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Pathological, demographic and laboratory characteristics of lupus nephritis patients in 2017-2019; an experience of a referral laboratory in Northeastern Iran

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ABSTRACT

Introduction: The chronic autoimmune disease systemic lupus erythematosus (SLE) causes inflammation in various body organs, including the skin, joints, kidneys, brain, heart, and lungs.

Objectives: This study aimed to evaluate the correlation between histopathological findings and the demographic and laboratory data of patients with lupus nephritis.

Patients and Methods: This descriptive-analytical study was conducted over a 2-year period starting in 2017 at the Northeast Iran in a referral laboratory located in Mashhad, Iran. Patients with a definitive diagnosis of lupus nephritis were retrospectively selected and classified according to the 2003 ISN/RPS classification system. Demographic and laboratory data were obtained from patients' documents, para-clinical findings in their files, and through phone interviews.

Results: Seventy-one cases with a definitive pathological diagnosis of lupus nephritis were included. The most common class of lupus nephritis was class IV (diffuse type), followed by class III (focal type) (43.7% and 21.1%, respectively). The incidence of malar rash was reported in 100% of class II, 73.3% of class III, 51.6% of class IV, and 64.3% of class V patients (p=0.05). Additionally, the incidence of hypocomplementemia was reported in 22.2% of class II, 40% of class III, 69% of class IV, and 50% of class V patients (*P*=0.05). The presence of anti-beta-2 glycoprotein I antibody was reported in 21.4% of cases with class V lupus nephritis too.

Conclusion: The most common classes of lupus nephritis were class IV and class III. Among the demographic, laboratory, and clinical characteristics, lupus nephritis was significantly associated with malar rash and hypocomplementemia.

Implication for health policy/practice/research/medical education:
This study evaluated the relationship between pathology findings and demographic/laboratory data of lupus nephritis patients. Conducted over two years in Northeast Iran, it included 71 patients. The most common types were class IV (43.7%) and class III (21.1%). Significant associations were found between lupus nephritis and factors like malar rash, hypocomplementemia, and anti-beta-2 glycoprotein I antibody. The findings highlight the prevalence of class IV and III lupus nephritis and their clinical correlations.

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Original

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition marked by the accumulation of immune complexes and the activation of complement, which results in inflammation and harm to various organs in the body (1). Clinical and serological manifestations vary widely among different patients and even during the course of a single patient's disease. The disease course in many patients is unpredictable making the management of the disease complex (2). Mucosal and skin, musculoskeletal, and kidney involvement are frequently observed in patients with SLE. Additionally, cases often show a certain level of kidney involvement throughout the progression of the disease. Kidney involvement has been observed in up to 70% of patients, with a clinical diagnosis termed lupus nephritis (3,4). Lupus nephritis is detected by the accumulation of immune complexes in the glomeruli, leading to inflammation in the kidneys (5). The gold standard for diagnosing and classifying lupus nephritis is a kidney biopsy (6). Patients with lupus nephritis are diagnosed by the existence of augmented levels of several autoantibodies, including those against double-stranded DNA, complement C1q (anti-C1q), and C3b (anti-C3b IgG), which can eventually lead to kidney failure (7). Patients can be categorized into one of six histological categories based on the World Health Organization (WHO) classification system. In this system, classes III-VI lupus nephritis are associated with the highest risk of kidney damage (5,8,9) with class VI lupus nephritis being the most advanced stage, often requiring dialysis or kidney transplantation (9). The use of biomarkers to detect patient subgroups permits for observing therapy response and detecting disease activity. Proteinuria, hematuria, creatinine clearance, urinary protein-to-creatinine ratio, and serum creatinine levels are some biomarkers for assessing lupus nephritis. A rise in anti-dsDNA serum levels and a reduction in complement serum levels are related to disease activity and increase the risk of lupus nephritis. However, these biomarkers lack the specificity and sensitivity needed to detect kidney activity and damage accurately (10).

