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The value of repeat biopsy in lupus nephritis flares

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Abstract

Whether a repeat renal biopsy is helpful during lupus nephritis (LN) flares remains debatable. In order to analyze the clinical utility of repeat renal biopsy in this complex situation, we retrospectively reviewed our series of 54 LN patients who had one or more repeat biopsies performed only on clinical indications. Additionally, we reviewed 686 well-documented similar cases previously reported (PubMed 1990–2015).

The analysis of all patients reviewed showed that histological transformations are common during a LN flare, ranging from 40% to 76% of cases. However, the prevalence of transformations and the clinical value of repeat biopsy vary when they are analyzed according to proliferative or nonproliferative lesions.

The great majority of patients with class II (78% in our series and 77.5% in the literature review) progressed to a higher grade of nephritis (classes III, IV, or V), resulting in worse renal prognosis. The frequency of pathological conversion in class V is lower (33% and 43%, respectively) but equally clinically relevant, since almost all cases switched to a proliferative class. Therefore, repeat biopsy is highly advisable in patients with nonproliferative LN at baseline biopsy, because these patients have a reasonable likelihood of switch to a proliferative LN that may require more aggressive immunosuppression.

In contrast, the majority of patients (82% and 73%) with proliferative classes in the reference biopsy (III, IV or mixed III/IV+V), remained into proliferative classes on repeat biopsy. Although rebiopsy in this group does not seem as necessary, it is still advisable since it will allow us to identify the 18% to 20% of patients that switch to a nonproliferative class. In addition, consistent with the reported clinical experience, repeat biopsy might also be helpful to identify selected cases with clear progression of proliferative lesions despite the initial treatment, for whom it is advisable to intensify inmunosuppression. Thus, our experience and the literature data support that repeat biopsy also brings more advantges than threats in this group.

The results of the repeat biopsy led to a change in the immunosuppresive treatment in more than half of the patients on average, intensifying it in the majority of the cases, but also reducing it in 5% to 30%.

Abbreviations: anti-dsDNA = anti-dsDNA antibodies, ISN/RPS = International Society of Nephrology/Renal Pathology Society, LN = lupus nephritis, SD = standard deviation, SLE = systemic lupus erythematosus.

Keywords: lupus nephritis, renal biopsy, repeat renal biopsy, systemic lupus erythematosus

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1. Introduction

Lupus nephritis (LN) remains a common complication and major determinant of outcome in systemic lupus erythematosus (SLE). Today, a baseline renal biopsy is highly recommended for all subjects with suspected LN. Biopsy allows the clinician to recognize and classify the type of renal involvement, assess its activity, and thus guide the intensity of treatment.[1,2]

LN flares represent a significant problem because of the potential for cumulative damage that may lead to deterioration of renal function even after a successful treatment.[3] The pathological class of LN may change to a different class during a disease flare.[2,3] Therefore, repeat renal biopsy has attracted much attention and its clinical relevance has been evaluated by a number of studies. However, whether a repeat renal biopsy is helpful in patients with suspicion of renal flare remains debatable, since some authors have proposed that patients with proliferative lesions on their original biopsy rarely switch to a pure nonproliferative nephritis during a flare and, in these cases, appropriate treatment adjustments can be based only on clinical and biologic signs and symptoms without additional biopsy.[2–6] This approach is reinforced because clinical studies support that mycophenolate mofetil with glucocorticosteroids can be used for induction and maintenance treatment in all of the serious forms of LN (class III, IV, and V), thus making it possible to eliminate the need to differentiate between each histological class of LN.[2–6]

In the present study, we retrospectively reviewed our series of LN patients who had one or more repeat renal biopsies perfomed only based on clinical indications in order to assess the rate of pathological class transformation and the changes in the intensity of treatment decided based on the results of the repeat biopsy. Whether repeat renal biopsies have a prognostic value was not addressed in the present study. Current evidence of the value of repeat renal biopsy in this complex situation is also analyzed through a systematic review of the English-language literature, based on a PubMed search.

2. Methods

2.1. Patient selection

The sample consised of 429 patients with SLE (from Internal Medicine, Nephrology, and Rheumatology departments; all fulfilling the American College of Rheumatology classification criteria)[7] treated between 1988 and 2014 at the Hospital Universitario de Bellvitge (Barcelona, Spain), a referral tertiary care hospital that does not attend to pediatric populations. Patients were registered in a specific database (ACHILLES project).

