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Research Article

Comparison of Histopathological Findings with Clinical Response among Patients Undergoing Consecutive Renal Biopsy for Lupus Nephritis in 2008-2021

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease involving several systems and has a high occurrence in areas such as the kidney, central nervous system, and vascular and serous structures. Furthermore, SLE poses a significant and increased risk of infections as well as an increase in morbidity and mortality. This increase is due to the presence of risk factors such as the use of corticosteroids, immunosuppressive drugs, and cytotoxic agents; changes in renal function; leukopenia, hypoalbuminemia; and alterations in both renal function and immunological profile (complement, anti-DNA).

Renal biopsy (RB) is a safe method for obtaining renal tissue for the diagnosis and prognosis of SLE. Although complications, such as hemorrhage, are rare, if they do occur, they usually do so during the first 8-24 hours of the procedure. This diagnostic method is the best tool to diagnose lupus nephritis. Hence, we conducted a study to determine the histological changes in patients with lupus nephritis who were evaluated with consecutive biopsies from 2008 to 2021.

Materials and Methods: An observational, analytical, and retrospective study was conducted using information collected from the RB database. Data on SLE and/or lupus nephritis recorded in this database by Clínica de la Costa uninterruptedly from 2008 to 2021. Patients with a diagnosis of SLE were selected based on at least four diagnostic criteria of the American College of Rheumatology. Those who had undergone renal puncture biopsy according to the consensus criteria of the group of systemic autoimmune diseases of the Spanish Society of Nephrology were selected.

Results: A significant increase was observed in chronicity rates.

Conclusion: Consecutive renal biopsy in LN allows early identification of the progress of the histopathological lesion. In this study, 30.7% of class III patients in their first renal biopsy presented histologicalprogress toward class IV in their consecutive biopsy.

Keywords: Systemic Lupus Erythematosus; Lupus Nephritis; Consecutive Kidney Biopsies

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease and is mainly characterized by the production of autoantibodies, which is associated with the deposition of immune complexes with complement activation and leads to inflammation and damage to the affected tissues [1-12]. The kidney is most frequently affected, although this deleterious effect can occur in almost all organs. SLE affects women more than men regardless of the type of population [6-14], but it especially affects those of reproductive age. The prevalence and possibility of developing lupus nephritis (LN) depends on the region of the world, race, and ethnicity, with black and Hispanic individuals being the groups with the worst prognosis and higher morbidity and mortality rates compared with Caucasians. These clinical differences and predispositions could be explained by the genetic component. However, SLE also occurs in patients who even though they are not genetically predisposed to this disease, they are exposed to environmental triggers. Several genes are associated with the abovementioned susceptibility to SLE, especially in the human leukocyte antigen (HLA) loci. For example, carriers of HLA DR3 and DR15 have higher susceptibility to LN, although the mechanisms of susceptibility and protection based on HLA are unknown [15-22].

Materials and Methods

An observational, analytical, and retrospective study was conducted using data obtained from the renal biopsy database of the Clínica de la Costa, which consists of a registry of SLE and/or lupus nephropathy from 2008 to 2021. Patients were selected according to the following inclusion and exclusion criteria:

Inclusion criteria

- Diagnosis of SLE and/or LN based on at least four diagnostic criteria of the American College of Rheumatology (ACR), including positive antinuclear antibodies (ANA) and/or anti-double stranded DNA (Anti-dsDNA) antibodies [22].
- Age ≥ 18 years

Exclusion criteria

- Age < 18 years.

In terms of the renal biopsy criteria used, the first renal biopsy was indicated, according to the consensus of the systemic autoimmune diseases group (GEAS) of the Spanish Society of Nephrology (SEN) (12) for patients with SLE who presented with unexplained deterioration of the renal function, confirmed proteinuria > 500 mg/24 hours, and/or altered urine sediment.

Initially, patients who met the inclusion–exclusion criteria were selected.

Data were collected from clinical histories and pathology reports and were as follows: sex, comorbidities (hypertension, diabetes mellitus, and chronic kidney disease), activity index in the first and second renal biopsies, anti-DNA, and hematuria. In addition, biochemical parameters corresponding to the time of the first and second renal biopsies were collected: hemoglobin, hematocrit, leukocyte and platelet count, creatinine, glycemia, natremia, chloremia, kalemia, uremia, prothrombin time, kaolin partial thromboplastin time, complement (C3 and C4) glomerular filtration rate, urinary pH, urinary density, urine culture, urinary sediment, and proteinuria in 24-hour urine.

