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A Clinicopathological Study of Refractory Lupus Nephritis in Tertiary Care Hospital in North East India

Dr. Manjuri Sharma[1], Benjamin Sangma[2], Prodip Kumar Doley[3], Gayatri Pegu[4]

Department of Nephrology, Gauhati Medical College & Hospital, Guwahati, Assam, India

Abstract: ***Background: Lupus nephritis is a dreaded and common manifestation observed in 50% of the individuals with systemic lupus erythematosus, an autoimmune clinical condition. Refractory lupus nephritis as per definition is failureto respond to any combination of immunosupressants and corticosteroids for atleast six months. Approximately 10% of lupus nephritis patients will ultimately develop ESRD. Objectives: The available literature and data on refractory nature of the lupus nephritis is very limited. Hence, we have aimed to investigate the clinical spectrum and rate of response to the treatment in our lupus nephritis patients in a Tertiary Care Hostipal in North East India. Methodology: This was a single center prospective observational study done over a period of 1 year. Patients were enrolled after fulfilling the SLICC - ACR criteria. Clinical manifestations were recorded and blood samples were analysed for the presence of anemia, thrombocytopenia, leucopenia, ANA, anti dsDNA, C3 and C4. The levels of C - reactive protein, creatinine, albumin, cholesterol and urine protein were also analysed. Renal biopsy was done in all the patients and categorised as per the ISN/RPS classification. The obtained values were subjected to statistical analysis and p<0.05 and p<0.01 were considered statistically significant. Results: Eighty one lupus nephritis patients were studied (females: 75, male: 6). The presence of elevated levels of dsDNA, C - reactive protein (at the beginning), creatinine, cholesterol, urine protein and reduced C3 and C4 altered the response rate significantly (p <0.01). The increased activity index value was also found to be significantly associated with non response in lupus patients. The increased chronicity index value and elevated C - reactive protein levels were also found to be positively associated with no response rate (p<0.05). Conclusion: Refractory lupus nephritis is significantly associated with higher ds DNA, C - reactive protein, creatinine, cholesterol, urine protein levels and reduced C3 and C4 level.***

Keywords: Lupus nephritis, immunosupression, non response, refractory

1. Introduction

Lupus nephritis is a severe and common manifestation observed in individuals with systemic lupus erythematosus (SLE), which is an autoimmune disease (Rahman & Isenberg, 2008) . Approximately around 60% of patients with SLE were reported to have lupus nephritis (Appel et al., 2007) . Lupus nephritis is a life threatening condition if not managed optimally. The major deadly consequences associated with lupus nephritis are end - stage renal disease and increased SLE patient morbidity and mortality. The term “refractory” lupus nephritis indicates an improper or lack of response of the patients towards the drugs and medications provided. As per the guidelines of European League Against Rheumatism and European Renal Association - European Dialysis and Transplant Association, the clinical condition is termed “refractory” on the failure of response or improvement within three to four months; or not reaching 50% response in six to twelve months; or complete cure in two years (Bertsias et al., 2012; Hahn et al., 2012) . The refractory lupus nephritis may be caused due to tolerance to therapy provided, adverse associated events, drug adherence or lack of efficiency to induction regimen (Kronbichler et al., 2019) . Around 30% of patients were reported to be refractory towards the treatment (Costa et al., 2021) .

As per previous study reported, chronic kidney disease and end - stage renal disease were the major concerns of refractory lupus nephritis. The other concerns include, increased death rate, drug toxicity and impaired quality of life. Fever is one of the clinical manifestations, which is present in more than 60% of lupus nephritis patients, which has been reported to be due to the higher disease activity (Inoue et al., 1986) . Refractory lupus nephritis was majorly found to be associated with increased disease activity (Weidenbusch et al., 2019) . The commonly used immunosuppressive drugs such as cyclophosphamide and mycophenolate mofetil were found to be refractory (Ginzler et al., 2005) . The lupus nephritis is considered to be refractory after patients fail to respond to the combination of any immunosuppressive drugs and corticosteroids for atleast 6 months. Rituximab may be effective against refractory lupus nephritis however both positive and negative results have been reported (Rovin et al., 2012; Mysler et al., 2013) . Most studies recommend switching between cyclophosphamide and mycophenolate mofetil alternatively or *vice versa* in treating refractory lupus nephritis. Apart from these drugs, rituximab, calcineurin inhibitors, prolonged course of cyclophosphamide may be considered as alternative treatments (Yo et al., 2019) .