From a total of 190 patients with LN, we selected for analysis 54 patients with 2 or more renal biopsies. Renal biopsy was repeated only on the basis of one of these clinical indications: increase, persistence, or recurrence of proteinuria, nephrotic syndrome, or active urinary sediment (hematuria and/or cellular casts), or increase in serum creatinine level or unexplained progression to renal failure. This study did not include patients with protocol biopsies performed to evaluate the response to therapy.

Medical records were reviewed, and clinical, laboratory, and treatment data were obtained from each patient. Data were collected retrospectively. Laboratory values, such as serum creatinine, albumin, urea, proteinuria, complement levels (C3 and C4), and antidouble-stranded DNA antibody (anti-dsDNA) titer, were selected during the 3 months before and the month after the renal biopsy was performed. Anti-dsDNA antibodies were determined using both fluorescence enzyme immunoassay (FEIA) and immunofluorescence on *Crithidia luciliae*.

Treatment regimens were determined by the referring physician. Treatments more frequently used for induction in proliferative classes were cyclophosphamide, azathioprine, or mycophenolate. For maintenance, the more frequently used drugs were mycophenolate or azathioprine. We considered a treatment change when the immunosuppressive treatment was modified after the renal biopsy (drug change, drug addition, or drug suspension).

In accordance with the guidelines of our institutional ethics committee, formal approval for this study was not required. The local ethics committee agreed that the findings in this report were based on normal clinical practice and were therefore suitable for dissemination. Informed consent was not obtained from the patients, but their clinical records and information were anonymized before analysis. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference for Harmonization.

2.2. Renal biopsies

All biopsies were assessed by experienced pathologists by light microscopy and immunofluorescence. Renal biopsy was evaluated according to the WHO classification of LN when the biopsy was performed before the year 2003, and according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of LN after that date. If biopsy specimens were classified according to World Health Organization classification, they were reassessed according to the ISN/RPS classifications. ISN/RPS classifications between the first and the second biopsy examinations were compared. If patients had more than 2 biopsies, the second and third, as well as third and fourth, biopsies were paired. Thus, the last biopsy performed before the repeat biopsy served as the reference biopsy.

Activity and chronicity indices were scored according to the 1983 proposal by Austin et al.[8] Class III, class IV, and combinations of III/IV plus V were considered proliferative classes. All of the rest were considered nonproliferative.

2.3. Literature search strategy and selection criteria

In addition to our case series, we analyzed current evidence of the value of repeat renal biopsy in cases of suspicion of renal flare using a systematic review of reports published in indexed international journals (excluding reviews, congress abstracts, or unpublished results). Searches were conducted in the PubMed database (i.e., including MEDLINE, National Library of Medicine, and PubMed Central) for the period between January 1990 and December 2015 using the strategies recommended by the Cochrane handbook. Search terms included "*Systemic lupus erythematosus*," "*lupus nephritis*," "*repeat renal biopsy*," "*second renal biopsy*," and "*serial renal biopsy*." Only English-language reports were selected for review. To standardize the information, we excluded patients aged less than 18 years. The references of the studies obtained were also examined to identify additional reports.

2.4. Statistical analysis

Statistical analysis was performed using SAS version 9.1.3 (SAS, Inc., Cary, NC). Qualitative variables were described by frequencies and percentages, and quantitative variables were

Table 1

Main clinical and laboratory data of our 54 patients with at least 2 renal biopsies.

	1st Biopsy	2nd Biopsy	*P*
Serum creatinine, μmol/L	84.4±24.9	114.3±197.9	.108
Proteinuria, g/d	2.9±3.7	3.3±3	.203
Microhematuria	29 (54%)	24 (44%)	d=9.26 (95% CI –9.32, 26.97), *P*=.197
Urinary casts	10 (19%)	7 (13%)	d=5.56 (95% CI –8.5,19.5), *P*=.459
Positive anti-DNAn	45 (83%)	40 (74%)	d=9.26 (95% CI –6.29, 24.34), *P*=.049
C3 low, n (%)	38 (70%)	28 (52%)	d=18.52 (95% CI 0.16, 35.22), *P*=.048
C4 low, n (%)	38 (70%)	24 (44%)	d=25.93 (95% CI 7.27, 42.20), *P*=.02
Arterial hypertension	17 (31%)	17 (31%)	d=0 (95% CI –17.10, 17.10), *P*=.866
Nephrotic range proteinuria	19 (35%)	23 (43%)	d=–7.41 (95% CI –24.86, 10.70), *P*=.462
Progression to renal failure	11 (20%)	15 (28%)	d=–7.41, (95% CI –23.09, 8.73), *P*=.368
Renal histology			
I		1	
II	9 (17%)	2	
III	8 (15%)	8	
IV	28 (52%)	29	
V	6 (11%)	12	
Mixed (III/V+V)	3 (5%)	2	
Activity index	7.9±4.7	6.6±5.3	.215
Chronicity index	1.1±1.5	2.2±2	.003

