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Lupus Nephritis by Class Distribution in Western Saudi Arabia

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ABSTRACT

Objective: The aim of the study was to see the local histopathology of lupus nephritis and to study there clinicopathological correlations. **Study Design:** Cross-sectional Study. **Settings:** King Fahad Hospital, Saudi Arabia. **Duration:** One year from March 2016 to March 2017. **Methodology:** 16 selected Lupus nephritis patients were reviewed for histopathological abnormalities and were classified according to ISN RPA classification the clinical and laboratory was correlating to the histopathological data. **Results:** 16 patients underwent renal biopsy who fulfilled the revised American rheumatism revised criteria for SLE and our criteria for doing the biopsy were included in the study. Out of 16 subjects 13(81) were females and 3(19) were males with a ratio of 4 to 1. The age of the patients ranged from 27-45 years in males and 22-48 in females. The mean age of females was 35 ± 13, while that of males was 36 ± 9 years. Association of lupus with other disease conditions like hypertension was present in 25 percent while 6% had diabetes mellitus. The most common clinical symptom presented was edema in 12 patients (75%). All classes had arthralgias and fever. **Conclusion:** The histopathology of LN is variable. The ISN/RPA class IV has got the highest prevalence then come Class III, V & mixed. Clinical features do not predict the histopathological class. Similarly, disease activity markers such as ESR, hypocomplementemia and anti-DNA titres showed a positive correlation with the renal biopsy.

Keywords: Lupus Nephritis, SLE, ESRD

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease involving any organ, but commonest of all is the kidney. SLE is more prevalent in females than males in all age groups, the female-to-male ratio is highest at age of reproduction, varying from 8:1 and 15:1 and is lowest children before the age of puberty. The prevalence of SLE and the chances of developing lupus nephritis differs from country to country and also race and ethnicities. The annual incidence of SLE, is relatively variable. It ranges from about 6-35 cases in 0.1 million people across all risk groups with lower in lower risk groups and higher in higher risk groups.[1,2]

In SLE, lupus nephritis is a major cause of mortality and morbidity and about ten percent cases can end-up in Lupus nephritis, later complicating into end-stage-renal-disease.[3] ESRD is increased in certain classes of Lupus nephritis. In class 4 Lupus nephritis the estimated risk may up to 44% over 15 years. Different pharmacological treatments are available.[4] Patients with Lupus nephritis have a higher mortality as compared to pts with lupus without lupus nephritis but survival improves from if disease goes into remission.[5]

The aim of the study was to see the local histopathology of lupus nephritis and to study there clinicopathological correlations.

Most of the lupus patients are asymptomatic for renal manifestations. The presence of renal involvement in lupus can be picked up by urine and renal functions. So, we designed a single center cross sectional study to determine the incidence of various abnormalities among the lupus nephritis cases at histopathological level. We have also tried to look at the clinicopathological relations of Lupus Nephritis.

METHODOLOGY

Study Design: Cross-sectional Study.
Settings: King Fahad Hospital, Saudi Arabia.
Duration: March 2016 to march 2017 over a period of 1 year
Inclusion Criteria: Patients more than 16 years fulfilling the diagnostic criteria (by ARA) of SLE, were included in our research after proper informed consent.[6] OPD patients and Inpatients were included.
Exclusion Criteria:

○ Patients with previous H/O of renal pathology. ○ H/O nephrotoxic drug therapy recently. ○ Patients with infection which was active. ○ Patients with coagulation abnormalities. ○ Anemia with Hb less than 7. ○ Refractory hypertension.

Methods: Sixteen patients with SLE along with lupus nephritis were analyzed for demographic, clinical and histopathological data. SLE. American Rheumatic Association criteria was used to diagnose SLE.

Patients were thoroughly evaluated from the nephrology and rheumatology point of view. Renal work up included complements, thorough glomerular disease serology urine analysis, urine protein quantification and renal function tests. The criteria for Renal biopsy was proteinuria more than 500 mg, active urine sediment with RBC more than 5, cellular casts greater than 1 and renal dysfunction Biopsy was performed under real time. Light microscopy and later immunofluorescence

were done. Disease severity was categorized as per ISN/RPS classification for Lupus nephritis.