The criteria of the ACR were used for the definition of "clinical response," and they were classified as "complete clinical response," "partial response," or "no clinical response."

Statistical analysis

Quantitative variables were expressed as mean and standard deviation or median (Mn) and interquartile range (IQR). Qualitative variables were expressed as absolute and percentage relative frequencies. Comparisons of quantitative variables were made using the t-test for comparison of means in related samples or the Wilcoxon test for related samples. Qualitative variables were compared using the McNemar test. Associated probability values <0.05 were considered statistically significant.

Results

Information was available for 48 patients >18 years of age who were diagnosed with SLE and/or LN and underwent renal rebiopsy.

Table 1 shows the baseline characteristics of the patients analyzed, corresponding to the times of the first and second renal biopsy. The median age of the patients at the time of the first biopsy was 36 years (range: 28-45). The youngest patient was 19 years old and the oldest was 65 years old. The composition of the patient group by sex was 79% women and 21% men, respectively. Regarding comorbidities, 13 cases of arterial hypertension (27%), no case of diabetes mellitus, and 29 cases of chronic kidney disease (60%) were reported in the group.

Regarding the comparison of results between the first and second renal biopsies, the median time elapsed between the first and second renal biopsies was 850 days (494–1471), with a minimum of 245 and a maximum of 4,065 days. In the first biopsy, the main lupus classes were class 4, with 26 cases (54%) and class 3, with 13 cases (27%). In the second biopsy, class 4 continued to be predominant, with 32 cases (67%) (Figure 1).

Characteristics	Summary	
Age (years), Average (SD)/Median (IQR)	37.38 (11.67)/36.00 (27.75 – 45.00)	
Sex, count (%)		
Male	10	(20.83)
Female	38	(79.17)
Time between biopsies, Average (SD)/Median (IQR)	1137.30 (905.88)/850 (494.50 - 1471.00)	
Comorbidities, count (%)		
Hypertension	13	(27.08)
Diabetes mellitus	0	(0.00)
Chronic kidney disease	29	(60.42)

Table 1: Baseline characteristics of the patients included in the study.

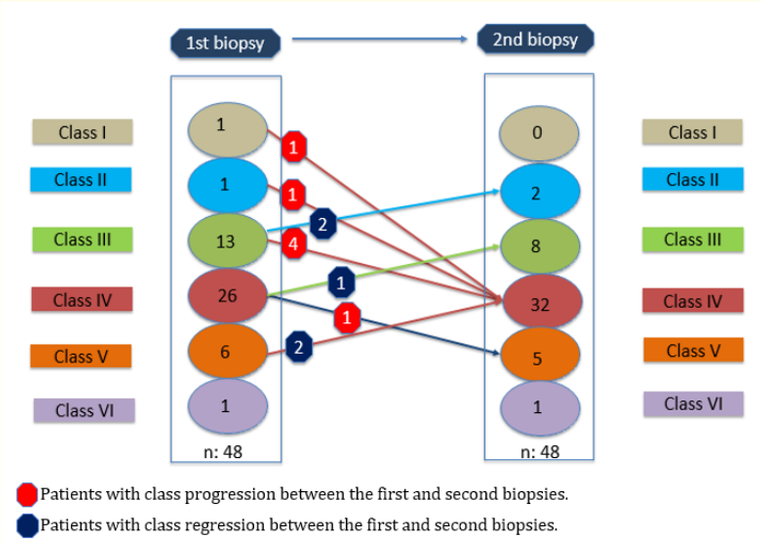

Figure 1: Histological class changes between the first and second biopsies.

Class transitions between the first and second biopsies are shown in Table 2. Table 3 shows the median (IQR/R) of the parameters analyzed in the patients at the time of the first and second biopsies. Significant differences were found in the chronicity index, which was higher at the time of the second biopsy (p-value < 0.001). Creatinine values were also significantly higher at the time of the second biopsy (p-value = 0.007). Complement C4 values also increased significantly between the first and second biopsies (p-value = 0.005). Furthermore, significant differences were found in glomerular filtration rate and proteinuria; however, in these cases, the values decreased between the first and second biopsies (p-values: 0.002 and 0.035, respectively).

