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Comparison of lupus nephritis and non-lupus nephritides in patients with systemic lupus erythematosus

Sistemik lupus eritematozuslu hastalarda lupus nefriti ve lupus dışı nefritlerin karşılaştırılması

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Abstract

Objective: Kidney biopsy may unusually show non-lupus nephritis (LN) causes in patients with systemic lupus erythematosus (SLE). This study aimed to reveal the causes of non-LN and to compare the clinical and laboratory features of LN and non-lupus renal disease in patients with SLE.

Methods: Patients with SLE followed between 2014 and 2020 at Hacettepe University Hospitals and who had kidney biopsy were the subject of the study. One hundred thirty four patients' kidney biopsies were evaluated retrospectively and grouped as LN and non-LN. Clinical characteristics, laboratory values at the time of kidney biopsy, and renal outcome were recorded.

Results: Of 134 (107 females, 27 males) patients, 116 (86.6%) were in the LN group, and 18 (13.4%) were in the non-LN group. The most common diagnosis was focal segmental glomerulosclerosis (n=6) in the non-LN group. The median (interquartile range) biopsy age of LN patients was young [21 (17.7) vs. 36.5 (17), p<0.001], and high titer antinuclear antibody positivity over 1/320 at SLE diagnosis was more frequent in this group (50.9% vs 22.2%, p=0.02). Non-renal SLE involvement was similar in both groups. Anti-dsDNA positivity, low C3-4, and presence of active urinary sediment were significantly higher in LN patients, while serum creatinine, albumin, and proteinuria were not different between the groups at the time of kidney biopsy. Additionally, median renal SLEDAI was more elevated in LN patients.

Conclusion: Anti-dsDNA positivity, low C3-C4, active urinary sediment, and high renal SLEDAI scores may give us some clues regarding renal disease in patients with SLE. However, it should be kept in mind that these serological abnormalities may also occur in non-lupus renal disease.

Keywords: Systemic lupus erythematosus, renal biopsy, non-lupus nephritides, lupus nephritis

Öz

Amaç: Böbrek biyopsisi, nadiren de olsa sistemik lupus eritematozus (SLE) hastalarında lupus nefrit (LN) dışı nedenleri gösterebilir. Bu çalışmada, SLE hastalarında lupus dışı nefrit nedenlerinin ortaya çıkarılması ve LN ile LN dışı renal hastalığın klinik ve laboratuvar özelliklerinin karşılaştırılması amaçlandı.

Yöntem: 2014-2020 yılları arasında Hacettepe Üniversitesi Tıp Fakültesi Hastaneleri'nde takip edilen ve böbrek biyopsisi yapılan SLE'li hastalar çalışmaya alındı. Yüz otuz dört hastanın böbrek biyopsisi retrospektif olarak değerlendirildi ve hastalar LN ve LN dışı renal hastalık olarak gruplandırıldı. Hastaların klinik özellikleri, böbrek biyopsisi sırasındaki laboratuvar değerleri ve renal son durumları hastane tıbbi kayıtlarından elde edildi.

Bulgular: Yüz otuz dört (107 kadın, 27 erkek) hastanın 116'sı (%86,6) LN grubunda, 18'i (%13,4) LN olmayan gruptaydı. LN olmayan grupta en sık tanı fokal segmental glomerüloskleroz (n=6) idi. LN hastalarının medyan (çeyrekler açıklığı) biyopsi yaşı daha genç [21 (17,7) vs. 36,5 (17), p<0,001] olup SLE tanısında 1/320'nin üzerinde yüksek titre antinükleer antikor pozitifliği bu grupta daha sıktı (%50,9 vs. %22,2, p=0,02). Böbrek dışı SLE tutulumu her iki grupta da benzerdi. Renal biyopsi sırasında LN hastalarında anti-dsDNA pozitifliği, düşük C3-4 ve aktif idrar sedimenti varlığı anlamlı olarak yüksek iken serum kreatinin, albümin ve proteinüri gruplar arasında farklı değildi. Ayrıca medyan renal SLEDAI skoru LN hastalarında daha yüksekti.

