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Comparison of clinicopathological characteristics among adult patients with early and delayed lupus nephritis

Anmol, Tabassum Elahi, Anusha Kumari, Amara Naseer

Department of Nephrology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan.

Correspondence: Anmol. **Email**: anmolshankarkirplani@gmail.com

ORCID ID: 0009-0000-7403-9926

Abstract

Objective: To assess clinicopathological characteristics in adult patients with early and delayed lupus nephritis.

Method: The comparative, cross-sectional study was conducted at the Department of Nephrology, Sindh Institute of Urology and Transplantation, Karachi, from January to June 2025, and comprised patients of either gender aged 18-50 years with biopsy-proven lupus nephritis. The patients were classified into early lupus nephritis group ELN (<1 year after systemic lupus erythematosus diagnosis) and delayed lupus nephritis group DLN (>1 year after the diagnosis). Baseline demographic, clinical, laboratory, serological and renal biopsy data was collected from all the patients. Histopathology was evaluated as per the International Society of Nephrology / Renal Pathology Society classification by using modified National Institutes of Health activity and chronicity indices. Data was analysed using SPSS 22.

Results: Of the 39 patients with mean age 32.6±8.4 years, 33(84.6%) were females. There were 22(56.4%) patients in group ELN and 17(43.6%) in group DLN. Delayed lupus nephritis was associated with a longer duration of systemic lupus erythematosus before renal involvement (p<0.001), higher frequency of hypertension (p=0.04), oliguria

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(p=0.04) and nephritic syndrome (p=0.04). Patients with delayed lupus nephritis also had higher serum creatinine (p=0.01), lower estimated glomerular filtration rate (p=0.02) and more frequent moderate-to-severe interstitial fibrosis and tubular atrophy (p=0.01) compared to those with early lupus nephritis.

Conclusion: Delayed lupus nephritis was associated with more severe renal dysfunction and greater chronic histopathological damage compared to those with early lupus nephritis.

Key Words: Chronicity index, Kidney diseases, Lupus nephritis, Systemic lupus erythematosus, Timing of diagnosis.

Introduction

One of the most severe organ presentations of systemic lupus erythematosus (SLE) and a significant morbidity and prognosis predictor in adults is lupus nephritis (LN) [1]. Nakano et al. in 2019 defined delayed lupus nephritis (DLN) as a disease that appears more than one year after the SLE diagnosis, which is around 5-15% of all LN cases that have a worse treatment outcome. Although the global prevalence of SLE is about 43.7 per 100,000, renal activity is seen in 40-60% of patients during the course of the disease. [2]. Young adults with SLE have LN as a primary cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [3].

The renal involvement of SLE is relatively more prevalent in Pakistan, where hospital-based studies have reported LN in 50-70% of adult patients [4]. This highlights the importance of renal disease burden in the region and the importance of prompt diagnosis and treatment to avoid negative renal outcomes. There is a paucity of data comparing clinicopathological features of patients with early LN (ELN) versus those with DLN in the Pakistani population in relation to the high prevalence of the disease [5].

Renal SLE is heterogeneous over time. There are patients who get nephritis at the initial stages of the disease, and there are those who have late renal involvement [6]. There has

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been some evidence that timing LN could have a profound effect on clinical presentation, histopathological severity, response to treatment, and outcome of renal prognosis [7].

A number of cohort studies have found that DLN individuals are more likely to have high chronicity indices, cumulative organ damage, and poor therapeutic responses compared to ELN patients [8]. ELN is characterised by more active systemic images, whereas DLN can have an insidious course of occurrence, resulting in late diagnosis and pathological alterations during renal biopsy [9].

Comparisons of the clinicopathology also show variations in the histological classes' distribution, and activity and chronicity scores, and the undesirable appearances of glomerulosclerosis and crescent formation in ELN and DLN [10]. Nevertheless, there is heterogeneity in the reported data, and thorough comparative research in the adult population, particularly in such regions as Pakistan, is limited.

Since LN is highly prevalent and has prognosis implications in Pakistan, it is important to conduct a systematic assessment of clinicopathological characteristics of ELN and DLN.

