) and chronicity indices ($R^2 = -0.26$, $P = 0.049$), and similarly C4 with activity ($R^2 = 0.24$, $P = 0.25$) and chronicity indices ($R^2 = -0.02$, $P = 0.015$). The duration of the illness had relatively better correlation and statistical significance (although at 90% CI) with the activity ($R^2 = 0.17$, $P = 0.056$) and chronicity indices ($R^2 = 0.45$, $P = 0.068$).

Discussion

There was a preponderance of female patients in the study. This finding is similar to most of the studies of SLE that have shown a predominance of females.^{7,8} The mean age of the study group patients at presentation was 28.31 ± 10.62 years. This is also in agreement with the studies conducted by various groups. Austin *et al.* and Esdaile *et al.* have reported young age (<23 yrs) as one of the indicators associated with increased rate of renal failure and a more rapidly progressive course.^{8, 9, 10} Among the study patients, hypertension was seen in 8 patients (25%). This is much lower as compared to studies by Esdaile *et al.* where 31 of 38 patients had hypertension and was associated with negative effect on outcome. Budman and Steinberg noted that hypertension can occur in the presence of relatively normal renal function and contribute directly to the renal damage and progression in LN.^{10, 11, 12, 13}

Similar to the previous studies, the most common clinical symptom noted was edema.^{14, 15} Typically, the clinical symptoms and signs suggestive of renal disease have very low sensitivity to predict renal disease in SLE, as

Fig. 1: Micrographs of LN affected biopsy samples at different stages



A. Mesangial LN with moderate mesangial hypercellularity (WHO class IIb, hematoxylin and eosin stain), **B.** Class III Mesangial glomerulonephritis showing segmental areas of increased mesangial matrix and cellularity indicated by arrows, **C.** Class IV mesangio-proliferative LN, **D.** Class V membranous LN - diffuse thickening of the glomerular capillary wall indicated by short arrows, focal areas of mesangial expansion and hyper-cellularity indicated by long arrows **E.** Class VI sclerosing LN, hematoxylin and eosin stain, (Class VI patient not included in the present study), **F.** Immunofluorescence micrograph of diffuse proliferative LN showing massive lumpy deposits of IgG.

Fig. 2: Distribution of activity and chronicity scores among various WHO classes of LN

