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Clinical spectrum and short-term outcomes of lupus nephritis: Experience from a state run tertiary care centre in southern India

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ABSTRACT

Lupus nephritis (LN) occurs in up to 40-50% of patients with systemic lupus erythematosus (SLE). Renal involvement remains the strongest predictor of morbidity and mortality among patients with SLE. To Study the clinical features and histopathology of patients with lupus nephritis and also to look for risk factors, prognostic markers and short term renal outcomes. This study is a ongoing prospective observational clinical study between February 2012 to February 2016. Patients with clinical features of lupus nephritis satisfying at least four of the ARA criteria for SLE. And newly diagnosed at the time of renal biopsy were included. Descriptive statistics, One-way ANOVA and Chi square test was applied during analysis. Total 100 patients were studied, The mean age at presentation was 27.3±9.8. Majority were females (F: M= 8:1). Arthritis (78%), rash (62%), and fever (68%) were the most common clinical manifestations at the onset. The mean duration of symptoms prior to diagnosis was 12±6.41 months. One third of the patients were hypertensives at the time of presentation. Leucopenia (21%), thrombocytopenia (18%), nephrotic range proteinuria (34%) serum creatinine (2.12±1.70), low C3(77%), low C4(38%), eGFR 49.11±15.15, activity index (7.45±11. 53), chronicity index (1.56±1.68), serum albumin (2.27±0.70) at presentation and (2.83±0.72) at 6 months. Majority belonged to class IV(76%) lupus nephritis followed by class III (10%), class II(4%), class V (4%) class V+VI(3%) V+III(3%). Majority (53%) presented with an eGFR between >60 ml/min, 10% with eGFR 15-30 ml/min and 8 % patients presented with an eGFR of <15 ml/min. Among outcomes, 41(%) complete remission, (27%) partial remission and (32%) no remission to treatment. Eight patients had crescents in the histopathology and two patients had thrombotic microangiopathy and three patients had APLA syndrome. All achieved only partial remission. Eight patients reached ESRD. Mortality was seen in 10% secondary to infection due poor follow up. An younger age at diagnosis, low GFR and high serum creatinine at presentation, high activity with chronicity indeces and class IV±V lupus in histopatholgy were considered to be a poor prognostic marker. The outcome of lupus nephritis with standard immunosuppressive regimens is reasonable, but immunosuppression is associated with a high rate of infection. Early identification of risk factors and prognostic markers helps to initiate aggressive treatment at disease onset to obtain the best response

Keywords: Lupus Nephritis, Remission, eGFR, Histopathology,

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease primarily occurring in young women and characterized by varied clinical and laboratory manifestations. Lupus nephritis (LN) occurs in up to 40-60% of patients with systemic lupus erythematosus (SLE)[1].Renal involvement remains the strongest predictor of morbidity and mortality among patients with lupus, and despite improvements in the management of lupus, the incidence of end-stage renal disease has not declined. Cyclophosphamide has remained the mainstay in the treatment of lupus nephritis and it is against this drug the other therapies are compared[2]. Studies involving subjects from the Indian subcontinent have been far and few. In the current study, we prospectively analyzed biopsy proven lupus patients for clinical features, prognostic markers and short term outcomes.

MATERIALS AND METHODS

This study was a prospective cross sectional observational study done between Feb 2012 to Feb 2016. Patients with clinical features of lupus nephritis satisfying at least four of the ARA(American rheumatological association) criteria for SLE[3]. Both out patient and in-patients and those newly diagnosed at the time of renal biopsy were included. Patients with end stage renal disease(ESRD), 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. Suspected cases of lupus nephritis were tested for ANA, Anti dsDNA and complements levels. Active lupus nephritis was defined by urine RBC >5/hpf or RBC/WBC/granular casts in the urine, proteinuria of more than 0.5 gm/day. Renal biopsy was performed in all patients. Renal biopsies were categorized according to WHO/ISN/RPS classification[4] and activity, chronicity index and SLEDAI index was applied.