Numerous studies showed that, lupus nephritis is a global health concern, affecting individuals worldwide. Understanding its epidemiology, risk factors, and optimal treatment strategies is crucial for public health efforts. The disease is of significant importance due to several reasons. Lupus nephritis can severely impact the quality of life and clinical symptoms such as edema, hypertension, and kidney dysfunction negatively affect quality of life. Moreover, lupus nephritis may lead to progressive kidney damage, resulting in chronic kidney disease and end-stage renal disease. On the other hand, treatment of lupus nephritis often involves immunosuppressive medications, which have side effects and managing the disease requires a careful balance between controlling inflammation and avoiding complications from treatment. Given its impact on both individual health and the broader healthcare system, lupus nephritis warrants attention from healthcare professionals and researchers to improve diagnosis, treatment, and overall outcomes for affected individuals (10).

Objectives

Given the importance of early recognition of lupus nephritis to inhibit irreversible kidney damage, the present study aimed to evaluate the connection between the severity of lupus nephritis and the demographic and laboratory findings of SLE patients.

Patients and Methods

Study design

The present cross-sectional study took place in a referral pathology laboratory in Northeast Iran. All renal biopsy slides of outpatient of lupus patients from the clinic and offices of nephrologists or rheumatologists, as well as kidney biopsies of patients from Ghaem hospital were referred to this laboratory. Every patient who had a laboratory test and a definitive diagnosis of lupus nephritis by renal biopsy was enrolled in this study (2016 to 2018). The renal biopsies had at least 10 glomeruli evaluated for lupus nephritis by an expert pathologist using a NIKON E200 microscope. Lupus nephritis was classified based on the 2003 ISN/RPS classification (7). The clinical and demographic data of each patient were extracted from the documents and files of the patients after obtaining informed consent. Para-clinical findings were completed by telephone or online. Patients with incomplete laboratory examinations, failure to complete the patient's tests at the time of renal biopsy, inadequate cooperation in providing history and performing laboratory tests, and those with an association of lupus with other immune diseases were excluded from the study. In our study, a body mass index (BMI) of <18.5 kg/m^2, 18.5-24.9 kg/m^2, and ≥30 kg/m^2 were considered as underweight, normal, and overweight, respectively. Regarding the SLE disease activity index (SLEDAI) classification, mild, moderate, and high SLEDAI were considered as <4, 4-10, and >10, respectively (11).

Statistical analysis

Study data were entered into SPSS version 22 software. Comparisons between different classes of lupus nephritis in the pathology reports were performed using chi-square or Fisher's exact tests. For comparing continuous quantitative data, the ANOVA test (or Kruskal-Wallis test if there was no normal distribution) was conducted which was followed by post hoc analysis to identify specific group differences. A P value < 0.05 was determined statistically significant.

Results

Among 71 patients with a definitive diagnosis of lupus nephritis, the mean age was 36.8 ± 11.6 years, since most

of the patients were female (81.7%, 58 patients). The mean SLEDAI score was 28.4 ± 8.8, indicating that all of the patients had high SLEDAI. Table 1 summarizes the demographic data of the study population. The mean time period from the development of SLE symptoms to lupus nephritis was 6.41 ± 6.12 years. The most common clinical manifestation of our patients was arthralgia (57 patients, 80.3%; Table 2). The mean urine protein was 3091 ± 2127 mg/24 h, since 51 patients had hematuria (72.9%). The mean levels of C3 and C4 were 98.07 ± 49.96 and 17.96 ± 20.79 mg/dL, respectively. The mean creatinine level was 1.12 ± 0.59 mg/dL (Table 3). We found class IV lupus nephritis was the most common type (43.7%; Figure 1).

The mean ± standard deviation of glomerular filtration rate (GFR) among patients with class II, III, IV, and V lupus nephritis were 96.1 ± 29.1 mL/min/1.73m^2, 102.6 ± 27.6 mL/min/1.73 m^2, 73.9 ± 32.6 mL/min/1.73m^2, and 82.9 ± 28.2 mL/min/1.73 m^2, respectively (P = 0.02). Meanwhile, post hoc analysis showed a significant difference in GFR between class IV and III lupus nephritis. Table 4 demonstrates the comparison of study variables among different classes of lupus nephritis. More than half of the patients in each class of lupus nephritis had malar rash. Additionally, hypocomplementemia was present in 22% of class II patients, 40% of class III patients, 69% of class IV patients, and 50% of class V patients (P = 0.29). While none of the patients with lupus nephritis had end-stage renal disease (GFR <15 mL/min/1.73m^2), abnormal GFR (GFR <60 mL/min/1.73 m^2) were reported in all classes (P = 0.38). Serum beta-2 glycoprotein 1 (B2GPI) IgG antibody was reported in 21.4% of patients with class V lupus nephritis while, it was negative in other classes of lupus nephritis.