described by mean or median±standard deviation (SD) and range. Continuous variables were compared using the Student *t* test or median test. Categorical variables were analyzed using the Chi-squared test or Fisher exact test when the expected values were less than 5, and by calculating the 95% confidence intervals (CIs) for the differences between proportions using Newcomb method. A multivariate logistic regression analysis was performed to identify clinical predictors of pathological class transformation. The construction of the regression model was perfomed by backward stepwise using both statistical and clinical judgment. Statistical significance was defined as $P \leq .05$.

3. Results

We identified 54 lupus patients with at least two renal biopsies. These patients had a total of 125 renal biopsies: 38 patients had 2 biopsies, 15 had 3, and 1 patient had 4 biopsies. Of the 54 patients, 49 were women (91%) and 5 (9%) were men, with a mean age at the time of first biopsy of 45±11 years. The median disease duration at the time of the second biopsies was 48±9 months. The average interval between the first and second biopsy was 24±16 months.

Their main laboratory data at the time of the first and second renal biopsies are summarized in Table 1. Clinical indications for biopsies were the increase, persistence, or recurrence of proteinuria, nephrotic syndrome, or active urinary sediment in 39 patients (72%), and increase in serum creatinine or unexplained progression to renal failure in 15 (28%). Regarding histopathological analysis, proliferative classes (class III, IV, or a combination of III/IV+V) were the most frequent (72%), followed by class II (15%).

Table 2

Changes in nephritis classification (ISN/RPS) from the first to second biopsies in our 54 patients.

Repeat biopsy	Reference Biopsy II	III	IV	V	Mixed III/IV+V
I	1				
II	1		1		
III	2	2	4		
IV	3	4	21	1	
V	2	2	1	4	3
Mixed III/IV+V			1	1	

ISN/RPS=International Society of Nephrology/Renal Pathology Society.

3.1. Pathological transition

The distribution of the ISN/RPS classes at first and second renal biopsies (N=108), and the transitions from one class to the other are shown in Table 2.

Of the 54 repeat biopsies, class switches occurred in 27 (50%) patients. When the first biopsies were proliferative classes (III, IV, or a combination of III/IV+V) (n=39), histological change occurred in 41% of cases (16/39), but only 18% of them changed to a nonproliferative class, usually to a class V (only 1 case improved to a class II). The rest remained in the proliferative class on the repeat biopsy, although the transitions from class III to class IV or vice versa, or the switch from a mixed class to pure class III or IV or vice versa were common.

Among nonproliferative classes, the great majority of patients with class II (7/9; 78%) showed transformation to a higher grade of nephritis (class III or IV in 5 cases and class V in the other 2), resulting in worse renal prognosis. Histological change occurred less frequently in patients with class V (2/6; 33%), but all cases switched to a proliferative class. Globally, pathological class transformation during nephritic flares were more frequent in patients with nonproliferative lesions (classes II and V: 10/15; 67%) than in those with proliferative lesions (classes III and IV: 13/36; 36%) in their reference biopsy ($P < .004$).

Table 1 also shows the results of the comparative study of the main clinical and laboratory data of the 54 patients at the time of the first and second biopsies. In the baseline renal biopsy, patients had higher immunological (positive anti-DNAn antibodies and hypocomplementemia) and histological activity (7.9±4.7 vs 6.6±5.3; *P*=.215). As expected, the mean chronicity index in the second biopsies was significantly higher (2.2±2 vs 1.1±1.5; *P*=.003). In the multivariate logistic regression analysis, no clinical predictor of pathological class transformation could be identified (the variables included in the regression model were

Table 3

Main characteristics of the series with repeat renal biopsy due to clinical indication.