Sonuç: Anti-dsDNA pozitifliği, düşük C3-C4, aktif idrar sedimenti ve yüksek renal SLEDAI skorları, SLE hastalarında böbrek hastalığı ile ilgili bize bazı ipuçları verebilir. Ancak bu serolojik anormalliklerin lupus dışı böbrek hastalığında da ortaya çıkabileceği unutulmamalıdır.

Anahtar Kelimeler: Sistemik lupus eritematosuz, renal biyopsi, lupus dışı nefritler, lupus nefriti

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Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with frequent renal manifestation. Renal involvement develops during the disease course in up to 60% of adult patients with SLE, while approximately 25-50% of patients experience renal symptoms at SLE onset.[1] Lupus nephritis (LN) is an immune complex glomerulonephritis that may also encompass renal vascular and tubulointerstitial compartments.[2] However, clinically significant kidney diseases unrelated to LN, an unusual condition but not rare, have been reported in patients with SLE. In a study of 252 kidney biopsies in patients with SLE, approximately 5% were diagnosed with non-LN.[3]

Kidney biopsy is the gold standard to determine whether the underlying pathology of the renal findings is due to LN or non-lupus renal disease.[4] Pathologic features of LN include cellular proliferative lesions, wire-loop lesions, and deposits of immunoglobulins and complement fractions in the glomerular basal membrane.[5] Demonstrating the absence of these findings by microscopic evaluation has an important role in the diagnosis of underlying non-LN renal disease.[2] Therefore, kidney biopsy is recommended in SLE patients to determine both the stage of renal involvement and the treatment option. Conventional laboratory biomarkers such as proteinuria, urinalysis, anti-dsDNA, and complement levels are insufficient to distinguish between LN and non-LN renal disease. These measurements may also be positive in SLE patients with non-LN reported as unusual combinations.[3]

In this study, we aimed to reveal the causes of non-LN and to compare the clinic and laboratory features of LN and non-lupus renal disease in patients with SLE.

Materials and Methods

i. Trial Design and Participants

Patients with SLE who were followed up at Hacettepe University Faculty of Medicine, Department of Rheumatology and Nephrology and underwent kidney biopsy were selected for this retrospective descriptive study. From 2014 to 2020, SLE patients were determined from the electronic patient files using the International Classification of Diseases (ICD)-10 code for SLE (M32). Patients fulfilling the SLE classification criteria based on clinical and laboratory characteristics were chosen for the study.[6,7] Patients who had kidney biopsy were selected from all patients with SLE and 188 LN were identified. However, 49 of them were excluded from the study because they were performed in different centers. The pathology reports of 139 patients with SLE and with renal biopsy were as follows: 116 patients with LN, 18 patients with non-LN, two biopsies normal, three biopsies insufficient. After removing normal and insufficient biopsy results, 116 patients with LN and 18 patients with non-LN whose biopsies were assessed at Hacettepe University Hospitals, Clinic of Pathology, were included in the study.

ii. Data Collection

Demographic data contained age at SLE diagnosis, gender, age at kidney biopsy, SLE disease duration, time from SLE diagnosis to kidney biopsy, and family history. Among the concomitant comorbidities, hypertension, diabetes mellitus, and additional rheumatological diseases were recorded. Clinical manifestations of SLE other than renal involvement were also noted.

Laboratory values at the time of kidney biopsy included biochemical estimated glomerular filtration rate (GFR) according to CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration], serum creatinine, serum albumin, 24-hour total urine protein and immunological parameters (ANA, C3, C4, anti-dsDNA antibodies, anti-Smith antibodies). Antinuclear antibody (ANA) titers examined by immunofluorescence technique were categorized as ≥1/320 and <1/320. Anti-dsDNA was calculated by ELISA, and levels were noted quantitatively. Additionally, anti-dsDNA, C3, and C4 levels were given as positive and negative regarding the upper level of laboratory results. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels have also been documented as inflammation markers.