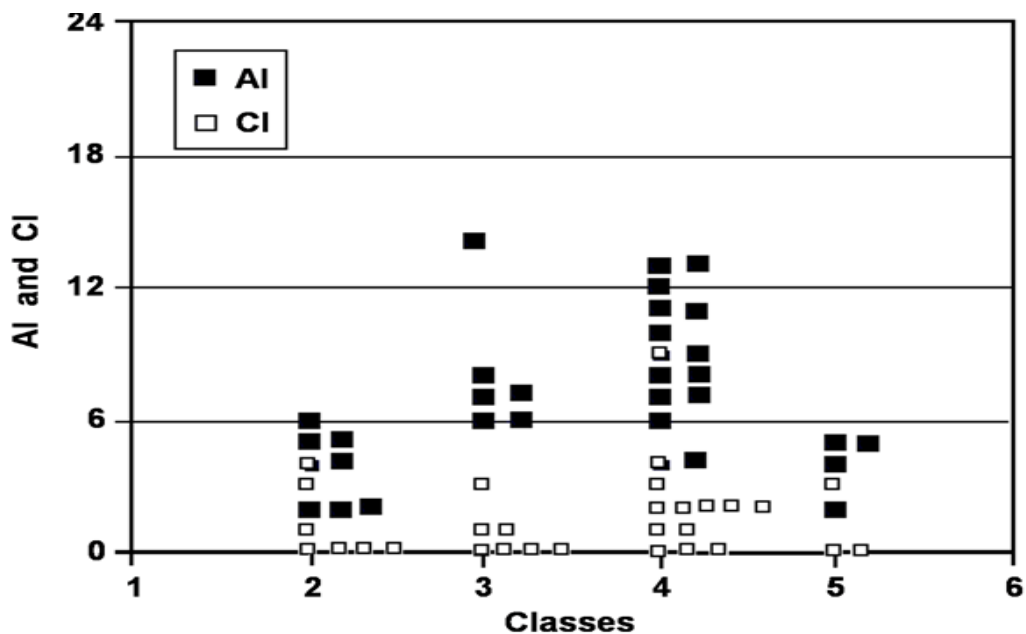


Table 3: Histopathological classification of laboratory parameters

Laboratory parameters	Histopathological classification				P Value [†]
	Class II (n=9)	Class III (n=7)	Class IV (n=13)	Class V (n=3)	
Hematology*					
Hemoglobin (%)	11.88 ± 2.38 (8.80-15.90)	10.90 ± 2.81 (8.20-16.10)	7.99 ± 3.67 (3.10-14.90)	11.40 ± 2.03 (9.60-13.60)	0.038
WBC (cells/mm ³)	5973 ± 3833 (900-12600)	9366 ± 2321 (4900-11600)	7572 ± 3354 (4500-14200)	4766 ± 1950 (2800-6700)	0.156
Platelet count (cells/mm ³)	1.67 ± 0.62 (0.66-2.40)	2.27 ± 0.84 (1.14-3.60)	1.89 ± 0.97 (0.76-3.60)	1.78 ± 0.46 (1.45-2.40)	0.573
Biochemistry[‡]					
Blood urea	42.17±35.44 (13-111)	31.40±17.05 (17-51)	130.65±135.35 (3.50-343.0)	-	0.195
Serum creatinine	1.56 ± 1.87 (0.50-6.10)	1.48 ± 1.44 (0.60-4.70)	4.07 ± 5.49 (0.60-17.90)	0.70 ± 0.10 (0.60-0.80)	0.308
Serum potassium	3.96 ± 0.91 (2.70-5.20)	4.70 ± 0.66 (3.70-5.50)	4.83 ± 1.07 (3.50-6.00)	4.00 ± 0.71 (3.50-4.50)	0.208
Urine analysis[‡]					
Urine albumin					
Traces	1 (11.1%)	-	-	-	
+	1 (11.1%)	1 (14.3%)	1 (7.7%)	-	
++	5 (55.6%)	3 (42.9%)	2 (15.4%)	-	
+++	2 (22.2%)	1 (14.3%)	10 (76.9%)	3 (100.0%)	
++++	-	1 (14.3%)	-	-	
24 h Urinary protein excretion > 500mg/24 hrs					
Urinary protein	6 (66.7%)	4 (57.1%)	8 (61.5%)	2 (66.7%)	
Urine casts	3 (33.3%)	1 (14.3%)	5 (38.5%)	2 (66.7%)	
Urine RBC (+)	3 (33.3%)	3 (42.8%)	7 (53.8%)	2 (66.7%)	
Urine WBC (+)	4 (44.4%)	7 (100.0%)	11 (84.6%)	2 (66.7%)	
Immunology[‡]					
DsDNA-Antibody (+)	5 (55.6%)	6 (85.7%)	10 (76.9%)	3 (100.0%)	
Complement C3 (level <85)	5 (29.4%)	3 (17.6%)	7 (41.2%)	2 (11.8%)	
Complement C4 (level <20)	4 (25.0%)	4 (25.0%)	6 (37.5%)	2 (12.5%)	

*reported as Mean ± SD, range of values shown in parenthesis

†calculated by ANOVA

‡reported as frequency and % of group population in parenthesis

Table 4: Distribution of immunocomplex deposits with classes of LN

Immunocomplex deposits	Histopathological classification			
	Class II (n=9)	Class III (n=7)	Class IV (n=13)	Class V (n=3)
Full house*	5	2	8	0
IgG	2	1	3	1
IgA	1	1	3	1
IgM	2	1	4	1
C3	2	2	3	2
None	1	2	0	2
NA	0	1	0	2

* full house= IgG, IgM, IgA and C3

patients are largely asymptomatic. Eight patients did not have edema and 24 patients did not have oliguria. Overall, 25% of the patients did not show any renal symptoms. The study by Gladman *et al.* also reported that 16% of the patients studied had no renal symptoms.¹⁶ This may indicate that by the time the patient presents with overt renal symptoms, the disease would have progressed to advanced stages. This might explain the reason for not observing any Class I patients in our study, as also, one of the criteria for performing renal biopsy was the presence of active urinary sediments or proteinuria. The present distribution of subjects into histopathological classes, class II: 28.1, class III: 21.9, class IV: 40.6 and class V: 9.4 are comparable to previous studies by Neuman *et al.* (10, 17, 53, 14) and Pollack *et al.* (26, 19, 37, 15) respectively.^{15, 17}

Present results are in agreement with the published studies of Pollak and Pirani who summarized five major analyses of biopsy in LN conducted in 376 patients. They have observed the overall frequency of Class II, III, IV and V to be 26%, 19%, 37%, and 15% respectively.¹⁷ A study of 150 patients by Neumann *et al.* showed a frequency of 10%, 17%, 53%, and 14% respectively for each of the classes. In the present study, Class IV has the highest incidence of immune deposits (full house = IgG, IgM, IgA and C3) as compared to other classes (Table 4), and none of the patients were devoid of immune deposits. In contrast, none of the patients in class V had full house immune deposits. This distribution concurs with the study of Michael *et al.*¹⁸ However, it contradicts the findings by Esdaile, which showed no predilection of immune complex to any class of LN. Activity and chronicity indices are used mainly for assessing the severity of the disease

and predicting the outcome. Present study showed class IV to have the highest activity and chronicity score. This is similar to the study by Appel *et al.*, which showed that these indices were of value in patients with diffuse proliferative glomerulonephritis (Class IV).⁹ Gladman *et al.* and Hans *et al.* have shown active and chronic lesions on biopsy with highest scoring in class II and class IV.^{5, 16} However, Paritichathkamond *et al.* noted that only CI score was associated with renal death, while Appel *et al.* found no association of fatality either with AI or CI.^{9, 13} However, their study suggested that these indices were of greater values in patients with diffuse proliferative LN.