Author (reference number)	No. of repeat renal biopsies	Interval from first to second renal biopsy	Transformation of histological classes (%), yes/no	Activity index at renal biopsy,* first/repeat	Chronicity index at renal biopsy,* first/repeat	Changing immunosuppresive therapy after repeat renal biopsy, yes/no
Esdaile et al[76]	42	25 mo	55% (23/42)/45%(19/42)	7 (4.4)/2 (3.9), $P=.0001$	1.6 (1.2)/2.7 (1.4), $P=.003$	NS
Moroni et al[75]	38	42 mo	45% (17/38)/55% (21/38)	7.3 (4.4)/5.2 (4.4), $P=.051$	1.5 (1.5)/4.9 (2.7), $P=.0001$	79% (30/38)/21%(8/38), increase: 60.5% (23/38), reduction: 18.5% (7/38)
Bajaj et al[74]	57	4.2 y	40% (23/57)/60% (34/57)	5.01 (0–18)/3.96 (0–19), $P=.064$	1.30 (0–7)/3.37 (0–12), $P=.0001$	77% (44/57)/23%(13/57), increase: 47% (27/57), reduction: 30% (17/57)
Sun et al[73],†	21	33 mo	38% (8/21)/62% (13/21)	NA	1 (1.3)/NA	38% (8/21)/ 62% (13/21), increase: 33% (7/21), reduction: 5% (1/21)
Daleboudt et al[4]	49	4.1 y	49% (24/49)/51% (25/49)	6.18 (4.43)/5.27 (3.84), $P=.315$	2.62 (2.53)/4.2 (2.39), $P<.001$	59% (29/49)/34% (20/49), increase: 43% (21/49), reduction: 16% (8/49)
Lu et al[72]	244	46.8 mo	75%(183/244)/25%(61/244)	6.8 (4.6)/NA	2.6 (2.4)/NA	NS
Wang et al[71]	50	≥ 6 mo	64% (32/50)/36% (18/50)	5.8 (3)/4.7 (2.6), $P=.061$	1.8 (1.2)/3.4 (2), $P=.0001$	44% (17/50)/66% (33/50), increase: 30% (15/50), reduction: 14% (7/50)
Pagni et al[70]	142	4.9 y	41%(58/142)/59%(84/142)	4.5 (3.8)/3.3 (3.3), $P=$NS	1.5 (1.8)/3.6 (2.7), $P=.0182$	NS
Alsuwaida[69]	11	2 y	64% (7/11)/36% (4/11)	3.1 (4.2)/5 (4.3), $P=.45$	2.5 (2.5)/5.8 (2.3), $P=.01$	18% (2/11)/82% (9/11), increase: 18% (2/11)
Greloni et al[68]	71	3.4 y	55% (39/71)/45% (32/71)	NA	6.1 (1.6)/2.9 (1.7)‡$P<.0001$	87% (62/71)/13% (9/71), increase/reduction: NS

NA = data not available, NS = data not specified.

* Activity and chronicity indexed are expressed as median or mean (standard deviation or range).

† Sun: the series only included patients with membranous (class V) lupus nephritis.

‡ Greloni: chronicity index values regarding patients with poor renal outcome at last follow-up.

age, duration of SLE, baseline renal function, proteinura, microhematuria, casts, immunological activity defined as positive anti-DNAn antibodies and/or hypocomplementemia, and histological activity and chronicity indices; details not shown).

After the repeat biopsy, 17 (31%) patients had a change of treatment regimen: 15 (28%) received an increase in immunosuppression; while in 2 (4%) cases, immunosuppressive therapy was decreased (dose) or stopped.

3.2. Patients with more than 2 biopsies

Fifteen of the 54 patients had a third renal biopsy and 1 had a fourth biopsy. Pathological class transformation occurred in 56% (9/16) of these cases. Among the 15 patients with a third biopsy, class switches occurred in 8 (53%): 2 patients with class II progressed to a proliferative class, 2 with class III changed to class IV, 2 with class IV changed to class V, 1 with class V changed to class IV, and 1 with class V progressed to class VI. The only patient who had a fourth biopsy also switched from class IV to mixed class IV + V.