The other clinical parameters analyzed, such as hemoglobin, hematocrit, platelet count, blood glucose, urea, urea nitrogen, sodium, potassium, urinary density, bacteria in urine, leukocytes in urine, protein in 24-hour urine, coagulation times, and C3 complement values, had no statistically significant changes between the first and second biopsies.

Of the 48 patients included in the study, 2 had complete clinical response (4.1%), 9 had partial response (18%), and 37 had no clinical response (77%).

Table 4 shows the classification of patients according to the presence or absence of hematuria (>3 red blood cells/field) and anti-DNA antibodies. Although slight changes were observed in both variables between the first and second biopsies, they did not achieve statistical significance (p-values: 0.2301 and 0.773, respectively).

Class at first biopsy n: 48	Class at second biopsy									
	Class 2 n: 2		Class 3 n: 8		Class 4 n: 32		Class 5 n: 5		Class 6 n: 1	
Class 1 (n: 1)	0	(0.00)	0	(0.00)	1	(100.00)	0	(0.00)	0	(0.00)
Class 2 (n: 1)	0	(0.00)	0	(0.00))	1	(66.67)	0	(0.00)	0	(0.00)
Class 3 (n: 13)	2	(15.38)	7	(53.85)	4	(30.77)	0	(0.00)	0	(0.00)
Class 4 (n: 26)	0	(0.00)	1	(3.85)	24	(92.30)	1	(3.85)	0	(0.00)
Class 5 (n: 6)	0	(0.00)	0	(0.00)	2	(33.33)	4	(66.67)	0	(0.00)
Class 6 (n: 1)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(100.00)

Table 2: Distribution of patients according to lupus class between the first and second biopsies.
The number of patients who had LN class changes is highlighted.

Laboratory Median (IQR)/(R)	First biopsy	Second biopsy	95% CI (1)	p-value
Activity index	6 (3.00 - 8.00)/(0.00 -16.00)	6 (2.50 - 8.00)/(0.00 - 16.00)	(-2.00; 2.00)	0.960
Chronicity index	2 (0.00 - 3.75)/(0.00 - 24.00)	3.5 (2.00 - 6.00)/(0.00 - 24.00)	(-3.00; -1.50)	<0.001(*)
Hemoglobin	10.5 (9.05 - 12.70)/ (6.90 - 18.60)	10.9 (9.47 - 12.37)/(6.10 - 19.10)	(-0.45; 0.60)	0.751
Creatinine	1.455 (0.91 - 1.87)/(0.33 - 3.60)	1.6 (1.00 - 2.37)/(0.50 - 6.00)	(-0.79; -0.10)	0.007(*)
Urea	55.3 (32.28 - 83.75)/(14.00 - 199.00)	58.95 (39.95 - 87.25)/(16.40 - 194.00)	(-12.60; 6.60)	0.532
Glomerular filtration rate	51.1 (35.67 - 76.98)/(16.70 - 231.00)	43.65 (25.05 - 67.18)/ (8.20 - 139.60)	(3.95; 16.60)	0.002(*)
Urine pH	7 (6.00 - 7.00)/(5.00 - 44323)	6 (6.00 - 7.00)/(5.00 - 44322)	(-0.50; 2.25)	0.363
Urine protein	200 (100 - 337.50)/(25.00 - 600)	100 (32.50 - 275.00)/(10.00 - 600.00)	(5.00; 198.90)	0.035(*)
Urine leukocytes	2 (2.00 - 6.00)/(0.00 - 60.00)	0 (0.00 - 2.00)/(0.00 - 60.00)	(0.00; 4.00)	0.068
Urine protein 24 h	1.969 (937 - 4157)/(150 - 39520)	1.827 (873 - 4123)/(247 - 16660)	(-352; 1089.50)	0.362
C3 Complement	73 (45.75 - 115.78)/(1.90 - 240.00)	68 (57.00 - 90.75)/(25.00 - 136.00)	(-4.30; 18.50)	0.177
C4 Complement	12 (7.70 - 19.00)/(0.45 - 42.70)	15.5 (11.25 - 23.50)/(8.00 - 48.80)	(-7.15; -1.50)	0.005(*)

Table 3: Laboratory parameters in the first and second biopsies.
(1) Confidence interval for the median of the paired differences (first biopsy–second biopsy), (*) Significant at 5%.