All the patients received induction therapy with intravenous pulse methyl prednisolone (500 mg once daily for three days). Sixty five patients received induction with intravenous pulse cyclophosphamide as per EUROLUPUS protocol[5] and 22 patients received induction with intravenous pulse cyclophosphamide as per NIH per protocol[6]. Leucocyte counts (to be kept above 3000/cu mm) done on the tenth day following administration. Dosage was adjusted to renal function, with a 25% reduction in dose for an eGFR(estimated GFR) of <15 ml/min. All the patients received oral prednisone, (1 mg/kg/day) for four weeks and then gradually tapered, according to clinical improvement, by 10 mg/week to a maintenance dose of 5-7.5 mg/day. Eleven patients received induction with mycophenolate mofetil (MMF), 500 mg two times daily, along with prednisone. Two patients received tacrolimus+MMF+prednisolone. All the patients received hydroxychloroquine and one third received ACE (angiotensin‑converting enzyme) inhibitors, or ARB (angiotensin II receptor antagonists). Renal flares were treated with increasing oral prednisone or additional IV methyl prednisolone pulses as required. Sixty of the 89 female patients were sexually active and were advised barrier contraception. They were counseled regarding the risks inherent to lupus in pregnancy and all of them agreed to defer pregnancy till disease quiescence.

The primary outcome measure was complete remission (CR). This was defined as per KIDIGO guidelines[7], return of SCr to previous baseline, plus a decline in the Upcr(urine protein creatinine ratio) to <500mg/g creatnine. A partial remission (PR) was defined as Stabilization (±25%), or improvement of SCr, but not to normal, plus a >50% decrease in uPCR. If there was nephrotic-range proteinuria (uPCR <3000mg/g, improvement requires a >50% reduction in uPCR, and a uPCR <3000mg/g. Treatment failure was defined as any of the following – proteinuria of more than 3gm/day, a rise in creatinine of 25% or more above the baseline or discontinuation of treatment due to side effects. Renal relapses were considered to be present if any of the following occurred (1) increase of proteinuria by 0.5 g/day to a value more than 1g/day in a patient previously in PR or CR (2)recurrence of active sediment (3) a decrease in estimated GFR by 30 ml/min.

Laboratory tests C3, lipid profile, anti-dsDNA were done at baseline and whenever relapse was suspected.

Secondary end points included eGFRs, and proteinuria, adverse effects, renal relapses, treatment failures, progression to ESRD, or death. Descriptive statistics are reported as frequency and percentage for categorical variables and as mean and standard deviation for continuous variables. One‑way ANOVA was carried out to detect the differences, if any, in the baseline clinical and laboratory (continuous) variables among patients with partial, complete, or no remissions at the end of study period. Similarly, Chi square test was carried out to detect differences in categorical variables in the same groups.

RESULTS

Total 100 patients included in the study with 89 being female. The mean age at presentation was 27.3±9.8 (range 10-47) years. Majority were females (F: M= 8:1). Baseline clinical and laboratory characteristics of patients are shown (Tables 1 and 2).

Arthritis (78%), fever (68%) and rash (62%) were the most common clinical manifestations at the disease onset. The mean duration of symptoms prior to diagnosis was 12±6.41 months. One third of the patients were hypertensives at the time of presentation.

Seventy seven patients had low C3 levels at presentation. Indicating the disease activity in majority of the patients. Forty four of 100 patients presented with baseline creatinine of <1.5 mg/dl, 28 (63.6%) achieved complete remission, 8 (18.1%) patients achieved partial response. Fifty patients presented with a baseline creatinine of ≥2.5 mg/dl, of them eight patients (18.1 %) achieved a partial response, and 4 patients (9.9%) a complete remission. Majority (53%) presented with an eGFR between >60 ml/min, 10% with eGFR 15-30 ml/min and 8 % patients presented with an eGFR of <15 ml/min at the initial presentation.

Twenty seven patients attained partial remission, 41 patients achieved complete remission, and 32 patients had no remission to treatment (Fig 1). Eight patients reached ESRD among them 7 patients had treatment failure secondary to drug default and 10 patients expired due to infection and all of them presented with refractory septic shock. Eight patients had crescents in the histopathology and two patients had thrombotic microangiopathy. Three patients had APLA syndrome. All achieved only partial remission.

Average time to achieve complete remission was 5.0 (±1.6) months and to achieve partial remission was 3.5 (±2.0) months. Significant improvement in the serum albumin before (2.27±0.70) and after 6 months (2.83±0.72) of treatment was observed (P value=<0.001). Indicating good response to therapy and also improved nutrition after initiation of therapy.