The renal SLE Disease Activity Index (SLEDAI) was calculated at the kidney biopsy. This score, which ranges from 0 to 16, involves four renal findings: hematuria, pyuria, proteinuria and urinary casts.[8] Renal biopsy results reported by a nephropathologist according to the ISN/RPS classification were recorded from pathology reports.[9] Non-LN causes were also recorded separately. The history of end-stage renal disease (ESRD), renal transplant, and death status, including the causes, were noted at the time of study enrollment. The requirement for regular dialysis and/or GFR <15 mL/min was determined as ESRD.[10]

Statistical Analysis

Statistical analysis was presented using the IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The variables were examined for normality using the visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov, skewness, and kurtosis). Continuous data were stated as median (interquartile range) or mean (standard deviation), and categorical variables were stated as percentages. Chi-square test was used to compare categorical variables, and Mann-Whitney U test/Student's t-test was used to compare continuous variables.

Results

The kidney biopsy results of the 139 patients screened were as follows: 116 LN, 18 non-LN renal pathologies, three biopsies failed, and two biopsies were normal (Figure 1). One hundred and sixteen (86.5%) LN patients' biopsies were staged according to the ISN/RPS criteria: 9 (7.6%) patients were class-II LN, 14 (10.4%) patients were class-III LN, 74 (55.2%) patients were class-IV LN, 12 (8.9%) patients were class-V LN, 3 (2.2%) patients were combined LN III+V, and 4 (3%) patients were LN IV+V. Eighteen (13.5%) patients with non-LN renal pathology were reported as 6 (4.5%) focal segmental glomerulosclerosis (FSGS), 4 (3%) membranous nephropathy, 3 (2.2%) thrombotic microangiopathy (TMA), 2 (1.5%) immunoglobulin (Ig) M nephropathy, 2 (1.5%) tubulointerstitial nephritis (TIN), and 1 (0.7%) proliferative glomerulonephritis with monoclonal IgG deposits.

i. Patients' Baseline Characteristics

One hundred-thirty four SLE patients and with kidney biopsies were included in this study. The median age at SLE diagnosis and kidney biopsy age was significantly younger in the LN group than non-LN group. One hundred and seven (79.8%) of patients were female, and the gender distribution was similar for both groups. All seven patients with family history of SLE were in the LN group. The SLE disease duration and the proportion of clinical involvement other than the kidney during the disease course of SLE were not different between the groups. High titer ANA positivity over 1/320 at SLE diagnosis was more frequent in the LN group, whereas anti-Sm, anti-dsDNA, and antiphospholipid antibody overall positivities were not distinct for both groups. The percentage of SLE patients with hypertension and antiphospholipid syndrome was significantly higher in the non-LN group than in the LN group (Table 1).

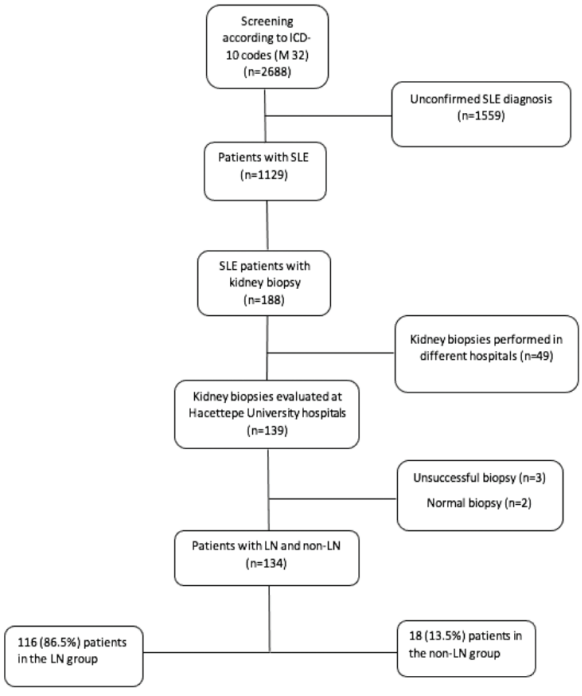

Figure 1. Flowchart of the study patients.
ICD: International Classification of Diseases, LN: Lupus nephritis, SLE: Systemic lupus erythematosus