Table 1. Demographic data of the lupus nephritis patients

Variable	Mean ± SD	Frequency	Percent
Age	36.8 ± 11.6		
Gender			
Female	-	58	81.7
Male	-	13	18.3
BMI (kg/m^2)	24.56 ± 5.03	-	-
Underweight	-	8	11.3
Normal	-	26	36.6
Overweight	-	10	14.41
Obese	-	27	38
SLEDAI	28.49 ± 8.85	-	-
High SLEDAI	-	71	100

SD, Standard deviation; BMI, Body mass index; SLEDAI, SLE disease activity index.

Table 2. The frequency of clinical manifestations in lupus patients

Variable	Frequency	Percent
Arthralgia	57	80.3
Seizure	5	7
Stroke	3	4.2
Myositis	46	64.8
Malar rash	47	66.2
Psychosis	6	8.5
Visual disorders	15	21.1
Arthritis	51	71.8
Mouth ulcers	28	39.4
Hair loss	49	69
Vasculitis	28	39.4
Pleural effusion	16	22.5
Pericardial effusion	9	12.7

Discussion

This study revealed that a significant proportion of the participants were diagnosed with type IV lupus nephritis, followed by type III. The results comparing different variables among patients categorized into various

Table 3. Laboratory findings of lupus nephritis patients

Variant	Frequency	Percent
No proteinuria (<150 mg/d)	2	2.9
Sub-nephrotic proteinuria (<3000 mg/d)	39	55.7
Nephrotic proteinuria (>3000 mg/d)	29	41.4
Hematuria	51	72.9
Positive ANA	61	89.7
Positive anti-dsDNA	43	63.2
Negative anti-dsDNA	9	13.2
Hypocomplementemia	30	42.3
Positive CRP	21	29.6
Elevated ESR	53	74.7
Stage 1 CKD with normal or high GFR	28	39.4
Stage 2 CKD	28	39.4
Stage 3A CKD	8	11.3
Stage 3B CKD	4	5.6
Stage 4 CKD	3	4.2
Stage 5 end stage CKD	0	0
Leukopenia	4	5.6
Lymphocytopenia	27	38
Thrombocytopenia	2	2.8
IgM cardiolipin antibody	5	7.6
IgG cardiolipin antibody	3	4.2
Anti-beta 2-glycoprotein I antibody (IgM)	9	12.7
Anti-beta 2-glycoprotein I antibody (IgG)	2	2.8
Lupus anticoagulant	9	12.7
Granular casts	16	23.5
Anti-U1-RNP	2	2.9
Anti-Smith antibody	5	7.4
Anti-Ro (SS-A) antibody	8	11.8
Anti-La (SSB) antibody	3	4.4

ANA: Antinuclear antibody; anti-dsDNA: anti-double stranded DNA antibody; CRP: Positive C-reactive protein; ESR: Elevated erythrocyte sedimentation rate; CKD: chronic kidney disease; GFR: glomerular filtration rate; SS-A: Sjögren's syndrome antigen A; SSB: Sjögren's syndrome antigen B.

