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Original Article

Clinico-Demographic Findings and Histopathological Patterns of Lupus Nephritis

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ABSTRACT

Introduction: *Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease exhibiting diverse clinicopathological manifestations. Renal involvement [lupus nephritis (LN)] occurs in a maximum of these patients during the disease, accounting for significant morbidity and mortality. LN exhibits diverse clinical features with variable glomerular histopathological patterns. The class of LN discerned on renal biopsy evaluation highly correlates with prognosis and guides appropriate therapeutic management. Prompt institution of immunosuppressive therapy, as determined by the renal pathologic lesion, results in favorable outcomes with better renal survival rates.* ***Aim of the study:*** *The study aimed to correlate the clinico-demographic findings and laboratory parameters of lupus nephritis with the histopathological patterns.* ***Methods:*** *This was a cross-sectional observational study conducted among thirty patients with lupus nephritis, admitted into the department of Medicine, Rangpur Medical College and Hospital, from January 2014 to December 2015. The sample was collected by the purposive sampling technique. Diagnosis of SLE was done on the basis of the American College of Rheumatological Criteria (ACR). After written consent from the patients, all patients were undergone renal biopsy and tissue was analyzed for histopathological examination. Data were processed and analyzed with the help of the computer program SPSS and Microsoft excel. Quantitative data are expressed as mean and standard deviation and qualitative data as frequency and percentage. Comparisons were done by tabulation and graphical presentation*

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in the form of tables, pie charts, graphs, bar diagrams, histograms, charts, etc. ***Result:*** *Among the thirty patients found to have lupus nephritis, female 27(90%) were predominance and 17(56.66%) of the patients were of childbearing age between 21 and 40 years, the mean age of the study patient was 25.16 ± 8.35 (SD) years. The most frequent clinical features were arthritis (93.33%), fever (80%), oral ulceration (66.66%), edema (66.66%), and hypertension (46.66%). Renal impairment was present in 12(40%) patients. Anti-ds DNA was positive (86.66%) in patients and antinuclear antibody (ANA) was positive (96.66%), 27 patients (90.0%) had low complement (C3 and C4) levels. Among all patients, 7 (23.3%) had ≥3 gram/day proteinuria. The common histological type was found in class IV, which was 14(46.66%), Class III, 8(26.66%) patients, and Class V, 6(20%) patients.* ***Conclusion:*** *Lupus nephritis (LN) is one of the serious manifestations of systemic lupus erythematosus (SLE). Despite great improvement in the management of lupus nephritis, it remains the most frequent cause of SLE-related mortality. It has diversities of clinical and histological presentations.*

Keywords: *Lupus Nephritis, Systemic Lupus Erythematosus (SLE), Histopathological Patterns.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease with variable clinical manifestations. Lupus nephritis (LN) is one of the most common and serious manifestations of SLE. Lupus is defined by its clinical picture, together with antibodies directed against one or more nuclear components, particularly anti-double-stranded DNA (dsDNA). It is best regarded as a syndrome, in which a variety of immunologic events may lead to a similar final common pathway, and thus present a similar clinical picture. Today, lupus nephritis is responsible for growing percentages of cases with end-stage renal failure that need dialysis or renal transplantation[1]. Lupus nephritis has been extensively studied during the last 20 years and renal biopsy results were classified according to WHO and other institutes. The WHO classification system, consider six histopathological classes and their subtypes for renal involvement in SLE patients. Lupus nephritis can mimic almost any morphologic pattern of glomerulonephritis, and it is emphasized that the diagnosis of Systemic Lupus Erythematosus is not based on morphologic features. Systemic Lupus Erythematosus is usually diagnosed according to the widely accepted criteria of the American College of Rheumatology[2]. Lupus nephritis, one of the most serious manifestations of systemic lupus erythematosus (SLE), usually arises within 5 years of diagnosis; however, renal failure rarely occurs before the American College of Rheumatology criteria for classification are met. Lupus nephritis is histopathologically evident in most patients with SLE, even those without clinical manifestations of renal disease. The symptoms of lupus nephritis are generally related to hypertension, proteinuria, and renal failure[3]. In systemic lupus erythematosus (SLE), many genetic-susceptibility factors, environmental triggers, antigen-antibody (Ab) responses, B-cell and T-cell interactions, and immune clearance processes interact to generate and perpetuate autoimmunity. Studies of human leukocyte antigens (HLA) reveal that HLA-A1, B8, DR2, and DR3 are more common in persons with SLE than in the general population. The presence of the null complement alleles and congenital deficiencies of complement (especially C1q, C2, and C4) are also associated with an increased risk of SLE. A genetic predisposition is supported by the 40% concordance among monozygotic twins[4]. Autoimmunity plays a major role in the pathogenesis of lupus nephritis. The immunologic mechanisms include the