The current study was planned to compare the clinicopathological features of ELN and DLN in adult patients, and to analysis the variability of clinical presentation, severity of the histopathological changes and possible prognostic effects. The null hypothesis was that in adult patients, DLN would be characterised by the presence of more severe histopathological alterations and lower clinical parameters at the time of presentation than ELN.

Patients and Methods

The comparative, cross-sectional study was conducted at the Department of Nephrology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, from January 1 to June 30, 2025. After approval from the Institutional ethics review board, the sample size was calculated for comparing two independent means using the formula: $n = 2\sigma^2 (Z\alpha/2 + Z\beta)^2 / \Delta^2$ where n is the required sample size per group, σ is the pooled standard deviation

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(SD), Δ is the desired difference between the two means, Zα/2 is the standard normal deviate for a two-sided alpha level of 0.05, and Zβ is the standard normal deviate for 80% power [11]. A clinically meaningful difference was assumed to be 1.5 points, the pooled standard deviation was 2.0, the level of significance was 0.05 (two-sided), and the power was 0.80. A clinically meaningful difference of 1.5 points was set as the difference that was expected between ELN and DLN groups based on the fact that the chronicity index has proven to be prognostically important in LN, and a chronicity index of >2 is correlated with poor renal response [12]. The assumed pooled SD of 2.0 was chosen because the SDs of the chronicity index scores in LN patients have been reported to be around 2.2-2.4 [13]. The values used were planning assumptions, as none of the directly relevant local studies provided reliable prior estimates of the difference in chronicity index between ELN and DLN.

Because of the rarity of LN, and the limited study period, all eligible patients who presented and were given either in-patient or out-patient treatment of interest were enrolled using consecutive sampling technique. Those included were patients of either gender aged 18-50 years with the diagnosis of SLE based on the American College of Rheumatology (ACR) criteria [14] and who were histopathologically confirmed as having LN based on the 2018 revised International Society of Nephrology / Renal Pathology Society (ISN/RPS) classification. [15]. Only patients who had sufficient renal biopsy specimens for analysis were selected. Patients who had previously been treated for LN were excluded and so were those undergoing transplantation. LN diagnosed within one year of SLE diagnosis was defined as ELN, while lupus nephritis diagnosed over one year after SLE diagnosis was defined as DLN. This operational definition was based on previous early onset and delayed onset LN studies [1].

Structured data-collection form was used to gather demographic data, such as age, gender and residence status, after taking written informed consent from all the participants. Also noted was the duration of SLE prior to LN onset, bodyweight, marital status, renal

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manifestations (proteinuria and haematuria), extra-renal SLE manifestations (arthritis, skin involvement) and hypertension (HTN).

Blood samples were drawn through a sterile procedure using venipuncture. The urine sample analysed for proteinuria was either a spot urine protein-to-creatinine ratio (PCR) sample or a 24-hour urine sample, whichever was most suitable for the patient. Complete blood count (CBC), serum creatinine and serum albumin were determined by automated laboratory analyses. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [16]. Serological parameters (antinuclear antibody, anti-double-stranded deoxyribonucleic acid [DNA] antibody, complement component-3 (C3), C4, lupus anticoagulant, antiphospholipid antibody and extractable nuclear antigen profile) were measured by standard immunoassay methods, if available. Laboratory and serological data were gathered as soon as possible upon initial evaluation to ensure that the disease status was captured prior to therapeutic intervention.

Histopathological examination of renal biopsy samples consisted of a total number of glomeruli, number of sclerosed glomeruli, percentage of glomeruli with crescents, and type of crescents (cellular, fibrocellular and fibrous). Other parameters evaluated were mesangial hypercellularity, endocapillary hypercellularity, duplication of the capillary wall, interstitial fibrosis and tubular atrophy. The degree of interstitial fibrosis and tubular atrophy was semi-quantitatively assessed as none, mild (<20%), moderate (20-50%) or severe (>50%). The concentration of immunoglobulin-A (IgA), IgG, IgM, C3 and C1q was measured by immunofluorescence and the staining intensity was scored from 0 to 3+ [8].