On one way ANOVA [Table 3], there were significant differences in the baseline activity and chronicity indices and eGFR, among patients with no, partial, or complete response. Patients with complete responses had a lower chronicity score and a shorter delay in treatment compared to patients with no remission ($P < 0.001$). Patients with no remission had both higher chronicity and activity indices ($P < 0.001$). The serum albumin significantly improved following treatment in patients who achieved complete remission ($P < 0.001$). The baseline proteinuria negatively correlated with the eGFR at end of the study. There was a trend toward higher SLEDAI index in patients with no remission ($P = 0.034$). This could be because of refractory active disease in these patients (Table 4 and Table 5).

There were no differences in the age at diagnosis, gender, clinical features (arthritis, rash, oral ulcers, CNS disease, serositis, photosensitivity), C3 levels, serum albumin, biopsy class, or therapy in patients with no, partial, or complete remission. The class of biopsy (class III or IV) did not correlate with the response. There was a significant correlation between eGFR at the study and age at diagnosis, hypertension and baseline renal function. Proteinuria at end of study correlated with the activity index, chronicity index and hypertension and baseline renal function. Remissionat the end of study correlated with age at diagnosis, hypertension, activity and chronicity. The specific treatment given with mycophenolate or cyclophosphamide or tacrolomus did not correlate with any of the outcome variables.

CNS involvement was present in 10/100 (10.0%) patients. Leucopenia was present in 21(21.0 %) and thrombocytopenia in 18(18.0%) patients. Hypothyroidism is seen 9 patients.Two or more organ involvement was present in 15 (15%) patients. Presence of other organ involvement did not influence the renal response.

Adverse events

The significant adverse events recorded were avascular necrosis of femur head in one patient, pulmonary tuberculosis in one patient, amenorrhea in ten patients, Herpes zoster in three patients, psychosis due to steroids was experienced by one patient, acute pancreatitis in one and cataract in one patient. Leucopenia necessitating either dose reduction or withdrawal of drugs was not recorded. Hemorrhagic cystitis was not seen in our patients.

DISCUSSION

There has been a considerable improvement in the survival of patients with lupus nephritis, which has been attributed to an increased awareness, early referral to nephrologists, introduction of cyclophosphamide , effectiveness of newer induction regimens, and an overall improvement in medical care. However for various reasons a significant proportion of patients with lupus nephritis do not achieve complete remission despite treatment with cyclophosphamide[8].

The mean age of subjects in our study (28.21±9.41) was similar to the subjects who participated in the NIH study by Gourley et al.[9] Compared to the Caucasian [10] and African American patients, [11] the patients in the present study had a higher creatinine level but a lower degree of proteinuria at baseline. They also had a younger age at onset and lower activity, but higher chronicity indices on renal biopsy[12]. Nephrotic syndrome was seen in 1/3 rd of our patients, which was comparable to studies done by Chrysochou et al[13], Bono et al,[14]. Beji et al[15] and however Martins et al[16] had less number of patients with nephrotic syndrome. Various studies have shown different number of people with renal failure at presentation. Renal failure was seen in 64% of our patients which was comparable to study done by Bono et al[14]. A younger age at diagnosis is considered to be a poor prognostic marker. In our study, the age of patients at diagnosis ranged from 10 to 47 years. Twenty one patients belonged to the age range of 10 to 20 years at the time of diagnosis. Over this age range, the age at diagnosis (as well as the present age) was negatively correlated with remission and eGFR at the study. This may have been due to a longer latency for treatment in those of older age. Other markers of poor prognosis – hypertension, lower eGFR at baseline, and a higher chronicity and activity indices at baseline were also corroborated in our study.The prognostic and therapeutic significance of the degree of activity (active inflammation) and chronicity (glomerular scarring, tubulointerstitial

fibrosis, and atrophy) in diffuse LN has been somewhat controversial[17].Although some investigators have proposed that high levels of chronicity are associated with progressive renal failure that is less likely to respond to immunosuppressive therapy[18], others have noted that the degree of activity and chronicity are often similar in patients who progress to renal failure and in those who maintain stable renal function. Majority of our patient belonged to class IV lupus nephritis(76%) and followed by class III(10%). Blood urea and serum creatinine were observed to be higher in Class IV as compared to other classes. This could be explained by the severity of renal lesion in Class IV. This finding confirm to other studies reporting that creatinine >2.4 is associated with poor survival outcome reflecting more severe renal disease. In our study class IV lupus nephritis who had more chronicity index had worst outcome in the form of partial remission and no remission similar results was observed with study by yung et al[19]. The rate of complete remission (41%) achieved in our study was similar to that achieved by Korbet et al,(43%)[20] but higher remission were achieved in other studies[21,22,23].A higher remission rate of 82% was achieved by Moroni G et al,but this was due to the use of oral cyclophosphamide with a higher cumulative dose[24] A recent study done at southern India by Annavarajula, et al. achieved partial remissionof 30.77% which was similar to our study (27%) and complete remission of 51.28% [25]. The rate of complete and partial remission from another study at eastern India showed 23.3% and 21% respectively which much lesser than our study[26].