Huang et al. (2019) have reported lupus nephritis to be refractory, if it fails to respond to any one of the drugs including, corticosteroids, cyclophosphamide, tacrolimus, mycophenolate mofetil, or cyclosporin for more than six months (Anders & Hiepe, 2019) . Furthermore, distinguishing between non - adherence to prescribed therapy and initial treatment failure can be difficult, and the time point at which non - response becomes treatment failure is uncertain. As per available literature, the switching between immunosuppressive drugs are effective against refractory lupus nephritis (Gururani et al., 2021) . The treatment of lupus nephritis with secukinumab, an anti - IL - 17A antibody showed significantly positive improvement by restoring the renal function completely.

The poor prognosis of refractory lupus nephritis necessitates regular monitoring of the patient response and the need to switch or augment therapy. Up to our current knowledge, only limited number of studies are available on the prognosis and treatment of refractory lupus nephritis. There is still variation in the first therapy choices because geographic, genetic, and other epidemiological factors influence treatment response and renal outcomes. Understanding the nature of a therapeutic response, the safety of therapy, and the need to recognize treatment failure and an appropriate switch to other agents is a very important treatment strategy. Hence, from the available data, the current study has been framed to analyse the spectrum of patients with refractory lupus nephritis inTertiary Care Hospital, in North East India.

2. Methodology

2.1 Participant Selection

This was a single center prospective observational study done for a period of one year from May 2021 to May 2022. All patients above 18 years of age and fulfilling the SLICC - ACR criteria were included in the study. Exclusion criteria included lupus ESRD patients, patients already on immunosupressants for the last 6 months, non compliant patients and patients not consenting for study. This study has been approved by the institutional human ethical clearance committee.

2.2 Sample collection

The patients were informed of the detailed research protocol and the expected outcomes. They were provided with questionnaires to obtain their demographic data, including age, gender, and other details like previous medical history, any other complications, previous hospitalization history, etc., A written consent form has been obtained from the participants. The Declaration of Helsinki, which was developed by the World Medical Association, has been followed for the collection of blood samples from lupus nephritis patients. The participants were clearly told about the ways of processing their blood clearly.

2.3 Sample Analysis

The blood samples were subjected to analysis of the ranges of hematological parameters such as hemoglobin, red blood cells, hematocrit, WBC, lymphocytes, and neutrophils. The analysis was carried out on the blood samples through the 3 - part hematological analyzer (Mindray, BC 2800) in the laboratory conditions. The other biochemical parameters like creatinine, albumin, cholesterol, C - reactive protein (CRP), serum complements C3 and C4 were analysed in a biochemical analyser. An analysis for the presence or absence of double stranded DNA has been performed.

All the patients were subjected to renal biopsy and categorised as per the ISN/ RPS classification (Weening et al., 2004) . The patients were also analysed for the presence or absence of fever, arthritis, oral ulcer, serositis, photo sensitivity, and central nervous system manifestations. The management was guided by the clinical manifestation and the renal biopsy findings. The induction medications was either cyclophosphamide (CYC) as per the NIH protocol or mycophenolate mofetil (MMF) at dose of 1.2gm/m^2. Patients also received hydroxychloroquine (6mg/kg/day) and other supportive medications. CRP, creatinine, albumin levels, along with urine sample analysis, were also performed after six months to predict the significant variation. Activity and chronicity indices were also calculated.

Complete response was defined as per KDIGO (KDIGO 2021 guidelines) that is the stabilization or improvement of in kidney function (+/ - 10% to 15 % of the baseline), reduction in proteinuria to <0.5gm/gm measured as PCR from 24 hour urine collection. Partial remission was defined as stabilization or improvement of kidney function (+/ - 10% to 15% of baseline, reduction in proteinuria by atleast 50% and to <3gm/gm measured as the PCR from a 24 hour urine collection. No response was defined as failure to achieve a partial or complete response at 6 months.

2.4 Statistical analysis

The statistical analysis of the obtained results was performed in SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N. Y., USA). The statistical significance values were set at $p < 0.01$ and $p < 0.05$.