production of autoantibodies directed against nuclear elements. The characteristics of the nephritogenic autoantibodies associated with lupus nephritis are as follows: Antigen specificity directed against nucleosome or double-stranded DNA (dsDNA) - Some anti-dsDNA antibodies cross-react with the glomerular basement membrane, higher-affinity autoantibodies may form intravascular immune complexes, which are deposited in glomeruli, Cationic autoantibodies have a higher affinity for the anionic glomerular basement membrane, and Autoantibodies of certain isotypes (immunoglobulin IgG_1 and IgG_3) readily activate complement. These autoantibodies form pathogenic immune complexes intravascularly, which are deposited in glomeruli. Alternatively, autoantibodies may bind to antigens already located in the glomerular basement membrane, forming immune complexes in situ. Immune complexes promote an inflammatory response by activating complements and attracting inflammatory cells, including lymphocytes, macrophages, and neutrophils[5]. Assessment and management of patients with suspected lupus nephritis are greatly facilitated through information obtained by renal biopsy. The pathologic findings of lupus nephritis are extremely diverse and may occur in all four renal compartments: glomeruli, tubules, interstitium, and blood vessels. Lupus nephritis can display almost any glomerular abnormality and almost any combination of abnormalities. Since glomerular lesions depend, in turn, on the type and the site of deposition of the immune complex, it is hardly surprising that glomerular lesions are equally varied, encompassing the whole spectrum of histopathological changes. These patterns of injury can be divided into three groups e.g. Mesangial Pattern, Endothelial Pattern, and Epithelial Pattern. In the mesangial pattern, mesangial hypercellularity and matrix accumulation result from mesangial immune complex accumulation, as can occur in mesangial proliferative lupus nephritis. The clinical diagnosis of the disease depends on a careful and very thorough assessment of the presenting clinical features, examination of all the organ systems, and selected investigations. On renal biopsy, the most frequent finding is class IV lupus nephritis, followed by class V, class III, and class II respectively[6]. The prevalence of male lupus is more common in classes IV and V than in other classes. Lupus nephritis classes I and II may occur in the absence of clinical abnormality. Class V is characterized by nephrotic syndrome which often is persistent, but renal function impairment develops slowly and is rarely severe[7]. Haematuria, massive proteinuria, low albumin, low complement, and renal insufficiency are more marked in proliferative lupus nephritis than other histopathological classes[8]. Considering the above-mentioned facts and the fact that there was no exact data about this disorder and its subtypes in our geographical region, we decided to evaluate the clinical, biochemical, and histopathological findings among patients with lupus nephritis and to determine the association between histopathological classes of lupus nephritis with clinical and biochemical findings.

OBJECTIVE

- To correlate the clinico-demographic findings and laboratory parameters of lupus nephritis with the histopathological patterns.

METHODS

This was a cross-sectional observational study conducted among thirty patients with lupus nephritis, admitted into the department of Medicine, Rangpur Medical College and Hospital, from January 2014 to December 2015. Thirty (30) patients with lupus nephritis fulfilling the inclusion and exclusion criteria were included finally in the study. Detailed history, physical examination, and essential investigations

were done on every patient. Renal biopsy was done on every patient at the Department of Nephrology of Rangpur Medical College and Hospital. The patients were followed-up daily during the first 24 hours with special attention to vital parameters. All the patients received the standard medical management of SLE and lupus nephritis. All the information was recorded in a structured questionnaire. Data were checked and rechecked for omissions, inconsistencies, and improbabilities. Data analysis was performed by Statistical Package for Social Science (SPSS), version-22. Data were edited, coded, and entered into the computer. Statistical analyses were done and the level of significance was measured by using appropriate hypothetical testing. The level of significance (p-value) is set at 0.05 and the confidence interval at 95%. Results were presented as text, tables, and diagrams.