ii. Clinical and Serologic Findings of Patients with Non-LN

Firstly, all patients had proteinuria ≥500 mg/day in this group. Anti-ds DNA was positive in all 6 patients with FSGS and the most common clinical finding was synovitis. Other clinical findings included leukopenia, serositis, and mucocutaneous findings. Similarly, the most common clinical finding in patients with membranous nephropathy was synovitis and only one patient did not have anti-ds DNA positivity. TMA was defined in 3 patients with AFAS and anti-ds DNA positivity was available in two of the patients. Significant clinical findings for SLE in these patients were as follows: Serositis, leukopenia, synovitis and cutaneous involvement. Anti-ds DNA was positive in 2 patients with IgM nephropathy and clinical findings were synovitis, lymphopenia and cutaneous involvement. Finally, both patients with TIN had low complement levels and cutaneous findings. One patient with proliferative glomerulonephritis with monoclonal IgG deposits had low complement levels, anti-ds DNA positivity, hematologic and cutaneous involvement.

iii. Laboratory Values

There were no differences in the median creatinine level, the rate of patients with increased serum creatinine level, the mean estimated GFR, the median serum albumin, and 24-hour urine protein between the groups. Unlike these, immunological values were quite different in the LN group. LN patients had more elevated anti-dsDNA positivity (81% vs. 46.7%, p=0.001) and median level was higher [421 (591) vs. 150 (310), p=0.005] than non-LN group. Consistently with the immunological activity in the LN group, C3-C4 levels were significantly lower than non-LN group (p<0.001). The percentage of active urinary sediment indicating inflammation in the glomerular capillary wall was higher in the LN patients (83.5% vs. 33.3%, p<0.001), and these patients also had higher median renal SLEDAI score than non-LN patients [12 (8) vs. 4 (4), p<0.001]. However, ESR and CRP levels were similar for both groups (Table 2). The multivariate analysis could not be performed because the number of patients in the non-LN group was low.

Table 1. Demographic and clinical characteristics of LN and non-LN patients

Variables*		LN patients (n=116)	Non-LN patients (n=18)	p
Age at SLE diagnosis, years		18.3 (16)	34.6 (17)	**<0.001**
Sex, female		93 (80.2)	14 (77.8)	0.81
Age at kidney biopsy, years		21 (17.7)	36.5 (17)	**<0.001**
SLE disease duration		8 (8.7)	8 (9.8)	0.47
SLE family history		7 (6)	0	NA
Clinical manifestations during the disease course				
Musculoskeletal		75 (66.4)	13 (76.5)	0.41
Mucocutaneous		60 (52.6)	7 (41.2)	0.38
Hematologic		47 (40.9)	6 (33.3)	0.54
	Leukopenia or lymphopenia	35 (30.2)	6 (33.3)	0.81
	Thrombocytopenia	14 (12.3)	2 (11.1)	0.88
	Autoimmune hemolytic anemia	10 (8.8)	0	NA
Serosal		26 (23.2)	3 (16.7)	0.54
Neurological		6 (5.3)	1 (5.6)	0.99
ANA titer at diagnosis, >1/320		59 (50.9)	4 (22.2)	0.02
Anti-Smith antibodies positivity†		8 (11.8)	1 (5.6)	0.64
APL antibodies positivity†		31 (33.7)	6 (54.5)	0.17
Anti-dsDNA positivity†		105 (90.5)	15 (83.3)	0.35
Hypertension§		31 (26.7)	12 (66.7)	**0.001**
Diabetes mellitus§		7 (6)	2 (11.1)	0.35
Sjogren's syndrome§		19 (16.4)	2 (11.1)	0.78
APLS§		6 (5.2)	4 (22.2)	**0.02**