For the activity and chronicity indices, the modified National Institutes of Health (NIH) scoring system [14] was used. The activity index was given a maximum of 24 points based on endocapillary hypercellularity, neutrophil infiltration/karyorrhexis, fibrinoid necrosis, hyaline deposits, cellular or fibrocellular crescents and interstitial inflammation.

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Global or segmental glomerulosclerosis, fibrous crescent, tubular atrophy and interstitial fibrosis were part of the chronicity index, with a maximum score of 12.

Data was analysed using SPSS 22. Histogram inspection, Shapiro-Wilk test and Q-Q plots were used to test data normality of continuous variables. Continuous data was normally distributed, and was expressed as mean ± SD and analysed by independent-samples t-test between ELN and DLN groups. Other parameters with non-normal distribution, such as duration of the disease, proteinuria, serum creatinine, etc., were reported as median with interquartile range (IQR), and analysed using the Mann-Whitney U test. Gender, residence status, type of LN and clinicopathological features were analysed and expressed as frequencies and percentages. Simple cross-tabulation and chi-square/Fisher's exact test were used to assess associations between categorical variables and LN group, as appropriate based on the number of cells expected. This part of the analysis was not stratified. Univariate comparisons were done along with group-wise comparisons. $P<0.05$ was considered statistically significant.

Results

Of the 39 patients with mean age 32.6±8.4 years, 33(84.6%) were females. There were 22(56.4%) patients in group ELN and 17(43.6%) in group DLN.

The mean age in group ELN was 30.9±7.6 years and in group DLN it was 34.8±8.9 years ($p=0.14$). There were 19(86.4%) females in ELN and 14(82.4%) in DLN group ($p=0.72$). The time interval between the onset of SLE and the onset of renal involvement was significantly longer in DLN than ELN ($p<0.001$). There was a higher prevalence of HTN in DLN compared to ELN ($p=0.04$), but a higher prevalence of haemodialysis on admission was not statistically significant ($p=0.09$). There were no significant differences observed between the groups with respect to bodyweight ($p>0.05$) (Table 1).

The most frequent symptom of presentation in both groups was oedema ($p=0.46$). DLN patients more frequently presented with oliguria ($p=0.04$) and nephritic syndrome

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(p=0.04). Macroscopic haematuria was also more common in DLN, but it was not significantly different (p=0.18). There were no significant differences in nephrotic syndrome and extra-renal manifestations between the groups (p>0.05) (Table 1).

At presentation, renal impairment was more marked in DLN, reflected by significantly higher serum creatinine (p=0.01) and lower estimated glomerular filtration rate (eGFR) (p=0.02). Serum albumin, haemoglobin and proteinuria were similar between the groups (p>0.05). Anti-double-stranded deoxyribonucleic acid (dsDNA) positivity was observed in 17(77.3%) ELN patients and 14(82.4%) DLN patients (p=0.68). Overall, 18(81.8%) ELN patients and 15(88.2%) DLN patients had hypocomplementemia, while a minority of patients had antiphospholipid antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) positivity (Table 2).

The most common histopathological pattern was diffuse proliferative LN in both groups (p=0.36). Crescents were more frequent in DLN than ELN (p=0.05). The activity index was comparable between the groups (p=0.51), whereas the chronicity index was significantly higher in DLN than ELN (p=0.01). In addition, moderate to severe interstitial fibrosis and tubular atrophy (IFTA) was also more common in DLN than ELN (p=0.01) (Table 3).

Discussion

The present study aimed to investigate the differences in clinical, laboratory and histopathological features between early lupus nephritis (ELN) and delayed lupus nephritis (DLN) in adult patients. All patients had a diagnosis of systemic lupus erythematosus (SLE) based on the European League Against Rheumatism/American College of Rheumatism (EULAR/ACR) classification criteria and renal biopsy interpretation was carried out using standardized renal pathology principles and the revised International Society of Nephrology/Renal Pathology Society (ISN/RPS)