RESULTS

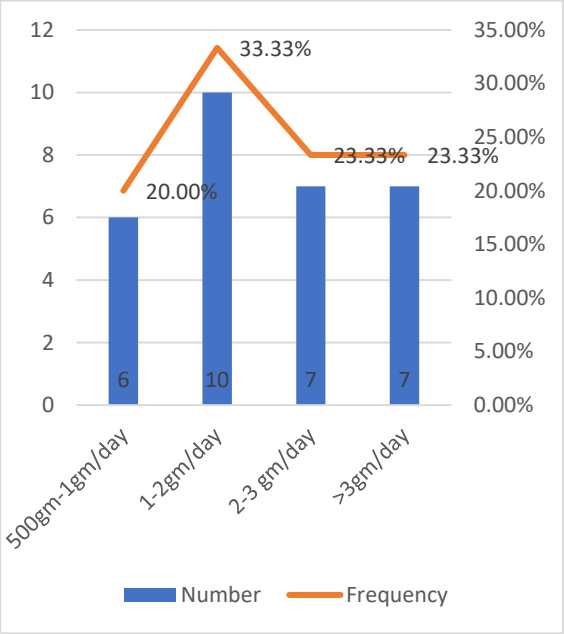

Figure 1: Distribution of total urinary protein (UTP) grading of the respondents (n = 30)

A total of 30 patients fulfilling inclusion/exclusion criteria were studied. Results and observations are given below.

Table 1: Age and sex distribution of the respondents (n=30)

Age (years)	Male	Female	Total
11 – 20	0	9 (33.3)	9
21 – 30	2 (66.6)	11 (40.7)	13
31-40	1 (33.3)	6 (22.2)	7
41-50	0	1 (3.70)	1
Total	3	27	30
Mean ± SD	28.83± 5.77	25.12± 8.47	25.16± 8.35

Table 1 shows the mean age of the study patient was 25.16 ± 8.35 (SD) years. Maximum patients (33.3%) were age group 11 to 20 years. Total females were 27(90%) and males were 3(10%

Figure 1 shows the distribution of 24-hour UTP loss. Regarding 24 h UTP loss 1-2 g/day protein loss was found in 10(33.4%) patients,2-3 gm/day protein loss was found in 7(23.3%) patients and >3g/day protein loss was found in 7(23.3%) patients.

Table 2: Evaluation of clinical presentations (n = 30)

Clinical presentation	Number of Patients	Percentage
Arthritis	28	93.33
Fever	24	80.0
Malar rash	7	23.33
Discoid rash	4	13.3
Photosensitivity	10	33.33
Oral ulceration	20	66.66

Pleuritis/ Pleural effusion	4	13.33
Pericarditis/ pericardial effusion	6	20.0
Neurologic disorder	2	6.66
Edema	20	66.66
Hypertension	14	46.66
Gross hematuria	5	16.66

Table 2 shows the clinical features of the study subjects. The most frequent clinical features were arthritis (93.33%), fever (80%), oral ulceration (66.66%), edema (66.66%), and hypertension (46.66%). The others clinical manifestations were photosensitivity (33.33%), pericarditis/pericardial effusion (20%), malar rash (23.33%), gross haematuria (16.66%), neurologic disorder (6.66%), discoid rash (13.3%),

pleuritis/pleural effusion (13.33%).