Classification of subjects to these classes, in terms of individual clinical parameters (Table 3), is also analogous to other studies: hypertension (Rajae *et al.*), serum creatinine and 24 h urine protein levels (Parichatikanond *et al.*), low C3 and C4 levels (Gladman *et al.*) and activity and chronicity indices (Hans *et al.*).^{13, 16, 18, 19}

In this study, edema was the predominant presentation among all four WHO classes of LN, but did not reach statistical significance for any particular class. The findings suggest that renal clinical manifestation is common among Classes II, III, IV and V, but studies have shown that features of nephrotic syndrome occurred commonly in Class V and to a certain extent in Class III and IV.^{7, 9} None of the non-renal systemic manifestations of SLE, including cutaneous, cardiac, pulmonary, and CNS seem to correlate with the WHO class.

The study group had eight patients with hypertension prior to diagnosing LN. Class IV had highest incidence

of hypertension (38.5%). In a comparative analysis using Fisher's exact test, patients with hypertension showed 3.3 times more likelihood for Class IV features on renal biopsy. This is similar to a study by Yoo *et al.* who described similar association between hypertension and Class IV.²⁰ This has been substantiated in other studies.^{12, 21} The mean systolic and diastolic BP was higher in Class IV as compared to other classes, though it did not reach statistical significance ($P > 0.05$).

Anemia was found to be statistically significant in Class IV as compared to other classes. This is comparable to study group of Austin *et al.* wherein anemia was found to be individually associated with an increased probability of renal insufficiency as seen in Class IV.¹⁴ This is probably explained by the higher risk for development of anemia secondary to renal failure and active hematuria in Class IV. Leucocyte count did not correlate with any classes. Esdaile *et al.* reported low platelet count in association with renal insufficiency ($P = 0.04$) on multivariate analysis.⁷ Such an observation was not found in the present study as we excluded patients with low platelet count for renal biopsy.

Blood urea and serum creatinine were observed to be higher in Class IV as compared to other classes.¹³ This could be explained by the severity of renal lesion in Class IV. This finding conform to other studies reporting that creatinine >2.4 is associated with poor survival outcome reflecting more severe renal disease.²² The study by Yoo *et al.* reported that more cases in Class IV showed progression to a severe lesion on subsequent biopsy with an increase in serum creatinine level.²⁰ The study showed a higher incidence of leucocyturia in Class IV as compared to other classes. However, it also showed a similar distribution of abnormal urine sediments in all classes. This is similar to studies by Austin *et al.* and Esdaile *et al.* where they found that there is no convincing difference in the degree of urinary sediment abnormality among the classes or outcome of LN, hence they are not of any diagnostic or prognostic significance.^{7, 8} In this study, although the autoantibody anti-dsDNA was present in 75% patients, they did not show any association with the classes of LN. However, studies by Esdaile and Austin showed elevated DNA binding as a valuable predictor of the severity of disease and its direct relationship to mortality.^{7, 8} On the contrary, Gladman *et al.* have showed that dsDNA is equally detectable in patients with and without proliferative lesions.¹⁶ Our study did not show significant association as the dsDNA test was quantitative.

The present study showed low complement levels in all four WHO classes and the lowest levels were noted in class IV. This is similar to the study by Gladman *et al.*, which found highest number of patients with low C3 levels in class IV (40%) and class V (54%), suggesting more common occurrence among patients who have proliferative lesions.¹⁶ However, Austin *et al.* found no statistically significant association of complement with WHO classes.⁷

Conventional parameters like complement levels and ESR have previously been used for assessing the activity of lupus and nephritis. It was found to have a positive correlation with the chronicity index. However, there was no correlation of ESR with the activity index, although C3 did show a positive correlation. Low C4 was associated significantly with chronicity index. All these observations indicate that conventional parameters of ESR and complement levels for lupus activity can be used to assess activity of LN. The conventional parameters may be helpful to sufficiently assess the disease activity on follow-up, but large multicentric studies are mandatory to ascertain these relationships.

Conclusion

The histopathological features of LN are diverse. The WHO class IV has the highest prevalence followed by Class III, II, and V in descending order. Based on clinical features, the degree of urine albumin, abnormal urinary sediments, presence or absence of hypertension and renal failure, it is not possible to predict the histopathological subtype. As the treatment differs between each class, it is important to accurately establish the class with renal biopsy so as to make appropriate therapeutic decisions. Although there is a clustering of some of the clinical parameters like edema, oliguria, hypertension, anemia, proteinuria and serum creatinine in WHO class IV, they are distributed among other classes as well. This was probably due to the larger number of patients in WHO class IV and the clinical parameters lacked sufficient predictive value for each class. Similarly, traditional markers of disease activity like ESR and complement levels showed a positive correlation with the renal biopsy scoring indices. So, it can be concluded that clinical parameters can be used while following up the patients for lupus activity, repeat renal biopsies can be reserved for patient who continue to have proteinuria, renal insufficiency, and abnormal microscopy; despite adequate treatment.

Competing interests

The authors declare that they have no competing interests.

Citation

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