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188 classification system with modified National Institutes of Health (NIH) activity and
189 chronicity indices [12–14].
190 The most important result of this investigation was the greater severity of renal
191 involvement at the onset of the disease in patients who had DLN than in those who had
192 ELN. Demographic parameters such as age, gender distribution and body weight were
193 similar between groups, but the period of SLE until the onset of renal involvement was
194 significantly longer in the DLN group, and the incidence of hypertension, oliguria,
195 nephritic syndrome, serum creatinine and estimated glomerular filtration rate (eGFR)
196 were higher in the DLN group. These observations indicate that worsening renal function
197 at diagnosis may be related to the delayed presentation of renal involvement. Previous
198 evidence suggests that early detection and prompt treatment of LN is an important factor
199 in preserving renal function; otherwise, it may lead to progressive renal damage and less
200 successful treatment results [15,16].
201 Oedema was the commonest presenting feature in both groups although not everyone met
202 the criteria for nephrotic syndrome. This finding also emphasizes the possibility that
203 oedema can develop as a result of the lupus nephritis, for reasons of sodium and water
204 retention, impaired renal function, and decreased serum albumin levels. The clinical
205 picture of lupus nephritis may differ significantly from nephritic to nephrotic depending
206 on the activity of disease, histological class, and patient's characteristics [17,18]. Hence,
207 one clinical datum must be interpreted with caution and along with the laboratory and
208 biopsy results.
209 There was no statistically significant difference between ELN and DLN groups with
210 regard to high prevalence of anti-double-stranded DNA (anti-dsDNA) positivity and
211 hypocomplementemia. These immunological abnormalities are frequently seen and have
212 consistent been associated with autoantibody production, complement activation, immune
213 complex deposition and inflammatory pathways in the pathogenesis of lupus nephritis. A

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complex interaction of innate and adaptive immune response to glomerular injury and progressive renal damage occurs through these immune-mediated mechanisms [19,20].

Diffuse proliferative lupus nephritis was the most common pattern of nephritis in both cohorts by histopathology. However, DLN patients had higher frequency of crescent formation, significantly higher chronicity index scores and higher frequency of moderate-to-severe interstitial fibrosis and tubular atrophy (IFTA). The similarity in activity indices among groups indicates that the difference between ELN and DLN may be more a consequence of the total amount of irreversible renal damage than a result of the presence of active inflammation alone. The clinical significance of distinguishing between early and delayed renal involvement has been established by previous studies showing that the timing of the onset of lupus nephritis may have a significant impact on renal presentation, pathological severity and long-term outcomes [21]. Additionally, recent strategies for the treatment of LN have focused on the correlation of the histological activity and chronicity indices with clinical indices for the assessment of prognosis and treatment decisions [22].

Careful interpretation of the increased chronic kidney damage observed among the patients with DLN is needed. While important differences were seen between groups, this analysis was univariate and no attempt was made to adjust for disease duration, hypertension, baseline renal function, treatment delay, or other clinical variables. Thus, these findings are associations and not unique predictors. In previous studies, it was reported that there is a spectrum of clinical outcomes in patients with lupus nephritis based on patient characteristics and the time of onset of renal involvement, which argues for the need of individual patient assessment and long-term follow-up [23].

The increased chronicity index seen in DLN patients is also significant as chronic histological damage is associated with irreversible renal injury and long-term kidney survival outcomes. The use of chronicity indices along with clinical parameters might help in better evaluation of prognosis and detection of patients at higher risk of progressive renal function [24, 25].

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The other limitations of the study include the small number of patients due to the rarity of the disease in the population and the short study timeframe. Due to the small sample size and the number of low expected cells for the subgroups, no formal post-stratification analysis could be performed. Several biopsy and immunofluorescence parameters, like total glomeruli, sclerosed glomeruli, crescent type, mesangial and endocapillary hypercellularity, capillary wall duplication, IFTA grade and staining intensity for IgA, IgG, IgM, C3 and C1q, were only descriptively analysed, if available. Formal inferential testing of these parameters was not performed due to low numbers of small subgroups. Besides, all analyses were univariate group-wise comparisons of ELN and DLN. Independent associations were not implied as no multivariate adjustment for potential confounders was done. As such, independent associations could not be determined. Lastly, the cross-sectional design precluded the estimation of long-term renal outcomes or treatment response.