Table 3: Laboratory profile of respondents (n = 30)

Name of test	Number of Patients	Percentage
Hematological		
Anemia	21	70
Leucopenia	2	6.66
Thrombocytopenia	3	10
Raised CRP (>6)	2	6.7
Raised ESR (>60)	26	86.66
Renal		
Cellular cast	12	40
Microscopic hematuria	18	60
Nephrotic syndrome	7	23.33
Mild renal impairment (GFR <90-60 ml/min)	8	26.66
Moderate to Severe renal impairment (GFR <60 ml/min)	4	13.33
Immunological		
ANA (positive)	29	96.66
Anti-ds DNA (Positive)	26	86.66
Low Complement (C_3, C_4)	27	90

Table 3 shows the laboratory findings of the study patients. At the time of renal biopsy 21 patients (70%) were anemic, 18 patients (60%) had microscopic hematuria and Proteinuria >0.5 gm/ 24 hours was noticed in all patients. Among them, 7 patients (23.33%) had a nephrotic range of proteinuria. Renal function was impaired in 12(40%) patients, mild renal failure (GFR <90 ml/min) in 8(26.6%) patients, moderate to severe renal impairment (GFR <60 ml/mi) 4(13.3%) patients. The other abnormalities were leucopenia 6.66%, thrombocytopenia 10%, cellular (RBC) cast in urine 40.0%, and raised ESR (>60 mm at the end of the first hour) 86.66% of patients. On serological test 29(96.66%) patients had a positive ANA, 26 patients (86.66%) had a positive anti-ds DNA and 27 patients (90.0%) had low complement (C_3 and C_4) levels.

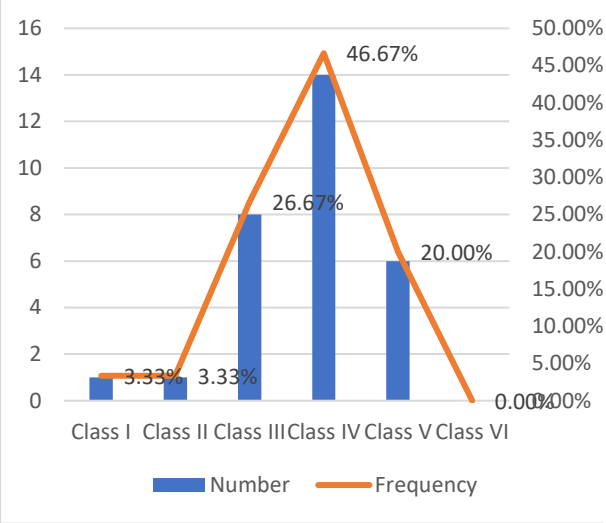

Figure 2: Histological classifications of lupus nephritis (n=30)

Histological classification of LN revealed that Class I, 1(3.3%); patient Class II, 1(3.33%) patients; Class III, 8(26.66%) patients; Class IV, 14(46.66%) patients, Class V, 6(20%) patients; Class VI, 0(0.0%) patients (Figure 2).

Table 4: Renal function values in the classification of lupus nephritis (n=30)

Renal function value	Histological classification of lupus nephritis			p Value
	Class III (n=8)	Class IV (n=14)	Class V (n=6)	
S.creatinine (mg/dl)	1.13±0.63	1.07±0.50	1.27±0.57	p >0.05
S.Creatinine (>1.5 mg/dl) N (%)	1(12.5)	3(21.42)	3(50)	p = 0.251
Cellular cast N (%)	4(50)	7(50.0)	00	p = 0.084
Microscopic Haematuria N (%)	5(62.5)	10(71.42)	3(50)	p = 0.652
Nephrotic syndrome N (%)	00	2(14.28)	5(83.33)	p = 0.001
Moderate to Severe renal impairment (GFR<60ml/min) N(%)	0 (0.00)	5(35.71)	2(33.33)	p = 0.002
24 h proteinuria (gm/day)	1.82±0.61	1.76±0.78	3.23±0.96	p = 0.002

Table 4 shows laboratory parameters of patients with different classes of lupus nephritis at the time of renal biopsy. Compared to patients with III, IV, and V lupus nephritis, Class IV and Class V lupus nephritis had greater serum creatinine, nephrotic syndrome, and proteinuria. Microscopic haematuria and cellular cast more in Class III and IV.