** n (%) for categorical values and median (IQR) for numeric values, if not otherwise specified; †: At least once positivity during SLE; §: Before or after SLE diagnosis*

ANA: Antinuclear antibodies, APL: Antiphospholipid, APLS: Antiphospholipid syndrome, IQR: Interquartile range, LN: Lupus nephritis, SD: Standard deviation, SLE: Systemic lupus erythematosus

Table 2. Laboratory values at the time of kidney biopsy

Variables*		LN patients (n=116)	Non-LN patients (n=18)	p
Creatinine level (mg/dL)		0.7 (0.5)	0.9 (0.6)	0.23
Creatinine > UNL		37 (32.5)	5 (27.8)	0.58
Estimated GFR (mL/min/1.73 m^2) mean (SD)		104 (51)	84 (34)	0.12
	≥60, n (%)	93 (81.6)	14 (77.8)	0.41
	30-59	7 (6.1)	3 (16.7)	
	<30	14 (12.3)	1 (5.6)	
Albumin (g/dL)		3.3 (1.2)	3.3 (1)	0.81
24-hour urine protein				
	≥1 gr/day, n (%)	72 (71.3)	15 (88.2)	0.17
	≥3 gr/day, n (%)	36 (35.6)	10 (58.8)	0.08
Anti-dsDNA levels (IU/mL)		421 (591)	150 (310)	**0.005**
Anti-dsDNA positivity		94 (81)	7 (46.7)	**0.001**
C3 level (mg/dL)		56 (41.5)	92.5 (41.5)	**<0.001**
C4 level (mg/dL)		8.9 (8.1)	18 (8.8)	**<0.001**
Low C3 and C4 levels		93 (80.2)	6 (33.3)	**<0.001**
Active urinary sediment		91 (83.5)	6 (33.3)	**<0.001**
Renal SLEDAI		12 (8)	4 (4)	**<0.001**
ESR (mm/h)		26 (27)	32 (46)	0.53
Normal CRP value		61 (67)	6 (60)	0.65

** n (%), if otherwise specified; median (IQR) for numeric values excluding GFR*

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, IQR: Interquartile range, LN: Lupus nephritis, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, UNL: Upper normal limit

iv. Outcome of Renal Pathology at the Time of Study Enrollment

The median SLE disease duration was eight years, and there was no distinction between the groups. Of 134 patients, fourteen cases with ESRD, 13 (11.2%) of which were in the LN group, and six patients with kidney transplant, 5 (4.3%) of which were in the LN group, were observed. All eight (7%) patients who deceased were in the LN group (Figure 2). The major reasons of death were infection and cardiovascular events in these patients.

Discussion

In this study, we emphasized the distinctions between LN and renal pathologies other than LN in terms of clinical characteristics, laboratory values, and renal outcomes in patients with SLE. Approximately 85% of our patients were in the LN group and the rate of anti-ds DNA positivity, low levels of C3 and C4, active urinary sediment, and median renal SLEDAI scores were higher in this group. In the non-LN group, the patients were older, and the rate of high ANA titer over 1/320 was lower at SLE diagnosis.

Renal signs and symptoms develop during the disease course in ~60% of adult patients with SLE.[1] Although LN is the most underlying cause, renal biopsy in patients with SLE may rarely show pathogenetic and morphological changes unrelated to SLE. However, how non-LN develops in patients SLE is not fully understood. In a study from the US, including 252 kidney biopsies, non-LN was reported in approximately 5% of patients with SLE. The most frequent renal lesion was FSGS, but several other diagnoses were also detected, such as thin basement membrane disease, IgM nephropathy, amyloidosis, hypertensive nephropathy, and allergic acute TIN.[3] This unexpected combination has been mentioned in many case reports, including minimal change disease, FSGS,[11,12] amyloidosis,[13,14] IgA nephropathy,[15,16] sarcoidal TIN,[17] and IgM nephropathy[18] in this literature.