Despite the limitations, however, the current study has its strengths, like the inclusion of biopsy-proven LN cases, standardised SLE and LN classification criteria and the direct comparison between ELN and DLN using clinical, laboratory and histopathological parameters. A significant reduction in selection bias within the available hospital population was achieved by making all eligible biopsy-confirmed patients part of the study consecutively throughout the study period.

Larger multicentre cohorts with longer follow-ups should be considered for future studies to assess renal survival, treatment response and progression to CKD. Adjusted analyses should be performed controlling for disease duration, HTN, baseline renal function, histological class, activity index and chronicity index, and they should be based on patient-level data. In addition, detailed histopathological and immunofluorescence variables should be reported in future studies so as to better determine if there is an increased risk for irreversible renal damage at presentation in DLN.

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Conclusion

There was more severe renal involvement at the time of presentation in DLN than in ELN cases. DLN patients had more HTN, oliguria and nephritic syndrome, with significantly elevated serum creatinine and decreased eGFR. DLN was associated with a higher chronicity index and more common moderate to severe IFTA on histopathology, indicating more irreversible renal damage at diagnosis.

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Table 1: Demographic and clinical characteristics of the patients at presentation (n+39).

Variable	ELN (n=22), n (%) or mean ± SD	DLN (n=17), n (%) or mean ± SD	p-value

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Age, years	30.9 ± 7.6	34.8 ± 8.9	0.14
Female gender	19 (86.4%)	14 (82.4%)	0.72
Male gender	3 (13.6%)	3 (17.6%)	—
SLE duration before LN, years	0.6 ± 0.3	4.2 ± 1.8	<0.001
Weight, kg	61.3 ± 9.2	63.1 ± 8.6	0.48
Hypertension, present	9 (40.9%)	12 (70.6%)	0.04
Hypertension, absent	13 (59.1%)	5 (29.4%)	—
Haemodialysis on admission, present	4 (18.2%)	7 (41.2%)	0.09
Haemodialysis on admission, absent	18 (81.8%)	10 (58.8%)	—
Oliguria, present	6 (27.3%)	9 (52.9%)	0.04
Oliguria, absent	16 (72.7%)	8 (47.1%)	—
Macroscopic haematuria, present	5 (22.7%)	7 (41.2%)	0.18
Macroscopic haematuria, absent	17 (77.3%)	10 (58.8%)	—
Oedema, present	16 (72.7%)	14 (82.4%)	0.46
Oedema, absent	6 (27.3%)	3 (17.6%)	—
Nephrotic syndrome, present	10 (45.5%)	8 (47.1%)	0.92
Nephrotic syndrome, absent	12 (54.5%)	9 (52.9%)	—
Nephritic syndrome, present	6 (27.3%)	9 (52.9%)	0.04
Nephritic syndrome, absent	16 (72.7%)	8 (47.1%)	—
Arthritis/arthralgia, present	13 (59.1%)	11 (64.7%)	0.72
Arthritis/arthralgia, absent	9 (40.9%)	6 (35.3%)	—
Skin manifestations, present	9 (40.9%)	8 (47.1%)	0.69
Skin manifestations, absent	13 (59.1%)	9 (52.9%)	—
Serositis, present	4 (18.2%)	5 (29.4%)	0.39
Serositis, absent	18 (81.8%)	12 (70.6%)	—

ELN: Early lupus nephritis, DLN: Delayed lupus nephritis, SLE: Systemic lupus erythematosus, LN: Lupus nephritis.

Table 2: Laboratory and serological parameters at the time of admission.