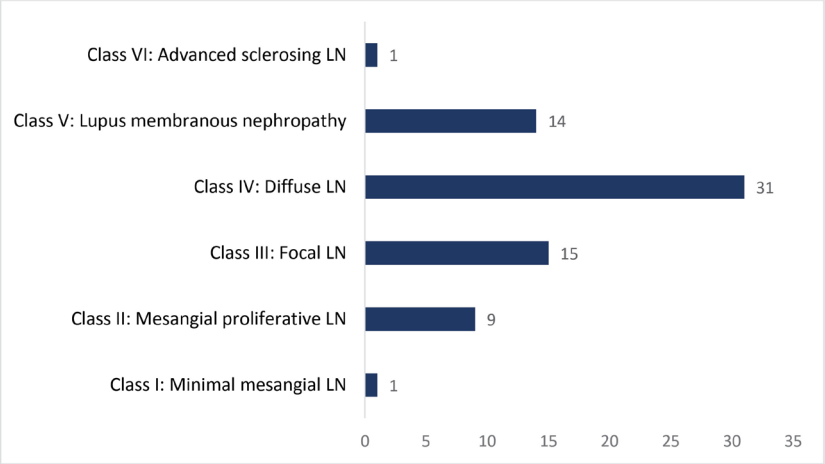

Figure 1. Lupus nephritis (LN) class among study population.

classes of lupus nephritis demonstrated a noteworthy or marginally significant association with malar rash, hypocomplementemia, and B2GPI IgG antibody across different classes of lupus nephritis. Hypocomplementemia was often reported in class IV, V, III, and II patients, while the B2GPI IgG antibody was reported only in class V patients.

The most common class of lupus nephritis was class IV, followed by class III. The study by Ahn et al, evaluating lupus nephritis in 171 patients, reported that the prevalence of mixed lupus nephritis (class III and IV) and pure (class III or IV) was 17.5% and 82.5%, respectively (12). Likewise, Shabaka et al evaluated the Spanish glomerulonephritis registry (28,791 biopsies) and reported that class IV (52%) was the most common type, followed by class III (19%) as the most common types (13). Previously, Song et al, evaluated 710 patients with lupus nephritis, reported that the most common type of lupus nephritis was class IV (14). Similarly, the study by Farah et al, evaluating 79 patients with lupus nephritis in Jordan showed that class IV is the most common pathological class of lupus nephritis (46.8%), followed by class V (19%) (15). Other studies also reported class IV as the most common class of lupus nephritis (16-18).

The results regarding the comparison of different variables among patients with different classes of lupus nephritis showed, a significant difference only between malar rash, hypocomplementemia, and IgG beta 2 glycoprotein I across different classes of lupus nephritis. In the present study, the presence of hypocomplementemia was significantly related to class IV and the severity of lupus nephritis. Moreover, among the classes of nephritis, class IV nephritis is of particular importance while it can progress to glomerulosclerosis and kidney failure if left untreated. Since the most common type of nephritis observed in our study was class IV nephritis, it can be concluded that in the presence of active disease, proteinuria, and hematuria, the probability of class IV nephritis is higher. Additionally, in our study, the serum levels of IgG beta 2 glycoprotein I was seen only in class V patients, indicating a higher probability of thrombosis in this class of nephritis.

In line with the results of the present study, the study by Song et al (14), also reported the lowest level of complement in class IV lupus nephritis patients. Their study showed a higher activity level of SLE in patients with class IV lupus nephritis. However, our study showed no significant difference in the level of disease activity (anti-dsDNA) in different classes of lupus nephritis. Nonetheless, classes IV and V had the highest percentage of positive tests. Furthermore, the results of the study by Song et al, showed that among patients with proliferative nephritis, the age at diagnosis of SLE is lower, and the frequency of proteinuria and urinary red blood cells is higher (14). In our study, the age of onset of lupus nephritis in class IV was lower than in other groups, however no significant difference compared to other classes was detected. Likewise the study by Farah et al, focusing on the clinical and laboratory profiles of 79 Jordanian patients with lupus nephritis, revealed a strong association between class IV lupus nephritis and kidney failure (15). This study confirmed, no significant correlation between lupus nephritis class and abnormal GFR measurements. Farah et al, also found that anti-double stranded DNA (anti-dsDNA) antibodies were significantly more frequent in class IV lupus nephritis patients, which contrasted with the findings of our study.