		Second biopsy result n: 48				p-value
		Positive		Negative		
First biopsy result n: 48	Hematuria					
	Positive	8	(33.33)	16	(66.67)	*0.230*
	Negative	9	(37.50)	15	(62.50)	
	Anti-DNA					
	Positive	28	(80.00)	7	(20.00)	*0.773*
	Negative	5	(38.46)	8	(61.54)	

Table 4: Distribution of patients according to the presence of hematuria and anti-DNA in both biopsies.

Discussion

The manifestations of SLE are quite varied [13,14], and up to 70% of the patients may have kidney involvement [10]. However, the symptoms of LN can be subtle. Diagnosis is made mainly through urinalysis, and the evaluation of creatinine and calculation of renal function are also important. Also, proteinuria should be evaluated and, according to its results, a renal biopsy should be performed in patients with proteinuria >500 mg/dl and no other changes or proteinuria and hematuria with impaired renal function that cannot be attributed to any other cause.

The diagnosis of SLE can be made according to its clinical characteristics, including its rheumatological, cutaneous, and renal manifestations. The diagnosis can also be made based on serological findings, such as ANA (10). Furthermore, it can be made based on the classification criteria of the ACR, according to which ≥4 of the 11 clinical and/or serological criteria must be met. The Systemic Lupus International Collaborating Clinics Research group introduced a new set of classification criteria, where ≥4 of 17 criteria must be met [10,15].

LN is a complication of SLE, which implies high morbidity for patients, with a greater predisposition to developing chronic kidney disease and the requirement for renal replacement therapy. It is also important to consider that patients with LN have a higher rate of mortality and die earlier than those with SLE without LN, which makes it imperative to diagnose this pathology in patients with SLE [6].

According to a study by Aroca., *et al*. the presentation of LN in the Colombian Caribbean is aggressive and refractory to treatment. This study reported that consecutive renal biopsy shows the persistence of the activity of the lesions and is a tool that enables improving the assessment of response to the treatment [7].

Nossent., *et al*. demonstrated that only a chronicity index of >3 is predictive of lower renal survival, whereas an age of >31 years at biopsy and a chronicity index of >3 are associated with lower patient survival. Clinical renal function tests are not reliable for discriminating between active lesions and chronic kidney damage [23,24].

Renal biopsy is the diagnostic method for LN [6,12]. Considering that chronic kidney disease and end-stage kidney disease are often the first manifestations of SLE, it is important to try to identify those patients who are at risk or those who are likely to suffer from LN so that an immediate renal biopsy [6] can be performed as many times as needed.

Renal biopsy is important to identify the nature of renal involvement [16], considering that there are other mechanisms that result in renal injury, which can only be diagnosed via renal biopsy. However, immune complex-mediated glomerulonephritis is the most common cause and requires a different management. This is the case of thrombotic microangiopathy and lupus podocytopathy [6].

There is a classification for biopsy reading and understanding: "the ISN/RPS system classifies LN based on where immune complexes accumulate within the glomeruli, the presence or absence of mesangial or endocapillary proliferation, the general extent of the glomerular involvement (focal or diffuse) and glomerular injury (global or segmental), and whether the glomerular injury is active (inflammatory) or chronic (sclerotic)" [6].

Patients in this study underwent a second renal biopsy based on clinical criteria, and all patients received treatment under the EUROLUPUS regimen from the moment of diagnosis of LN and according to relapses.

In a systematic review by Narváez., *et al.* which was based on 686 well-documented cases of patients with rebiopsies performed on clinical indications alone, the pathologic class transformation rate ranged from 40% to 76% of the cases (mean 53%). The results of the rebiopsy led to a change in immunosuppressive treatment in 18%-79% of the patients (mean 57% of cases), thus intensifying it in most cases (between 18% and 60.5%; mean 39%) but also reducing it by 5%-30% [25,27].