Data Analysis: Data was analyzed and mean with standard deviation was calculated for quantitative data and frequency with percentage was calculated for qualitative data. Chi-square, and Fisher exact test were applied to know the significance of proportions parameters across different classes. Odds ratio was calculated to see the relationship of variables and nephritis type along with variance calculation to see the significance of pattern in different histopathological types.

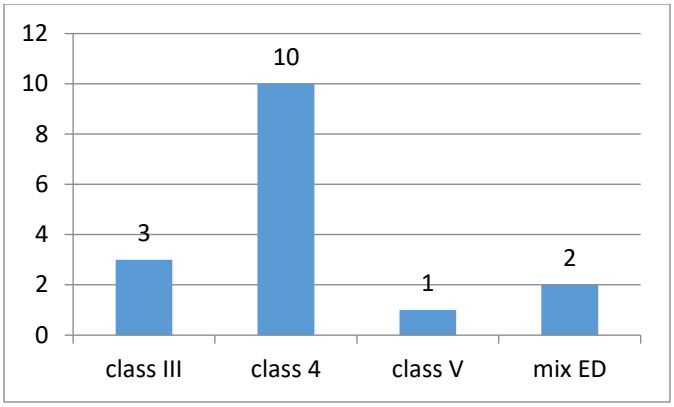
RESULTS

16 patients underwent renal biopsy who fulfilled the revised American rheumatism revised criteria for SLE and our criteria for doing the biopsy were included in the study.

Table 1: Demographic data and distribution

Age group (years)	Male (%)	Female (%)
20 -30	1(33)	9(69)
31- 40	-	3(23)
41- 45	1(33)	1(7.6)
> 50	1(33)	-
Total	3(100)	13 (100)
Mean ± SD (Range)	36 ± 9 (27-45)	35 ± 13 (22 – 48)

Out of 16 subjects 13(81) were females and 3(19) were males with a ratio of 4 to 1. The age of the patients ranged from 27-45 years in males and 22-48 in females. The mean age of females was 35 ± 13, while that of males was 36 ± 9 years. Demographic details are shown in table 1.



Symptoms & Signs among Classes of LN

The clinical features at presentation of the patients diagnosed with lupus nephritis are shown in table 2. Association of lupus with other disease conditions like hypertension was present in 25 percent while 6% had diabetes mellitus. The most common clinical symptom presented was edema in 12 patients (75%). All classes had arthralgias and fever.

Edema in all the 4 classes of LN was 60%, 70% and 80% in Class III, IV, and V.

HTN was seen in four patients of LN, Class III, 25% in Class IV and 75% in Class V.

Clinical & laboratory variable in various LN types

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

Symptoms / Signs	Total (%)	Mixed	Class III (n=3)	Class IV (n=10)	Class V (n=3)	P value
On presentation						
Fever	7 (43.8)	1	2	4	-	1.0
Arthralgia	10 (62.5)	1	1	7	1	1.0
Photosensitivity	4 (25.0)	1	1	2	-	0.39
Myalgia	5 (31.2)	0	1	3	1	1.0
Rash	4 (25.0)	1	1	2	-	0.68
Edema	12 (75.0)	3	3	5	1	1.0
Oral ulcers	3 (18.8)	0	-	2	1	0.33
Alopecia	3 (18.8)	1	-	2	-	0.17
Cough	2 (12.5)	0	-	2	-	1.0
Oliguria	4 (25.0)	1	-	3	-	0.68
Malar rash	2 (12.5)	0	-	2	-	0.48
Discoid rash	1 (6.25)	0	-	1	-	0.25
Edema	11 (68.8)	1	2	7	1	0.48
Oral ulcers	1 (6.25)	-	-	1	-	1.0
Alopecia	2 (12.5)	-	-	2	-	1.0
Gangrene	1 (6.25)	1	-	-	-	1.0
Pleuritis	2 (12.5)	-	-	2	-	1.0
Hepatomegaly	2 (12.5)	-	1	1	-	1.0
Splenomegaly	3 (18.8)	-	1	1	1	1.0
Ascitis	1 (6.25)	-	-	1	-	0.48
Psychosis	1 (6.25)	-	-	1	-	1.0
Joint tenderness	4 (25.0)	-	-	2	-	0.59
Joint Swelling	3 (18.8)	-	1	2	-	1.0
Deformities	1 (6.25)	-	-	1	-	1.0
Hypertension	4 (25.0)	-	1	3	-	0.22