3. Results

3.1 Statistical Analysis

Table 1 depicts the association between study variables and response at 6 months using chi - square test. Majority 34 (53.1%) of no response had positive ds DNA, 9 (52.9%) of partial response had negative ds DNA and 22 (34.4%) of complete response had positive ds DNA. From the p - value 0.000 which is less than 0.05 hence there is an association between ds DNA and response at 6 months.

Majority 33 (66.0%) of no response had low C4, 9 (29.0%) of partial response had normal C4 and 19 (61.3%) of complete response had normal C4. From the p - value 0.000 which is less than 0.05 hence there is an association between C4 and response at 6 months. When comparing CRP level with response at 6 months, majority 26 (61.9%) of no response had elevated CRP level, 13 (31.0%) of partial response had elevated CRP level and 25 (64.1%) of complete response had normal CRP level. From the p - value 0.000 which is less than 0.05 hence there is an association between CRP and response at 6 months. When comparing CRP at 6 months and response at 6 months, majority 7 (87.5%) of no response had elevated CRP at 6 months, 16 (21.9%) of partial response had normal CRP at 6 months and 28 (38.4%) of complete response had normal CRP at 6 months. From the p - value 0.029 which is less than 0.05 hence there is an association between CRP at 6 months and response at 6 months.

The difference in mean study variables between response at 6 months were analyzed using analysis of variance (ANOVA). The p - values are less than 0.05 for creatinine (**0.001**), cholesterol (**0.001**), B24Hr UP (**0.000),** Activity

Index (**0.000),** Chronicity Index (**0.024),** Creatinine at 6 months (**0.000)** and 24Hr UP at 6 months (**0.000).** In creatinine, no response has high mean 2.13±1.58 when compared to partial response 1.15±1.05 and complete response 1.00±0.72. In Cholestrol, no response has high mean 186.94±46.47 when compared to complete response 168.29±34.88 and partial response 143.94±26.13. In B24Hr UP, partial response has high mean 4.87±2.32 when compared to no response 3.81±1.35 and complete response 2.39±0.78. In Activity Index, no response has high 11.47±3.45 when compared to partial response 8.12±3.50 and complete response 6.11±3.08. In Chronicity Index, no response has high mean 3.06±1.67 when compared to partial response 2.29±1.36 and complete response 2.07±1.22. In Creatinine at 6 months, no response has high mean 2.91±0.89 when compared to partial response 0.82±0.45 and complete response 0.55±0.22. In 24Hr UP at 6 months, no response has high mean 2.34±1.24 when compared to partial response 1.68±0.70 and complete response 0.33±0.07 (Table 2).

4. List of Tables

Table 1: Comparison of study variables and response at 6 months

	No response (n=36)	Partial response (n=17)	Complete response (n=28)	*p* value
	n (%)			
Gender				
Male	5 (83.3)	1 (16.7)	0 (0.0)	0.105
Female	31 (41.3)	16 (21.3)	28 (37.3)	
Fever				
No	12 (42.9)	7 (25.0)	9 (32.1)	0.808
Yes	24 (45.3)	10 (18.9)	19 (35.8)	
Arthritis				
No	7 (36.8)	3 (15.8)	9 (47.4)	0.403
Yes	29 (46.8)	14 (22.6)	19 (30.6)	
Oral ulcer				
No	22 (53.7)	8 (19.5)	11 (26.8)	0.211
Yes	14 (35.0)	9 (22.5)	17 (42.5)	
Serositis				0.602
No	25 (42.4)	14 (23.7)	20 (33.9)	
Yes	11 (50.0)	3 (13.6)	8 (36.4)	
Photo sensitivity				
No	19 (41.3)	9 (19.6)	18 (39.1)	0.613
Yes	17 (48.6)	8 (22.9)	10 (28.6)	
CNS manifestation				
No	34 (47.2)	15 (20.8)	23 (31.9)	0.298
Yes	2 (22.2)	2 (22.2)	5 (55.6)	
Anemia				
Normal	5 (41.7)	2 (16.7)	5 (41.7)	0.837
Anemia	31 (44.9)	15 (21.7)	23 (33.3)	
Leucopenia				
Normal	29 (43.9)	14 (21.2)	23 (34.8)	0.982
Leucopenia	7 (46.7)	3 (20.0)	5 (33.3)	
Thrombocytopenia				
Normal	28 (43.1)	14 (21.5)	23 (35.4)	0.883
Thrombocytopenia	8 (50.0)	3 (18.8)	5 (31.3)	
ds DNA				
Positive	34 (53.1)	8 (12.5)	22 (34.4)	**0.000****
Negative	2 (11.8)	9 (52.9)	6 (35.3)	
C3				
Normal	10 (37.0)	6 (22.2)	11 (40.7)	0.614
Low	26 (48.1)	11 (20.4)	17 (31.5)	
C4				
Normal	3 (9.7)	9 (29.0)	19 (61.3)	**0.000****
Low	33 (66.0)	8 (16.0)	9 (18.0)	
CRP				
Normal	10 (25.6)	4 (10.3)	25 (64.1)	**0.000****
Elevated	26 (61.9)	13 (31.0)	3 (7.1)	
LN Class				
Class II	2 (66.7)	0 (0.0)	1 (33.3)	
Class III	5 (33.3)	4 (26.7)	6 (40.0)	
Class IV	15 (44.1)	8 (23.5)	11 (32.4)	0.928
Class V	6 (60.0)	1 (10.0)	3 (30.0)	
Class III+V	2 (66.7)	0 (0.0)	1 (33.3)	
Class IV+V	6 (37.5)	4 (25.0)	6 (37.5)	
Induction				
CYC	32 (44.4)	15 (20.8)	25 (34.7)	0.994
MMF	4 (44.4)	2 (22.2)	3 (33.3)	
CRP at 6 months				
Normal	29 (39.7)	16 (21.9)	28 (38.4)	**0.029***
Elevated	7 (87.5)	1 (12.5)	0 (0.0)	