A much higher remission rate (78%) was achieved with a longer duration of treatment by Ioannidis et al.[23] Comparing remission rates between studies of lupus nephritis is also limited by the varying definitions used to define remission. For instance, proteinuria of less than 1 g considered to be suggestive of remission by Gourley et al,[9] in the NIH studies is much lesser stringent than the criteria proposed by the KIDGIO which we considered in our study. The other factors which assumed significance in predicting remission were a higher eGFR. Annavarajula et al study found predicting remission were a higher eGFR and concurrent use of ACE inhibitors. We did not use ACE inhibitor in all patients and hence we were not able to analyze this association. Serum creatinine was found to be predictive in studies by Illei GG[21]and Moroni G[24] et al which is similar to the present study. The reported rates of relapse vary from 25% at 5 years, to 46% at 10 years [27,28]. The duration of follow up was too short to provide meaningful rates of relapse. Twenty percent of our patients experienced treatment failure. This is slightly higher compared to the rate of treatment failure in the Euro Lupus trial (16% in the low dose cyclophosphamide arm; 20% in the high dose arm),[5] the probably reason could be due to more number our patients had higher chronicity indices.

Strenghths of our study was good number of the study subjects. All patients underwent biopsy and were included in the study, standard protocol of treatment was initiated, rigid follow up to look for outcome. However limitation were it is a short term study looking for the outcome, which may not be sufficient time to observe the outcome. Analysed all aged population, not excluded children due to different type of manifestation in them.

CONCLUSION

An younger age at diagnosis, low GFR and high serum creatinine at presentation, high activity and chronicity indeces and class IV±V lupus in histopatholgy were considered to be a poor prognostic marker. The outcome of lupus nephritis with standard immunosuppressive regimens is reasonable, but immunosuppression is associated with a high rate of infection. Early identification of risk factors and prognostic markers helps to initiate aggressive treatment at disease onset to obtain the best response.

Table 1: Baseline clinical characteristics of 70 patients

Clinical parameters	NUMBER OF PATIENTS
Age (years)	28.21±9.41
Gender (M/F)	11/89
Arthritis	78
Rash (malar or peripheral)	62
Serositis (Pleuritis or pericarditis)	19
Fever at presentation	68
CNS manifestations	10
Oral ulcers	34
Photosensitivity	31
Hypertension at onset	33

Table 2: Baseline laboratory values in patients

Characteristics	Values(%)
Leucopenia	21
Thrombocytopenia	18
Anti dsDNA positive	91
Nephrotic range proteinuria	34

Hemoglobin (g/dl)	8.55±2.18
Serum Albumin (g/dl) at presentation	2.27±0.70
Serum Albumin (g/dl) at 6 months	2.83±0.72
C3 low	77
C4 low	38
Urine protein excretion (g/24 h)	3.49±2.18
Serum creatinine (mg/dl)	2.12±1.70
eGFR (ml/min)	49.11±15.15.07
Activity index	7.45±11.53
Chronicity index	10.50±4.09
SLEDAI	1.56±1.68
Biopsy class	7.45±11.53
II	
III	4
IV	10
V	76
V+VI	4
V+III	3
eGFR at presentation	3
>90 ml/min	
60-90 ml/min	33%
30-60 ml/min	20%
15-30 ml/min	29%
<15 ml/min	10%
	8%