All lab tests including which were the standard of care for lupus pts were performed on the subjects. Class IV and Class III mainly had anemia. Whereas anemia in Class IV (7.99±3.67 gm %) was seen to be statistically significant (P < 0.05) when compared to various other subtypes of lupus. No statistical significance was observed regarding, WBC count and platelet count regarding predilection to any particular class. Serum urea and creatinine both were deranged in all the subtypes. The amount of renal dysfunction in class 4 was much more as compared to other classes mean serum creatinine 4.07 ± 5.49.

Table 3: Histopathological classification of laboratory parameters

Laboratory parameters	Histopathological classification				P Value
	Mixed N=2	Class III (n=3)	Class IV (N=10)	Class V (n=1)	
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/mm3)	5973 ± 3833 (900-12600)	9366 ± 2321 (4900-11600)	7572 ± 3354 (4500-14200)	4766±1950 (2800-6700)	0.156
Platelet count (cells/mm3)	1.67 ±0.62 (0.66-2.40)	2.27 ± 0.84 (1.14-3.60)	1.8910.97 (0.76-3.60)	1.7810.46 (1.45-2.40)	0.573
Biochemistry*					
Blood urea	42.17±35.44 (13 -111)	31.40117.05 (17-51)	130.651135.35 (3.50-343.0)		0.195
Serum creatinine	1.56 ± 1.87 (0.50-6.10)	1.48 1 1.44 (0.60-4.70)	4.07 ± 5.49 (0.60-17.90)	0.70 10.10 (0.60-0.80)	0.308
Serum potassium	3.9610.91 (2.70-5.20)	4.701 0.66 (3.70-5.50)	4.831 1.07 (3.50-6.00)	4.00 1 0.71 (3.50-4.50)	0.208
Urine analysis*					
24. h Urinary protein excretion > 500 mg /24 hrs					
Urinary protein	2 (100%)	3 (100%)	10 (100%)	1 (100%)	
Urine casts	1 (50%)	1 (33%)	4 (40%)	1 (100%)	
urine RBC (+)	1 (33%)	2 66%)	7 (70%)	-	
Urine WBC (+)	1 (50%)	3 (100%)	9 (90%)	1 (100%)	
Immunology					
Ds DNA-Antibody	1 (50%)	3 (66%)	7 (70%)	1 (100%)	
Complement C3 (level <85)	2 (100%)	1 (33.3%)	5 (50%)	-	
Complement C4 (level <20)	2 (100%)	1 (33.3%)	6 (60%)	-	

Proteinuria was present in all the histopathological subtypes of LN ranging from trace to 4 + albumin by in urine by dipstick. Proteinuria >500mg/day was noted in 100 percent of patients. There was no specific distribution for the classes of LN. On microscopy, all the cases showed some sedimentation details are shown in table 3. Red cells >5 cells/HPF were seen in the urine complete examination in almost 60% cases, along with white cells >5 cells/HPF in about 80%, cases, casts in 40%.

DISCUSSION

There were predominant females in the study. This study is in agreement to other studies of lupus that have shown a female preponderance.[7-9] Mean age of cases included in the study on presentation was 35 ±13 in females, and 36 ±9 in males. This is also in harmony with the other studies. Few studies have reported age less than 20 as a risk factor associated with renal disease and a progressive disease process.[9-11] Prevalence of hypertension in our study was 4 out of 16 patients (25%). When compared to other studies on lupus nephritis it is much less, where prevalence of hypertension was about 70 percent and was associated with worse outcomes.8,9. Another study noted that HTN can occur with normal renal function and can contribute to progressive disease in LN.[11-14]