Parameter	ELN (n=22), n (%) or	DLN (n=17), n (%) or	p-value

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	mean ± SD	mean ± SD	
Serum creatinine, mg/dL	2.1 ± 1.3	3.4 ± 1.9	0.01
eGFR, mL/min/1.73 m²	46.7 ± 18.5	32.4 ± 15.6	0.02
Serum albumin, g/dL	2.6 ± 0.5	2.3 ± 0.6	0.11
Haemoglobin, g/dL	9.8 ± 1.4	9.2 ± 1.6	0.19
UPC / 24-h protein, g/day	3.2 ± 1.7	3.6 ± 1.9	0.48
Anti-dsDNA positive, present	17 (77.3%)	14 (82.4%)	0.68
Anti-dsDNA positive, absent	5 (22.7%)	3 (17.6%)	—
Low C3 and/or C4, present	18 (81.8%)	15 (88.2%)	0.56
Low C3 and/or C4, absent	4 (18.2%)	2 (11.8%)	—
Antiphospholipid antibody positive, present	2 (9.1%)	3 (17.6%)	0.43
Antiphospholipid antibody positive, absent	20 (90.9%)	14 (82.4%)	—
ANCA positive, present	3 (13.6%)	4 (23.5%)	0.44
ANCA positive, absent	19 (86.4%)	13 (76.5%)	—

ELN: Early lupus nephritis, DLN: Delayed lupus nephritis, eGFR: Estimated glomerular filtration rate, UPC: Urine protein-to-creatinine ratio, ANCA: Anti-neutrophil cytoplasmic antibodies, dsDNA: Double-stranded deoxyribonucleic acid, C3/C4: Complement components 3 and 4.

Table 3: Renal biopsy findings and activity/chronicity index values.

Histopathological feature	ELN (n=22), n (%) or mean ± SD	DLN (n=17), n (%) or mean ± SD	p-value
ISN/RPS Class III/IV, present	14 (63.6%)	13 (76.5%)	0.36
ISN/RPS Class III/IV, absent/other classes	8 (36.4%)	4 (23.5%)	—
Crescents, present	8 (36.4%)	11 (64.7%)	0.05
Crescents, absent	14 (63.6%)	6 (35.3%)	—
Activity index, 0–24	9.6 ± 3.8	10.4 ± 4.1	0.51
Chronicity index, 0–12	2.8 ± 1.6	4.6 ± 2.1	0.01
Moderate-to-severe IFTA, present	5 (22.7%)	10 (58.8%)	0.01
Moderate-to-severe	17 (77.3%)	7 (41.2%)	—

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IFTA, absent			

ELN: Early lupus nephritis, DLN: Delayed lupus nephritis, ISN: International Society of Nephrology, RPS: Renal Pathology Society, IFTA: Interstitial fibrosis and tubular atrophy.

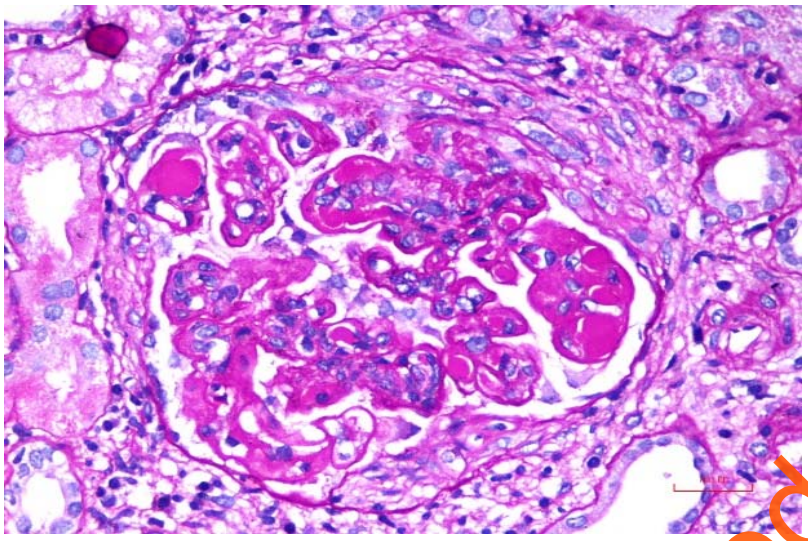

Figure: Crescent formation in lupus nephritis.

AUTHORS' CONTRIBUTIONS:

A: Concept, data analysis and drafting.

TE: Supervision, critical revision and final approval.

AK: Data collection, literature review and assistance.

AN: Data interpretation, review and editing support.

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