This finding was similar in our study group where it was observed that of the total of 48 patients, 1 patient belonged to class I and 1 patient belonged to class II in the initial biopsy. Both patients (100% of the patients in initial stages) had a significant class progression in the consecutive biopsy toward class IV, (Figure 1), thereby leading to a worse renal prognosis and a change in the established treatment. This finding confirms the importance of rebiopsy in patients with LN who are in early stages in the first renal biopsy, as proposed in other studies. For instance, in the study by Narváez., *et al,* 78% of the patients in class I and II in the initial biopsy changed to class III or IV in a subsequent biopsy [27].

However, in our study, we were able to observe a class progression in 30.7% of the patients with initial class III, who progressed to class IV in the control biopsy, whereas 15% regressed to class II. A class IV regression was observed in only 1 patient (3.8%) toward class III, which does not imply any degree of greater clinical importance given that the proposed treatment for both classes (III and IV) would be the same [28,29].

No significant changes were observed in the activity index (AI) during the first and second kidney biopsies in our study. This is contrary to the findings reported by Malvar., *et al*. who assessed 69

consecutive patients who had undergone a rebiopsy after 6 months of induction therapy. They found a significant improvement in AI between the two biopsies. However, among those with a complete renal response, only 50% had an AI of ≤3 and 29% had an AI of ≥5 [17]. In our study, there was a significant change in the index of chronicity, which was higher at the time of the second biopsy, from an average index of 2 to 3.5 (p-value < 0.001) (Table 3).

Regarding the correlation between clinical and histological findings, there was class progression in 14.5% of the patients in our study. It is remarkable that there was a 57% change from non-proliferative classes to proliferative classes (100% of class I and II patients and 40% of class V patients changed to class IV), thus observing a significant increase in creatinine values at the time of the second biopsy from 1.4 to 1.6 (p-value = 0.007). Also, C4 complement values increased significantly during the period between the first and second biopsies from 12 to 15.5 (p-value = 0.005).

Significant differences were also found in the glomerular filtration rate and urinary protein in our study. In these cases, the values decreased between the first and second biopsies (p-values = 0.002 and 0.035, respectively), contrary to what was observed in another study where, among the patients who achieved a complete histological remission (AI of 0), 62% showed residual proteinuria >500 mg/day. These results indicate a discrepancy between clinical and histological remissions in LN [17].

We determined that leukocyturia disappears in the second biopsy and that there is a decrease in urinary pH. Although these results were not statistically significant, we can suggest that there is a decrease in these parameters owing to a lower presentation of nephritis and an improvement in tubular function with increased capacity for urine acidification during the second kidney biopsy.

In a prospective study involving 36 patients to assess the usefulness of consecutive renal biopsy in patients with complete clinical remission for at least 12 months who had received at least 36 months of immunosuppression, patients were followed up prospectively for LN flares over 24 months. LN flares occurred in 11 patients, and 10 of them had residual histologic activity in the second biopsy. All patients with a National Institutes of Health AI >2 had a relapse of LN [30,31].

The AI and duration of SLE were independent predictors of flare up [31].

A repeat renal biopsy may be useful to monitor maintenance immunosuppression in LN, and patients in histological remission may be eligible for treatment withdrawal [31].

It is noteworthy that our study was retrospective and that the clinic where it was performed was not standardized to perform biopsy as per protocol in LN. Therefore, it was not possible to correlate the histological findings with patients who exhibited a stable clinical progress.

As mentioned by Aroca, LN is aggressive and refractory to treatment in the Colombian Caribbean [7]. In this investigation, we were able to determine that a large part of the patients were nonresponders (77%), whereas 18% had a partial clinical response and only 4.5% had a complete response. It was determined that one of the greatest inconveniences, and at the same time a determinant of poor prognosis, was the lack of continuity of clinical follow-up and noncompliance with treatment by patients, whether for financial reasons, difficulty in accessing health services, or lack of patient education. A guideline was established based on these findings for reducing patient absenteeism with permanent communication networks, active search for the patient, and transportation or maintenance subsidies, if required, to guarantee follow-up and treatment compliance.

Conclusion

Consecutive renal biopsy in LN allows early identification of the progress of the histopathological lesion. In this study, 30.7% of class III patients in their first renal biopsy presented histological progress toward class IV in their consecutive biopsy. This procedure would be of immense clinical importance for offering optimal treatment to these patients.

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