**p<0.01, *p<0.05

Table 2: Difference in mean variables between response at 6 months

	No Response (n=36)	Partial Response (n=17)	Complete response (n=28)	*p* value
	Mean±SD			
Age	30.39±10.70	25.76±12.20	26.39±10.28	0.223
Creatinine	2.13±1.58	1.15±1.05	1.00±0.72	**0.001****
Albumin	2.27±0.46	2.26±0.47	2.34±0.55	0.811
Cholesterol	186.94±46.47	143.94±26.13	168.29±34.88	**0.001****
B24Hr UP	3.81±1.35	4.87±2.32	2.39±0.78	**0.000****
Crescent	0.19±0.40	0.29±0.47	0.07±0.26	0.147
Activity Index	11.47±3.45	8.12±3.50	6.11±3.08	**0.000****
Chronicity Index	3.06±1.67	2.29±1.36	2.07±1.22	**0.024***
Creatinine at 6 months	2.91±0.89	0.82±0.45	0.55±0.22	**0.000****
Albumin at 6 months	3.02±0.60	3.19±0.46	3.21±0.37	0.293
24Hr UP at 6 months	2.34±1.24	1.68±0.70	0.33±0.07	**0.000****

**p<0.01, *p<0.05

5. Discussion

The severity of lupus nephritis has been reported to be higher in male and children along with higher incidence (Brunner et al., 2008) . In our study, the number of male patients (n = 6) and female patients (n = 75), which is commonly seen as reported in earlier studies. Our findings were similar to the reports of Huang et al. (2010) , who have stated that females are more prone to SLE than male.

Irrespective of gender, around 48% patients showed no response to the treatment and only 37% showed complete response. No significant difference was observed in response rate based on gender in our study.

One of the most common manifestation in a patient with lupus nephritis is the presence of fever. Studies have reported an occurrence of 36 to 86% in patients with lupus disease. Around 71% of our study participants were had fever on presentation, which is considerably high. The fever in lupus has been reported to be accompanied by reduced C3 level, which in turn results in increased disease activity (Zhou & Yang, 2009) . This is in coherence with our results, which has shown lower C3 levels in around 72% of patients (almost same as number of patients diagnosed with fever). Fever may also be a manifestation of active lupus. Although the complement levels of C4 showed highly significant variation, C3 levels were not significant in our study. The response rate of patients did not significantly vary irrespective of the presence or absence of fever and altered C3 levels.

Lindsay et al. (2019) found that in patients with SLE lupus nephritis patient the prevalence of arthritis was significantly higher. We have also observed a very high prevalence of arthritis in more than 80% patients, in which most of them showed no response to the treatment. We did not observe any significant variation in response rate despite of higher prevalence of arthritis in lupus nephritis patients.