DISCUSSION

For the purposes of this study, lupus Nephritis refers to the patient of SLE fulfilling ≥ 4 ARA criteria and having one or more of the following criteria: UTP > 0.5 gm / 24 hour/1.73m^2 body surface area. Urinary active sediment- R.B.C and/or R.B.C cast. Our first analysis involved finding out the clinical and laboratory profile of lupus nephritis patients. The second analysis was to clarify the relationship of clinical and laboratory findings with renal biopsy findings. These issues may be particularly relevant for observational studies that use particular clinical manifestations, histopathological findings, and relevant pathological findings, in which sources of bias may be sufficiently large to either obscure a real difference in rates or create an apparent one. Using the results and previous studies as examples, these issues were addressed in

turn. In our study age the study, the patient was 25.16 ± 8.35 (SD) years. Maximum patients (33.3%) were age group 11 to 20 years. Total females were 27(90%) and males were 3(10%). The findings are consistent with another study at home and abroad. A study in a tertiary center of Bangladesh, by Huq MZ[9,] reported that the mean age was 28.2 ± 7.2 years. Another study at BSMMU in 2006 showed the mean age of Lupus Nephritis patients of 25.5±8.8 years[10]. Similar studies were carried out in Singapore[11] and China[12] showing the mean age of the patient 35.4± 8.2 years and 33±14 years respectively. However, the mean age of the patient in our country corroborates the mean age of the patients in Iran but differs from the mean age of the patient with Lupus Nephritis in China and Singapore. This supports the fact that our patients with Lupus Nephritis were a decade younger than their Chinese counterparts indicating an earlier age of disease onset, more severe form of the disease, or earlier mortality. The present study shows that the most common clinical presentations were arthritis (93.33%), fever (80%), oral ulceration (66.66%), edema (66.66%), and hypertension (46.66%). A clinicopathological study on Lupus Nephritis by Huq MZ[9] demonstrated that common clinical presentations were edema and malar rash (73.3% and 70.0% respectively). Another study on Lupus Nephritis by Ali et al in 2008 found edema as the most common presenting feature at the time of diagnosis. They found that about 90% of patients present with oedema[13]. Nezhad ST, 2008 showed common clinical features are arthralgia (61.8%) and edema (61.1%)[14]. This establishes the fact that clinical manifestations vary according to the geographic location of the patients with Lupus Nephritis. In the present study histopathologically, Class I, 1(3.3%); patient Class II, 1(3.33%) patients; Class III, 8(26.66%) patients; Class IV, 14(46.66%) patients, Class V, 6(20%) patients; Class VI, 0(0.0%) patients. Huq MZ[9] demonstrated that the most common histopathological class was class IV. A total of 31 cases (51.7%) cases belonged to this class. The next common classes were class III (20.0%) and class V (18.3%) respectively. Halland A M. et al[15] 1991 in their study found class IV: 62.7%, class III: 25.4% class II: 11.7%, and Class V: 7.8%. Parichatikanond P et al[16], 1986, in their study found class IV 58.6%, class II: 17.9%, Class V: 12.9%, Class III: 9.9%. Similar frequencies of WHO classification were found by Khoo J J et al[17], in their studies showing 60%, and 65.7% of their cases belonged to WHO class IV respectively. Another study by Hiramatsu et al found the relative frequency of each class was: Class I- 0%, Class II-13%, Class III-17%, Class IV-60%, and Class V-10%[18]. Finally considering the findings of this study, it is evident that some of the clinical and biochemical parameters were associated with histopathological classes of lupus nephritis and these parameters could be used to identify patients with proliferative lupus nephritis in resource-limited centers where the performance of a biopsy is not possible or where renal biopsy is contraindicated. In this study, from observation of clinical and laboratory findings of different histopathological classes of lupus nephritis, it was evident that class I and II patient had minimal clinical and renal findings, proteinuria was in the non-nephrotic range and renal function was almost normal.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

The histological features of lupus nephritis are diverse. In this study class IV has the highest prevalence followed by Class III and V in descending order. It is not possible to predict the histopathological subtype on the basis of clinical features, the degree of urinary abnormalities, the presence or

absence of hypertension, and renal failure. But, this study showed some meaningful relationship between raised serum creatinine and nephritic syndrome and increased 24 hours urinary protein excretion with a worse class of lupus nephritis. As the treatment differs between each class, it is important to accurately establish the class with renal biopsy to make appropriate therapeutic decisions. Renal biopsy is still beneficial for better evaluation of renal status and determination of lupus nephritis class. So it can be said that lupus nephritis has varied clinical features with different histological types.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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