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Consecutive renal biopsy in a cohort of patients with lupus nephritis of the Colombian Caribbean

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ABSTRACT

Background: Renal biopsy is the gold standard for the diagnosis and classification of lupus nephritis (LN). However, a consecutive biopsy can predict the clinical course and optimize the therapeutic strategies.
Objectives: To compare the histopathological findings with clinical responses.
Patients and Methods: Thirty patients with active LN were included. Renal biopsies were performed at the time of diagnosis and subsequently under clinical criteria according to consensus of Spanish Society of Nephrology. The response to treatment was defined as complete response, partial responder or non-responder. The histological change in second biopsy towards LN classes I, II or III/IV-C was defined as histological response (HR).
Results: In initial renal biopsy, 28 (93%) patients showed proliferative LN; III-A or A/C (n; 7), IV-A or A/C (n: 19) and mixed; III+IV/V (n; 2). LN class V was presented in two cases. The clinical response was; complete response (10%), partial response (20%), and non-response (70%). HR was manifested in 37% and non-histologic response in 63% of patients. Around 33% of patients with complete response/partial response showed active lesions in the consecutive renal biopsy.
Conclusions: In Colombian Caribbean, LN is aggressive and refractory to treatment. The consecutive renal biopsy allowed to demonstrate the persistence of the activity of the lesion in almost half of the patients, which may provide additional information to create better response criteria. The consecutive renal biopsy is a tool that allows improving the evaluation of the response to treatment in the LN.

Implication for health policy/practice/research/medical education:
This research presents evidence on the need to protocolize the consecutive biopsy to incorporate the results of the histopathology to the clinical follow-up of the patient.

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1. Background

Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematosus (SLE), and is associated with a high morbidity and mortality. Its clinical evolution is characterized by periods of remissions and relapses (27%–66%), with a variable course. The

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prognosis linked to immunological, hormonal, genetic and environmental factors (1-4).

Renal biopsy is the golden standard for the diagnosis, classification and treatment of LN according to histopathological findings. The relationship between the histology and the clinical evolution of LN is very well documented.

Patients with proliferative LN (classes III and IV) are characterized by severe impairment of renal function with a risk of developing chronic kidney disease stage 5 (CKD-5) higher than 50% compared with non-proliferative classes (I, II and V) (1,4).

Lightstone L, states that consecutive renal biopsies should be a standard procedure to define the response after immunosuppressive treatment. To identify those patients who require a more prolonged or intensive therapy and likewise, to avoid overtreatments (5).

Patients with LN classes I or II receive supportive treatment, while those with proliferative or mixed classes require immunosuppressive agents to induce remission of the inflammatory activity, reduce relapses and prevent progression into renal failure.

Treatment of class VI, does not include cytotoxic agents (6). The combination of histological and clinical findings is the best way to define the response to treatment in patients with LN (7).

Hill et al demonstrated that the initial renal biopsy for the diagnosis of LN offers little information on the long-term renal survival, whereas a biopsy performed after six months of the induction therapy allows to predict the clinical course of the disease. However, there is no consensus, when second renal biopsy should be carried out routinely during follow-up (8,9).

2. Objectives

Patients with LN in whom a consecutive renal biopsy was indicated were evaluated in the present study. The objective is to compare the histopathological findings with the clinical response and thus evaluate the contribution of the consecutive renal biopsy in LN.

3. Patients and Methods

3.1. Study design

This is an observational, analytical and retrospective study. Of 400 patients with a diagnosis of LN belonging to the Registry of Nephropathy of Colombia (NEFRORED©),(10) 30 patients (60 biopsies) who underwent a first biopsy and a second biopsy were included to the study. All patients were assessed by the Department of Nephrology between 2008 and 2017. The diagnosis of SLE was made based at least on four diagnostic criteria of the ACR (American College of Rheumatology), including positivity of antinuclear antibodies (ANA) and/or anti-double stranded DNA antibodies (Anti-dsDNA) (11).

3.2. Criteria for renal biopsy

First renal biopsy, was indicated, according to the consensus of the group of systemic autoimmune diseases (GEAS) of the Spanish Society of Nephrology (SEN) (12) for patients with SLE who had unexplained deterioration of renal function, confirmed proteinuria greater than 500 mg/24 hours and/or active urinary sediment (red blood cells ≥5 per field; leukocytes ≥5 per field). Excluding factor for indication of first renal biopsy was presence of triggering factors for acute kidney injury of toxic, prerenal or obstructive type.