Fig 1 Bar diagram showing outcome of the treatment

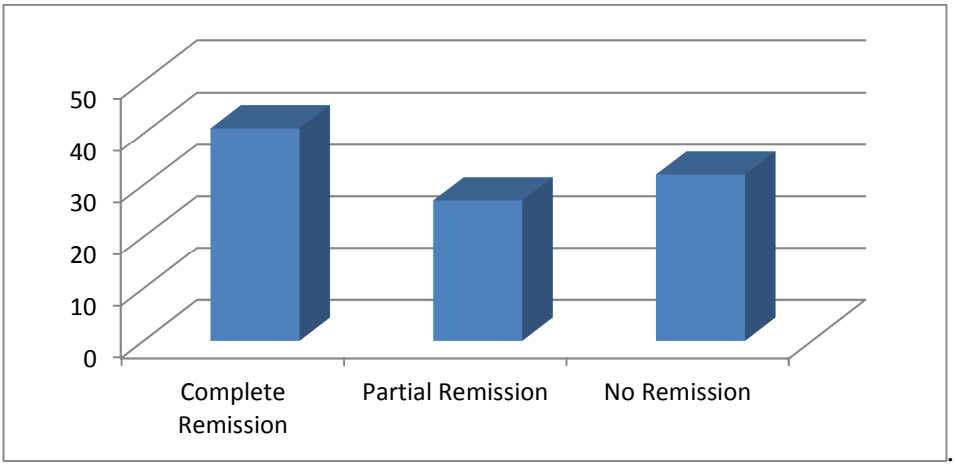

Table 3: One way ANOVA between important baseline clinical and laboratory variables and patients categorized into no, partial and complete remission

variables	Response to treatment			Total	P value
	No Remission	Partial remission	Remission		
Age in years	29.34±9.99	28.11±9.17	27.39±9.24	28.21±9.41	0.682
Urineprotein24 hour	3.48±2.25	3.87±2.77	3.23±1.63	3.49±2.18	0.500
GFR	36.69±11.70	45.74±9.59	61.02±10.95	49.11±15.15.07	<0.001**
Creatinine Presentation	2.83±0.97	1.99±2.10	1.64±1.70	2.12±1.70	0.010**
Creatinine at 6 months	2.93±2.18	1.39±0.55	0.95±0.55	1.70±1.56	<0.001**
Hemoglobin (g/dl)	8.48±1.66	8.35±1.45	8.74±2.86	8.55±2.18	0.752
TLC	8207.19±6650.85	6395.56±2659.98	6589.46±2590.92	7054.78±4365.65	0.192
Platelet Count	2.22±1.32	1.72±0.82	2.25±0.95	2.10±1.07	0.101
Albumin Presentation	2.37±0.75	2.07±0.63	2.31±0.69	2.27±0.70	0.235
Albumin at 6 months	2.47±0.63	2.70±0.65	3.20±0.67	2.83±0.72	<0.001**
SLEDAIindex	11.78±4.23	5.78±2.90	5.17±16.96	7.45±11.53	0.034*
SBP (mm Hg)	132.69±19.76	125.56±15.53	124.59±20.25	127.44±19.09	0.166
DBP (mm Hg)	84.13±12.06	83.19±9.99	79.37±11.90	81.92±11.56	0.176
Activity Index	14.25±3.76	10.70±2.48	7.44±2.36	10.50±4.09	<0.001**
Chronicityindex	2.72±1.37	1.70±1.79	0.56±1.16	1.56±1.68	<0.001**

Table 4: Pearson's and point bi-serial correlation between outcomes and baseline variables

Baseline variables	Biseriel /Pearson correlation with remission	
	R value	P value
Age at diagnosis	-0.073	0.470
Hypertension	0.073	0.166
Nephrotic syndrome	-0.097	0.176
eGFR baseline	0.662	<0.001**
Activity index	-0.627	<0.001**
Chronicity Index	-0.497	<0.001**

Table 5: Pearson's and point bi-serial correlation between eGFR and proteinuria

Variables	Pearson correlation with eGFR		Pearson correlation with proteinuria	
	r value	p value	r value	p value
Age at diagnosis	-0.083	0.413	0.029	0.778
Proteinuria	-0.151	0.133	-	-
eGFR baseline	-	-	-0.151	0.133
Activity index	-0.607	<0.001**	0.074	0.465
Chronicity Index	-0.402	<0.001**	-0.017	0.667
SLEDAI Index	-0.314	0.001**	-0.105	0.299
Hb	-0.116	0.251	0.011	0.916
TLC	-0.050	0.622	-0.083	0.412
Platelet count	0.103	0.309	-0.088	0.383
Alb at presentation	0.091	0.367	-0.149	0.139
Creatinine at presentation	-0.462	<0.001**	0.252	0.011**

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