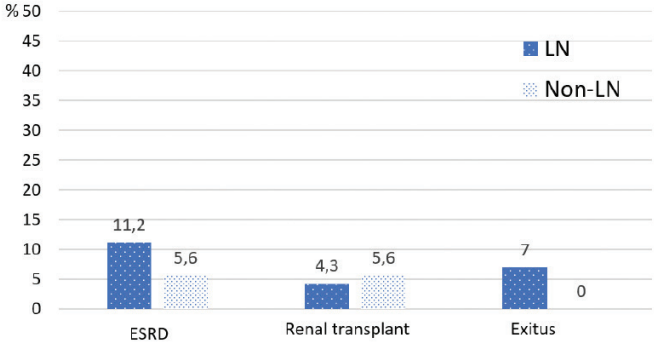

Figure 2. Renal end status of LN and non-LN patients at the time of study enrollment
LN: Lupus nephritis

In our study, the rate of non-LN increased up to 13% also including renal TMA, and the most common cause was FSGS. This result highlights the significance of biopsy in the assessment of renal findings in patients with SLE.

Renal TMA, which can occur with or without LN, is characterized by renal microvascular occlusion and intrarenal aggregation of platelets, along with erythrocyte damage.[19] 22-32% of patients with SLE and accompanying APS have APS nephropathy.[20,21] Histologically, APS nephropathy may be acute or chronic lesions. Acute lesions include TMA, whereas chronic/late-stage lesions include reduplication of glomerular capillary basement membranes with segments of tuft sclerosis.[22] The kidney pathology results of the patients with SLE and APS in our kidney biopsy series were as follows: LN (n=6), TMA (n=3), and FSGS (n=1). Clinicians should be aware of these histological differences for diagnosis and treatment in SLE patients with APS.

LN is usually diagnosed in the third and fourth decades.[23-26] Young age at SLE diagnosis is related with an elevated risk of developing LN.[1,27] In renal pathologies other than LN, which were reported as unusual combinations in SLE diagnosis, a major part of the patients are in the fifth decade or older.[12-14,16-18] In our cohort, the kidney biopsy age was in the third decade in LN patients and the fourth decade in non-LN ones. This result may suggest that renal abnormalities are related to LN in young SLE patients with renal findings.

The prevalence of hypertension in SLE has been described to rise to 77% in some cohorts.[28] The main cause of HT in SLE is renal glomerular damage and renal vascular endothelial dysfunction.[29] Therefore, hypertension is also seen in other glomerular diseases such as FSGS, membranous nephropathy, and IgA nephropathy. We determined the percentage of hypertension to be higher in the non-LN group than in the LN group. This result can be explained by the fact that rare glomerular diseases other than LN increase the risk of already existing HT in patients SLE.

Decreased kidney function, proteinuria >0.5 g/24 hours, or active urinary sediment, which are indications for renal biopsy in patients with SLE, may not occur only in LN.[30] Renal pathologic findings differentiate LN from non-LN with high specificity and varying sensitivity.[31] Conventional laboratory biomarkers such as proteinuria, creatinine clearance, anti-dsDNA, and complement levels are insufficient in anticipating LN. Furthermore many new biomarkers have been investigated in LN, but none have been validated yet in large cohorts.[32] Although conventional laboratory measurements are not an ideal biomarker for LN, they are frequently used by clinicians in clinical practice. In

a study from Greece involving 297 biopsy-confirmed LN patients, increased positive anti-dsDNA titer rates along with low C3 levels have been found to be a hallmark of proliferative forms of LN.[23] In another recent study, it was shown that there was a significant relationship between anti-dsDNA level and class IV LN.[24] In our study, more than 80% of LN patients were in the proliferative form, and compared with the non-LN group, the rate of anti-dsDNA positivity, median anti-ds DNA level, and low C3-C4 level at the biopsy time were significantly high in the LN group. However, in the non-LN group, it was conspicuous that approximately half of the patients had anti-dsDNA positive, and one-third had low C3 and C4 levels. This result revealed that although serological activity was higher in patients with LN, similar laboratory values could also be found in patients with non-LN.