The indications for second biopsy were; 1) an increase or reappearance of proteinuria, nephrotic syndrome or active sediment, 2) an increase in serum creatinine or unexplained deterioration in renal function, 3) refractoriness to immunosuppressive treatment or 4) uncertainty regarding the degree of activity/chronicity of renal lesions to decide to change the treatment (12).

3.3. Evaluation of renal function and immunology

For analysis of the renal function were included serum creatinine (mg/dL), the estimation of glomerular filtration rate (eGFR) through the MDRD (Modification of Diet in Renal Disease) formula and the measurement of proteinuria in 24 hours (g/24 h). CKD was defined as an eGFR <60 mL/min (13). The immunological analysis consisted of the measurement of anti-DNA antibodies and C3/C4 complements through the techniques of antibodies by indirect immunofluorescence (IFA) and nephelometry, respectively.

3.4. Histopathology

All renal biopsies were classified by the nephropathologist of the institution, blinded for clinical and laboratorial data. The samples were analyzed by light microscopy and immunofluorescence using standard techniques. The activity and chronicity indexes were quantified through the scoring system developed by the National Institute of Health (NIH). A score from 0 to 3+ (absent, mild, moderate or severe) was assigned to each lesion. The values of necrosis, karyorrhexis and cell crescents were multiplied by a factor of 2. The maximum score for the activity index was 24 points and for the chronicity index was 12 points (4). The histopathological classification of LN was carried out according to the Society of Nephrology/Renal Pathology Society (ISN/RPS) (14).

3.5. Response criteria

The patients in this study were classified taking into account the clinical response criteria established by the ACR according to the proteinuria in 24 hours, eGFR and the urinary sediment in the following remission groups: 1) complete remission (CR); patients with proteinuria ≤0.5 g/24 hours, eGFR ≥60 mL/min/1.73 m^2 (or decrease to initial values or ±15% of the baseline value in those with glomerular filtration rate <60 mL/min/1.73 m^2 and inactive urinary sediment (leukocytes <5 and red blood cells < 5 per high-power field). 2) partial remission (PR); in patients with a baseline proteinuria ≥3.5 g/24 h, or a decrease in proteinuria <3.5 g/24 h. Additionally in those with values <3.5 g/24 h, a reduction of proteinuria >50% compared with the baseline. Stabilization (±25%) or improvement of the eGFR with respect to initial values. 3) finally patients with no remission (NR) were individuals who do not meet the above criteria (12).

In addition, a histopathological response was included. The persistence of LN classes III/IV-A or A/C and the transformation into class V were defined as non-histological response (NHR), while the change into LN classes I, II or III/IV-C was defined as histological response (HR).

3.6. Treatment

All patients in this study were induced with intravenous cyclophosphamide (CPA) (500 mg) bimonthly during three months (six pulses in total) or mycophenolate mofetil (MMF) (2-2.5 g/d) for 6 months. Corticosteroids (prednisone) were initiated at 1 mg/kg/d (maximum 60 mg/d) for 15 days and then decreased every 15 days until reaching 10 mg/d. The patients received 500 mg of intravenous methylprednisolone daily for three days in case that they debuted with activity. In addition, all patients received angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists (ARA-II). The administration of antimalarial agents was concomitant in all patients. The duration of induction therapy was 6 months. This cycle was restarted in those patients who evidenced, the persistence of high activity levels in the consecutive renal biopsy and/or presence of nephrotic syndrome or decreased renal function. In these cases, the patients who received CPA for induction were switched to MMF and vice versa.

Maintenance therapy consisted of MMF (1.5-2 g/d) or azathioprine (AZA) (2 mg/kg/d). Individuals showed clinical improvement and HR in consecutive renal biopsy, continued with 10 mg/d of prednisone for 6 months with progressive reduction to 5 mg/d (12).

3.7. Ethical issues

This study was carried out in accordance with the Declaration of Helsinki. This study was approved by the Bioethics Committee of the Clínica de la Costa, in the city of Barranquilla, Colombia. All patients gave their informed consent to be included in this study.