Sverzutet al. (2008) have reported a case of an SLE patient who had been diagnosed with oral complications like oral ulcerative lesions and progression of lupus nephritis. Oral ulceration have also been reported as a common clinical manifestations in lupus patients. Oral complications are reported to be present in more than 70% of SLE patients globally (Bader - Meunier et al., 2005) . But based on our current findings, we report that the oral manifestations are present in lupus patients but the variations in response rates were not significant.

Pleural inflammation is generally regarded as serositis (Kelly et al., 2017) , which is one of the lupus disease manifestations. Clive Kelly et al. have reported a female patient with SLE accompanied by serositis. A recent study by Nie et al. (2022) has reported to found an association with serositis in LN patients. Although these findings report a positive correlation between serositis and SLE, we report a negative correlation based on our results. The prevalence of serositis in SLE was moderate, and the response rate was not found to be affected by the presence or absence of serositis.

Rovin et al. have stated that SLE patients were observed to have lower C3 as well as C4 levels along with higher anti - dsDNA (Rovin et al., 2005) . In approximately 67–72% of patients, C3 and C4 levels were lower in our current study, which is supported by the previously reported studies. More than 85% of patients with lupus nephritis showed the presence of ds - DNA, which is highly significant in our study. Anemia has been found to be significantly associated with lupus nephritis and SLE. Since lupus nephritis is an inflammatory disease of the kidney, the red blood cells and hemoglobin levels are highly influenced by the disease activity (Ardalan, 2013) . Herewith, our findings report the highest prevalence of anemia in around 92% of lupus nephritis patients. The anemic patients showed complete response as well as a similar number of patients showed no response to the treatment, which makes it an insignificant factor in response measurement.

Studies have reported a positive correlation between CNS and SLE. Muscal and Brey (2010) , Kakati (2017) . Contrastingly, CNS manifestations were not found to be significantly present in the lupus nephritis patients of our study, and the response rates were irrespective of presence or manifestations.

Along with anemia, the other hematological manifestations like thrombocytopenia and leucopenia are reported to be commonly present in SLE patients. Although these conditions were common in lupus nephritis patients, the presence was not found to be significant. The response rates were also not significant. The urine protein and creatinine ratio levels more than 0.5 mg/mg has been reported as the characteristic feature of lupus nephritis. The urinary protein excretion of more than 5 g per day has been stated as the clinical presentation of refractory lupus nephritis. Our current findings also support this observation, as the patients have showed significant variation in the levels of urine protein, when analysed during the examination and after six months follow - up period. The urine protein has been observed to have a highly significant association with the severity of lupus nephritis. The creatinine levels were higher in the lupus patients on the first analysis, which was significant and very higher ranges were observed in the analysis after six months period, indicating the highly significant variation. These reports are in accordance with the observations of Hahn et al. (2012). The elevated creatinine and cholesterol levels have influenced the response rates significantly.

It has been reported that urine sedimentation of RBCs are higher than five per high - power field (Kronbichler et al., 2019) . As per the results of Contreras et al. (2006) , Austin et al. (1986) and Hsieh et al. (2011) the levels of creatinine have also been found to be higher along with the increased inflammation rates, which in turn increase CRP levels. The CRP levels were significantly higher in our current study, which is in accordance with the previous reports. The elevated CRP levels influenced the response rate of the patients before and after the follow - up period.

Race has also been found to influence the severity of lupus nephritis (Ong et al., 2011) . According to the EULAR/ERA - EDTA recommendations, patients with refractory illness should switch from CYC to MMF or *vice versa*. Those who developed resistance to CYC were switched to MMF. The CYC resistant patients showed better improvements while receiving treatments with MMF, and their renal functions were better (Dooley et al., 1999) . The data on MMF - resistant patients switched to CYC is still uncertain. Our study included patients who were treated with both CYC and MMF. The response rates were similar for both the induction treatment groups.

6. Conclusion

The lupus nephritis patients who were refractory to treatment were analysed in our study. From the current findings, we suggest that demographic and biochemical factors did not influence the response rate of the patients to the treatment. However, the presence of dsDNA, lower complement C4 levels, higher CRP, creatinine, and urine protein levels influenced the response rates of lupus nephritis patients, with a higher no - response rate. The activity and chronicity indices were also found to be significant.

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