Active urinary sediment reflecting renal inflammation is used as one of the response criteria of the American College of Rheumatology in patients with LN.[33] However, active sediment is not specific to SLE and LN.[34] Mavragani et al.[23] emphasized that active urinary sediment indicators >5 urinary leukocytes/hpf and cellular casts >1/hpf predict proliferative forms of LN. In the study reporting the reasons of nephritis other than LN in patients with SLE, active urinary sediment was found in three-quarters of the patients.[3] We found the rate of active urinary sediment in more than 80% of the patients in the LN group and one-third of the patients were in the non-LN group. Although active urinary sediment may firstly indicate LN in patients with SLE, it may also be detected in renal pathologies other than LN.

In contrast to serological and urinary laboratory values, the role of inflammatory markers in the evaluation of SLE activity is limited. ESR, one of the non-specific markers of inflammation, is useful for evaluating activity in patients with SLE, but the response of CRP during the disease flares appears inadequate.[35] In a study involving 111 LN patients from Italy, it was determined that ESR and CRP at the time of kidney biopsy were not correlated with clinical/histological parameters and were not a predictive factor in differentiating of LN forms.[25] In our study, the median ESR was 26 mm/h, and it was not distinct between the groups. Additionally, approximately 60% of the patients in both groups had normal CRP values. Therefore, in daily practice, inflammatory markers such as ESR and CRP seem insufficient to understand the underlying cause of renal findings in patients with SLE.

Despite current treatment alternatives, the percentage of ESRD development is between 4% and 28% in LN patients.[36] Kidney transplant is the treatment option for the majority of patients with ESRD due to LN. According to the results of the United States Renal Data System, approximately 60% of 9.659 patients with LN-ESRD underwent renal transplantation and were associated with improved survival.[37] In our study, ESRD rate was 11.2% and the renal transplant rate was 4.3% in the LN group. We did not use a statistical comparison since there was only one patient who developed ESRD and underwent renal transplantation in the non-LN group. Unfortunately, we could not find any information about the non-LN outcome of patients with SLE in the literature.

Study Limitations

Some strengths and limitations of our study should be addressed. The main limitation was the retrospective plan of the study, which inhibited clear conclusions about the patients' follow-up. The other limitation was the small number of non-LN patients because of the single-center nature of our study. Despite these limitations, the strength of our study was that all patients' renal findings were proven by kidney biopsy and the presence of laboratory data at the time of biopsy.

Conclusion

Although unusual, patients with SLE may admit with various renal lesions unrelated to LN. This study demonstrates that renal pathologies other than LN should be clinically suspected in patients with SLE who have low anti-dsDNA levels, normal complement levels, and inactive urinary sediments but still present with renal abnormalities such as proteinuria. However, it should be kept in mind that serological abnormalities, albeit at low rates, may be seen in patients with non-LN. Kidney biopsy is the cornerstone of differentiating renal pathologies in patients with SLE.

Ethics

Ethics Committee Approval: This study was approved by the Hacettepe University Ethics Committee (approval number: GO 2020/07-14, date: 31.03.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.D., İ.E., Design: E.D., T.Y., U.K., İ.E., Data Collection or Processing: E.D., A.T., Analysis or Interpretation: E.D., E.B., U.K., Literature Search: E.D., T.Y., E.B., M.A., A.S., S.Ö., M.Ü., Y.E., İ.E., Writing: E.D., U.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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