3.8. Statistical analysis

The data are expressed as medians and interquartile ranges. The simple correspondence analysis was used to determine the association between variables. The χ^2 test was used to evaluate the difference in means between two groups. A *P* value <0.05 was defined to be considered as statistically significant. The analysis were carried out in the statistical package of R Project (15).

4. Results

4.1. Outcomes in first biopsy

4.1.1. Histopathology and renal function

Of total of patients (n = 30), 26 (87%) were women. Around 28 (93%) had LN of proliferative classes; III-A or A/C (n = 7), IV-A or A/C (n = 7) and mixed: III+IV/V (n = 2). LN of class V was presented in (n = 2) cases. None of the cases had advanced sclerosing lesions (class VI). The average activity index was 6 (range 2-14) and the mean chronicity index was 2 (range 0-7).

The mean serum creatinine was 1.5 mg/dL (range 0.6-3.6). About 76% of patients showed an eGFR <60 mL/min. The average proteinuria in 24 hours was 1.9 g (range 0.3-5.7).

4.1.2. Immunology

Anti-dsDNA antibodies were detected in all patients, with an average of 194 UI/ml (range 70-285). Around 66% had C3 hypocomplementemia, [mean C3 = 75 mg/dL (range 22- 135)] and C4 complement was low in 63% of patients. The clinical, laboratorial and histological parameters at baseline and during follow-up are shown in Table 1.

4.2. Outcomes in second biopsy

4.2.3. Histopathology and renal function

The average time elapsed to the second biopsy was 2.2 ± 1.5 years and revealed LN class I (n = 0), class II (n = 2), class III-C (n = 5), class IV-C (n = 4), class III-A or A/C (n = 0), class IV-A or A/C (n = 12), class III+IV/V (n = 2) and class V (n = 5) (Table 1).

In initial first biopsy of patients with LN of class IV 19/30 (63%), we found10/19 cases persisted with active lesions in the second biopsy. Within the LN of class III 7/30 (23%), only 2/7 cases changed into LN class II. It

Table 1. Clinical, laboratorial and histological parameters in first and second renal biopsies

Variables	First biopsy	Second biopsy	*P* value
Female	26 (87%)	-	-
Male	4 (13%)	-	-
Age	34 (20 - 62)	-	-
Proteinuria (g/24 h)	1.9 (0.3 – 5.7)	1.7 (0.2 – 4.2)	NS
Creatinine (mg/dL)	1.5 (0.6 – 3.6)	1.7 (0.6 – 5.8)	NS
eGFR (ml/min/1.73 m^2)	51.1 (16.7 - 132.9)	48.8 (9.6 - 118)	NS
C3 (mg/dL)	75 (22 - 135)	68 (25 - 120)	NS
C4 (mg/dL)	16 (5 - 38)	15 (6 - 25)	NS
Anti-dsDNA (IU/mL)	194 (70 - 285)	213 (152 - 299)	NS
Histological Class (ISN/RPS)			
I-II	-	2	-
III A or A/C	7	-	-
III C	-	5	-
IV A or A/C	19	12	-
IV C	-	4	-
III+ IV/V	2	2	-
V	2	5	-
Activity index	6 (2 - 14)	5 (1 - 16)	<0.013
Chronicity index	2 (0 - 7)	3 (0 - 8)	<0.004

Abbreviation: eGFR, estimation of glomerular filtration rate; C3, complement component 3; C4, complement component 4; ISN/RPS, International Society of Nephrology/Renal Pathology Society classification.

was also detected that 2/30 (6%) cases with mixed LN changed to class V, while there were no changes in LN class V by the second biopsy. The overall percentage of transformation into non-proliferative classes was 6%. All histopathological changes are shown in Table 2.

The activity index decreased ($P<0.013$), while there was an increase in the chronicity index ($P<0.004$). There was an increase in serum creatinine ($P>0.05$) and a reduction of protein excretion in 24 hours without statistical significance ($P>0.05$). Around 76% of patients exhibited an eGFR <60 mL/min.

4.2.4. Immunology

Anti-dsDNA antibodies increased by the second biopsy without statistical significance ($P>0.05$). The C3 and C4 complement levels decreased ($P>0.05$) and remained low in 40% and 46% of patients, respectively.