In our study, the majority of cases with different classes of lupus nephritis presented with a malar rash. The study by Mavaraghani et al demonstrated that patients with class II nephritis had a lower rate of malar rash compared to those with class III, IV, and V lupus nephritis, indicating an increase in the frequency of this clinical symptom during the course of lupus nephritis (19). Similar to the present study, Moe et al also showed that age, time interval between lupus diagnosis and lupus nephritis diagnosis, gender, oral ulcers, central nervous system, and SLICC/

Table 4. Comparison of study variables among patients with different classes of lupus nephritis

Variable	Class II	Class III	Class IV	Class V	*P* value
Mean age (y)	41.2 ± 9.9	38.2 ± 12.6	33.7 ± 6.7	39.7 ± 14.9	0.21[a]
Gender					
Female	7 (77.8)	10 (66.7)	28 (90.3)	11 (78.6)	0.27[b]
Male	2 (22.2)	5 (33.3)	3 (9.7)	3 (21.4)	
BMI (kg/m^2)					
Underweight	1 (11.1)	1 (6.7)	5 (16.1)	1 (7.1)	0.06[b]
Normal	3 (33.3)	4 (26.7)	17 (54.8)	4 (28.6)	
Overweight	3 (33.3)	3 (20)	3 (9.7)	0	
Obese	2 (22.2)	7 (46.7)	6 (19.4)	9 (64.3)	
Median time to develop nephritis (years)	6 (3-11.5)	4 (2-19)	3 (2-7)	5 (2-10)	0.39[c]
Clinical manifestations					
Seizure	0	1 (6.7)	3 (9.7)	1 (7.1)	0.80[b]
Stroke	0	0	2 (6.5)	1 (7.1)	0.64[b]
Myositis	7 (77.8)	9 (60)	20 (64.5)	10 (71.4)	0.79[b]
Malar rash	9 (100)	11 (73.3)	16 (51.6)	9 (64.3)	0.051[d]
Psychosis	0	2 (13.3)	3 (9.7)	1 (7.1)	0.71[b]
Visual disorders	2 (22.2)	4 (26.7)	5 (16.1)	4 (28.6)	0.76[b]
Arthritis	5 (55.6)	12 (80)	22 (71)	12 (85.7)	0.39[b]
Mouth ulcers	3 (33.3)	8 (53.3)	12 (38.7)	5 (35.7)	0.70[d]
Hair loss	4 (44.4)	12 (80)	22 (71)	11 (78.6)	0.25[b]
Vasculitis	5 (55.6)	8 (53.3)	10 (32.3)	4 (28.6)	0.31[b]
Pleural effusion	1 (11.1)	4 (26.7)	9 (29)	2 (14.3)	0.56[b]
Pericardial effusion	0	3 (20)	6 (19.4)	0	0.83[b]
Arthralgia	7 (77.8)	12 (80)	26 (83.9)	12 (85.7)	0.95[b]
Laboratory findings					
Hematuria	5 (55.6)	8 (57.1)	26 (83.9)	10 (71.4)	0.17[b]
No proteinuria (<150 mg/dL)	0	1 (6.7)	1 (3.2)	0	0.40[b]
Sub-nephrotic proteinuria (<3000 mg/dL)	4 (44.4)	11 (73.3)	14 (45.2)	9 (64.3)	
Nephrotic proteinuria (≥3000 mg/dL)	5 (55.6)	3 (20)	16 (51.6)	5 (35.7)	
ANA	8 (88.9)	12 (80)	30 (96.8)	12 (85.7)	0.32[b]
Positive anti dsDNA	V (77.8)	11 (73.3)	27 (93.1)	14 (100)	0.065[b]
Negative anti dsDNA	2 (22.2)	4 (26.7)	2 (6.9)	0 (0)	
Hypocomplementemia	2 (22.2)	6 (40)	20 (69)	7 (50)	0.29[d]
Positive CRP	2 (25)	4 (26.7)	4 (42.9)	5 (38.5)	0.66[d]
Elevated ESR	7 (87.5)	12 (80)	26 (86.7)	10 (71.4)	0.63[b]
Abnormal GFR (< 90 mL/min)	4 (44.4)	7 (46.7)	20 (64.5)	10 (71.4)	0.38[d]
Leukopenia	2 (22.2)	1 (6.7)	3 (9.7)	3 (21.4)	0.49[b]
Lymphocytopenia	4 (44.4)	8 (53.3)	17 (54.8)	4 (28.6)	0.40[b]
Thrombocytopenia	1 (11.1)	0	1 (3.2)	0	0.38[b]
Anti-cardiolipin IgM	1 (11.1)	1 (7.7)	1 (3.4)	2 (14.3)	0.62[b]
Anti-cardiolipin IgG	0	1 (8.3)	3 (10.3)	0	0.50[b]
B2GPI (IgM)	2 (22.2)	4 (30.8)	3 (10.3)	2 (14.3)	0.40[b]
B2GPI (IgG)	0	0	0	3 (21.4)	0.009[b]
Lupus anticoagulant	1 (11.1)	1 (7.1)	2 (6.9)	1 (7.1)	0.83[b]
Granule cast	1 (11.1)	4 (28.6)	7 (23.3)	3 (23.1)	0.80[b]
Anti-U1-RNP	0	1 (6.7)	5 (16.7)	2 (16.7)	0.48[b]
Anti-Smith antibody	2 (22.2)	9 (60)	8 (26.7)	5 (41.7)	0.12[d]
Anti-Ro antibody	2 (22.2)	9 (60)	14 (46.7)	6 (50)	0.35[d]
Anti-La antibody	3 (33.3)	2 (13.3)	7 (23.3)	2 (16.7)	0.66[b]