In agreement with other studies, edema was seen in most of the cases.[15,16] Clinical features related with renal involvement of the disease process, had low sensitivity and most of the patients were not having symptoms. 4 patients didn't have edema and 12 patients didn't have oliguria. About 25% cases showed no renal signs and symptoms. In another study, 16% cases among the studied were not having any renal symptoms.[17] This is an indication that when the patient presents with obvious renal symptomalogy, the Lupus nephritis had already progressed, this becoming a major reason why class 1 patients are not seen commonly on presentation, most of patients have already developed complications. In our study, distribution of cases into histopathological sub-types was: class III: 18.75, class IV: 62.5, class V: 6.25 and mixed 12.5 percent are comparable to previous studies[16,18]

In a study of 376 pts of lupus nephritis they found the frequency of Class II, III, IV and V to be 26%, 19%, 37%, and 15% respectively. A study of 150 patients showed class II 10%, III, 17%, IV 53%, and V 14%.

Division of subjects into in terms of clinical variables (Table 3), is also similar to other studies: HTN, serum creatinine and 24-hour urine protein quantification and hypocomplementemia.[12,17,19,20]

Studies have shown nephrotic presentation was mainly in Class V and to some extent in Class III and IV. [7,9] Although edema was the common clinical symptom but it did not reach clinical significance. Extrarenal symptomology did not correlated with the ISN/RPA class.

Class IV had highest hypertension incidence (40.1percent). In a comparative analysis, cases also having hypertension had about three times more likelihood for having Class IV disease features on histopathology. Another study described a similar association.[13.21,22] In Class IV the mean systolic, diastolic BP and MAP was higher in comparison to other classes, although a statistical significance (P >0.05) was not reached.

In Class IV, anemia was statistically significant when compared with other subtypes. This is in agreement with another study wherein anemia was found to be associated with progressive renal insufficiency.[15] One study reported low platelet count in association with renal insufficiency (P = 0.04) on multivariate analysis.[8] In our study thrombocytopenia was one of the exclusion criteria.

Renal function tests seems to be worse in Class IV in comparison to other classes.[14] This can be due to severe renal disease in Class IV. This correlates with recent literature that creatinine more than 2 is associated with poor survival.[23] Another study reported that most of the patients with Class IV subtype had disease progression after second biopsy with worsening in renal functions.[21] Our study showed the incidence of wbc in urine in Class IV to be increased as compared to other classes. Similar studies found no significant differences in the degree of abnormality of urinary sediment among the classes or outcome of LN, so loses the prognostic or diagnostic significance.[8,9] Although anti-dsDNA was found in 75% patients, the association with different classes of LN did not reach statistical significance. However, studies have shown increased DNA titres as an important biomarker for the severity of disease and mortality.[8,9]

Increased antids DNA levels usually occurs before both clinical and subclinical evidence of proliferative LN, suggesting direct pathogenecity23Absolute Antids DNA level and rate of increase predicts future proliferative lupus nephritis.[25] Anti-Clq antibody has been associated with lupus nephritis but lacks predictive value for disease progression or histopathology,[26] similarly MCP1 and Uil8 have insufficient predictive ability.[27] The present study found hypocomplementemia in all except class 5. This is similar to another study showing largest no. of cases having a low C3 levels in class IV (41%) and class V (53%), especially in pts with proliferative lesions.[17] However, one study found that there was no significant relation of the complement abnormalities in different subtypes.[8]

CONCLUSION

The histopathology of LN is variable. The ISN/RPA class IV has got the highest prevalence then come Class III, V & mixed. Clinical features do not predict the histopathological class. Similarly, disease activity markers such as ESR, hypocomplementemia and anti-DNA titres showed a positive correlation with the renal biopsy. Concluding our study with the recommendation that clinical parameters of the disease process showed be seen when cases are followed-up regularly with repeated biopsies in patients not achieving partial or sustained remission.

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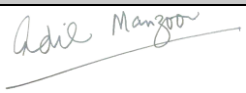
Dr. Adil Manzoor Consultant Nephrologist & Transplantation Medicine King Fahd Hospital Madina, Saudi Arabia	Main script writing, Literature review, Data Collection n	
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