4.3. Clinical and histopathological response

Clinical response (complete response or partial response) was evidenced in 9 (30%) patients at the time of the second biopsy. Complete response was observed in 3 (10%) patients and 6 (20%) had partial response while 21 (70%) no remission. There were significant differences in the 24-hour proteinuria, the eGFR and the C3/C4 complement during the baseline and the follow-up in the patients with no remission versus partial response/complete response. The association between the clinical response and the laboratorial and histological parameters at the time of the second biopsy is shown in Table 3.

Of three cases with complete response, 33% showed non-histologic response while 6 cases had partial response. Additionally, 66% were non-histologically responded. Non-responder patients 21/30 (70%), 14 (46%) also showed non-histologic response. However, 5/14 (35%) of the cases did not have active lesions in second biopsy. About 33% of the patients with complete response/partial response evidenced active lesions in the consecutive renal biopsy.

HR was observed in 11 (36%) patients and non-histologic response in 19 (63%). In the non-histologic response group, the second biopsy showed predominance of proliferative and mixed LN (n = 14) compared with non-proliferative (n = 5). LN class III-C (n = 5) was the most frequent within the group of histologically responded. The non-histologic responded patients showed higher levels of proteinuria ($P=0.004$) and anti-dsDNA ($P>0.05$) compared with the histologically responded cases. High levels of anti-dsDNA were evidenced in 6/11 histologically responded patients.

5. Discussion

Renal biopsy is the cornerstone for the diagnosis and classification of LN, however, consecutive renal biopsy

Table 2. Histopathological changes from the first biopsy to the second biopsy according to classification (ISN/RPS)

First biopsy	Second biopsy		
	I/II or III/IV C (n=11)	III/IV A or A/C ± V (n=14)	V (n=5)
III A or A/C (n=7)	6	1	0
IV A or A/C (n=19)	5	13	1
V (n=2)	0	0	2
III-IV/V (n=2)	0	0	2

A, active lesions; A/C, active and chronic lesions; C, chronic lesions; ISN/RPS, International Society of Nephrology/Renal Pathology Society classification.

Table 3. Comparison between the clinical response and laboratorial and the histopathological parameters at the time of the second biopsy

	NR (n=21)	PR (n=6)	Complete response (n=3)	*P* value
Laboratorial parameters				
Creatinine (mg/dl)	2.0 (0.6–5.8)	1.4 (0.8–1.9)	0.8 (0.7–1.0)	NS
Proteinuria (g/24 h)	2.0 (0.8- 4.2)	1.7 (0.7- 3.5)	0.3 (0.3- 0.3)	0.0131
eGFR (mL/min/1.73 m²)	41.1 (9.6–118.4)	55.7 (42.8–92.7)	89.2 (67.5–104.8)	0.0045
C3 (mg/dL)	62.5 (25.0–95.0)	68.0 (58.0–95.0)	110.0 (100.0–120.0)	0.0004
C4 (mg/dL)	15.0 (6.0–24.0)	14.2 (10.0–18.0)	22.4 (18.0–25.0)	0.0183
Anti-dsDNA (IU/mL)	214.0 (152.0–287)	15.5 (6.0–25.0)	186.0 (168.0–208.0)	NS
Histological class (ISN/RPS)				
I-II	0	0	2	-
III/IV (C)	7	2	0	-
III/IV (A) or (A/C)	9	2	1	-
III/IV (A)+V	2	0	0	-
V	3	2	0	-
Activity index	6.3 (2.0–14.0)	4.0 (2.0–8.0)	7.3 (2.0–12.0)	NS
Chronicity index	3.7 (0.0–7.0)	1.3 (1.0–2.0)	4.3 (1.0–8.0)	NS
HR, n	7	2	2	-
NHR, n	14	4	1	-

A, active lesions; A/C, active and chronic lesions; C, chronic lesions; ISN/RPS, International Society of Nephrology/Renal Pathology Society classification; eGFR, estimation of glomerular filtration rate; C3, complement component 3; C4, complement component 4; NR, no response; PR; partial response; CR, complete response; HR, histological response; NHR, no histological response.

during the follow-up of the patient is not very frequent (16). In this study, consecutive renal biopsies were performed in patients with LN according to clinical criteria.

Currently, there is no consensus indicating when the renal biopsy should be performed routinely during follow-up. However, three types of key moments for the performance of the renal biopsy have been proposed; 1) Post-induction biopsy, also known as protocol biopsy, is performed after six months of induction therapy, 2) biopsy during maintenance treatment in an average of 12-42 months and 3) biopsy by clinical criterion with a mean of 2-5 years (8,9).