Note: BMI: Body mass index (≤18.5 kg/m^2: underweight; 18-25 kg/m^2: Normal; 25-30: Overweight; >30 kg/m^2: Obese), GFR: Glomerular filtration rate. [a]ANOVA; [b] Fisher's test; [c] Kruskal-Wallis test; [d] Chi-Square test.

ACR (Systemic Lupus International Collaborating Clinics/ American College of Rheumatology) damage index were similar across different classes of lupus nephritis. Additionally, in line with the results of their study, the frequency of hypocomplementemia in class IV was higher than in other classes of lupus nephritis (20).

Conclusion

The most common classes of lupus nephritis observed were class IV, followed by class III. Lupus nephritis showed a significant correlation with malar rash and IgG beta 2 glycoprotein I among the demographic, laboratory, and clinical characteristics. No significant differences were found between the different classes of lupus nephritis in terms of other clinical factors and laboratory symptoms such as age, gender, body mass index, SLEDAI index, average duration of disease, hematuria, proteinuria, ANA positivity, anti-dsDNA serum level, positive CRP, elevated ESR, abnormal GFR, leukopenia, lymphocytopenia, thrombocytopenia, hypocomplementemia, anticardiolipin antibody, IgM beta 2 glycoprotein I, lupus anticoagulant, granular casts, anti-U1-RNP, anti-Smith antibody, anti-Ro antibody and anti-La antibody.

Limitations of the study

This study was conducted in a referral center. However, there are several limitations. One limitation is the lack of access to all clinical details due to the retrospective nature of the study. Additionally, the study included only one case of class I and VI lupus nephritis, making it impossible to compare the characteristics of these patients with those of other classes. Further prospective studies are warranted to overcome these limitations.

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Authors' contribution

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Validation: Forouzan Amerizadeh.
Visualization: Mohsen Taghiabadi.
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Writing – review & editing: Forouzan Amerizadeh

Study Highlights

What is the current knowledge?

- Lupus nephritis is a significant manifestation of SLE.
- Class IV lupus nephritis is commonly observed and associated with severe kidney damage.
- Hypocomplementemia and B2GPI IgG antibodies are potential markers for lupus nephritis severity.

What is new here?

- This study confirms class IV as the most common and severe type in an Iranian cohort.
- Significant correlation found between lupus nephritis severity and presence of malar rash, hypocomplementemia.
- B2GPI IgG antibodies are exclusively present in class V lupus nephritis, indicating higher thrombosis risk.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethical code#IR.MUMS.MEDICAL.REC.1399.569). This research was conducted as part of a thesis for the internal medicine specialization program of Mohsen Taghiabadi (Thesis #990756). Prior to any intervention, all participants provided written informed consent. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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