The clinical importance of the consecutive renal biopsy is based on the great prognostic value that it provides when determining the persistence of active lesions and the progression of chronic damage (16). The presented clinical and histopathological are discordant as indicated in other series (7,17,18). In our study, it was detected a persistence of active lesions in the renal histology despite the clinical response in almost half of patients, while in a group of non-responders to treatment patients, no active lesions were found in the consecutive renal biopsy. Alsuwaida et al (18) demonstrated that the finding of activity in consecutive renal biopsies after 12-18 months despite clinical response, is a predictor of poor renal survival in an average of 8.7 years. Our findings show the importance of extending the follow-up of the patients

to evaluate the long-term renal survival.

The persistence of high activity and chronicity indexes is associated with a poor renal survival (7,8,17,19). In this study, the chronicity index increased significantly by the second biopsy. Moroni et al (19) demonstrating that an increase of one unit in the value of the chronicity index means an increase of 20% in serum creatinine.

Proteinuria is one of the most used biomarkers to evaluate the activity in LN (12,20). In this study we found the non-histologic responded patients had proteinuria levels higher than the HR, in concordance with the finding of Gunnarsson et al (21) Anti-dsDNA antibodies have been previously studied for their association with the frequency of relapses in lupus (22,23). It was found that, the cases of non-histologic responded had high levels of anti-dsDNA. In contrast, histopathological responded patients also evidenced high levels of Anti-dsDNA. The explanation for histopathological responded with persistence of immunological abnormalities is still not clear, but it may reflect the latency between resolution of inflammation and recovery of the renal tissue (17). Therefore, it is necessary to evaluate the renal function of patients with LN through biomarkers that are closer to the renal inflammatory activity (20,24,25), because in our study, common biomarkers such as proteinuria, anti-dsDNA, and C3/C4 complement are not reliable in LN. The terms histopathological responded and non-histologic responded have not yet been included in a general consensus and have been used infrequently. The transformation into class V represents an active LN that requires therapeutic intervention and may be a subject of discussion, whether or not it should be considered as histopathologically responded (7). The change of focal proliferative lesions (class III) into diffuse lesions (class IV) may indicate the progression of the same type of nephritis but not the transition of different classes. The difference between both is based on determining the percentage of glomeruli (</>50%) with proliferative lesions, which can bias the sampling, mainly in biopsies with percentages close to 50 (16). The overall percentage of histological changes into non-proliferative classes was 6%, similar to other series (7,16,17). Our study has the limitation of the predominance of LN of proliferative over non-proliferative classes, which makes difficult the comparison between both outcomes.

The main objective of treatment in LN is to preserve renal function and prevent progression into chronic kidney failure (4). Although mortality in LN has improved, the survival of renal function is stationary (7). The LUMINA (Lupus in Minorities: Nature versus Nurture) cohort has demonstrated higher frequency and severity of LN in Afro-descendant (51%) and Hispanic (43%) patients compared with Caucasian (14%) (26). In this study, more than half of patients showed CKD both in the initial and in the consecutive biopsies. In our environment, multi-ethnicity and the high frequency of LN of proliferative classes have influenced on poor outcomes (1,27,28).

6. Conclusions

In conclusion, "in Colombian Caribbean, LN is aggressive and refractory to treatment", consecutive renal biopsy allowed to demonstrate the persistence of activity of the lesions in almost half of the patients, which can provide additional information to create better response criteria. The consecutive renal biopsy is a tool that allows to improve the evaluation of the response to treatment in LN.

Limitations of the study

The main limitation of the study was the collection of the samples since it is not protocolized to perform a consecutive biopsy, which depends mainly on the criteria of the treating nephrologist.

Authors' contribution

AMG; concept, design and approval of the final manuscript. JMJ; experiments, analysis of information and draft of the manuscript. GTH; design of the experiments, data analysis and final draft design. DVA; data collection and information analysis. MBA; data collection and information analysis. NQE; data collection and information analysis. GTR; Pathological Analysis of the slides and histology. CPL; pathological analysis of the slides and histology. GMC; pathological Analysis of the slides and histology. CBA; design and approval of the final manuscript. All the authors approved the final manuscript and agreed to its publication.

Conflicts of interest

The authors declared no conflicts.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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