3.3. Literature review

The MEDLINE search resulted in 70 articles. After evaluation of the full text, 36 of these articles were excluded: 6 corresponded to pediatric cases[9–14]; 6 were a review or an editorial[2,15–19]; 11 corresponded to case reports[20–30]; 12 were studies with not relevant data or that analyzed a different issue[31–42]; and 1 was excluded due to duplicate/multiple publication.[43] In addition, we excluded 22 studies[44–65] in which the repeat biopsy was done after induction or maintenance therapy to determine the effect of treatment on kidney histology (protocol biopsy), and 2 studies because their clinical characteristics were not sufficiently detailed to be individually analyzed.[66,67]

Therefore, 10 articles were finally selected for review,[2,68–76] identifying 686 well-documented cases of patients with repeat biopsy performed only based on clinical indications (increase, persistence, or recurrence of proteinuria, nephrotic syndrome, or active urinary sediment; increase in serum creatinine or unexplained progression to renal failure; suspicion of renal flare or class change, or refractoriness to standard therapy). The main characteristics of these 10 series are summarized in Table 3. The rate of pathological class transformation in these studies ranged from 40% to 76% of cases (mean 53%). The results of the repeat biopsy led to a change in the immunosuppressive treatment in 18% to 79% of the patients (mean 57% of cases), intensifying it in the majority of the cases (between 18% and 60.5%; mean 39%), but also reducing it in 5% to 30%.

The distributions of the ISN/RPS classes at initial and repeat renal biopsies are shown in Table 4. The transitions from one class to the other are shown in Table 5; due to the low number of cases with classes I or VI in the reference biopsy, they were excluded from the table.

Similar to our results, most patients with class II (77.5%) progressed to a higher grade of nephritis (proliferative classes III, IV, or mixed in 63% of cases, class V in 13.5%, and class VI in 1%), resulting in worse renal prognosis. When previous biopsy showed class V, transition to other classes occurred less frequently (43%) and changes were also in almost cases (40%) into proliferative classes.

By contrast, most patients (351/484; 73%) with proliferative classes in the reference biopsy (III, IV, or mixed III/IV + V) remained in the proliferative class on the repeat biopsy (although

Table 4

Distribution of the ISN/RPS classes at the first and repeat renal biopsies in 686 well-documented published cases of patients with repeat biopsy performed only on clinical indications.

	Reference biopsy					
Repeat biopsy	I	II	III	IV	V	VI
I	2	3	0	1	0	0
II	1	15	8	40	2	0
III	0	13	26	25	4	0
IV	0	29	34	158	13	0
V	1	11	9	37	62	1
VI	0	1	1	15	1	2
Mixed II + V	0	0	0	2	1	0
Mixed III + V	0	6	7	21	19	0
Mixed IV + V	0	3	2	11	9	1

	Reference biopsy		
Repeat biopsy	II + V	III + V	IV + V
I	0	0	0
II	0	0	2
III	0	1	4
IV	0	12	9
V	0	8	9
VI	0	0	1
II + V	1	0	0
III + V	1	17	8
IV + V	0	5	11

ISN/RPS = International Society of Nephrology/Renal Pathology Society.

the transitions from class III to class IV or vice versa, or the switch from a mixed class to pure class III or IV or vice versa were common). Since biopsies were performed only based on clinical indications, in those cases who switched to a nonproliferative class (133/484; 27%), the progression to a class V or VI was more frequent (82/484; 17%) than the improvement to a classes I or II (51/484; 11%).

4. Discussion

Relapses occur between 27% and 66% in patients with LN,[3–6,68–76] even after an initial complete remission. LN flares represent a significant problem because of the potential for cumulative damage that may lead to deterioration of renal function as well as toxicity due to additional immunosuppression.[3] Histological transformation from one class to another during a LN flare is very well recognized,[68–76] and there is evidence showing that relapsing nephritis has a worse renal prognosis.[2,3] In this clinical scenario, the usefulness of repeat renal biopsy is a controversial issue, for 2 reasons: the doubts about its influence on patient's management and the risk of possible complications, mainly related to bleeding. Considering the risk-benefit ratio, some authors are reluctant to repeat biopsies since there is no clear evidence in which patients undergoing a second biopsy will have clear therapeutic consequences that justify its risk.[2–6]

To determine the role of repeat biopsies, this study investigated how often a clinically relevant switch occurred when repeat biopsies were performed for renal flares. The results of our series, as well as the literature review, confirm that histological transformation is very prevalent during an LN flare, ranging from 40% to 76% of cases,[68–76] and supports the usefulness of a repeat biopsy in guiding treatment of LN flares, both to identify those patients for whom it is necessary to intensify immunosuppression therapy and to avoid unnecessary increased immunosuppression therapy in others.[4,68,70,71,73–75] However, the frequency of histological transformation and the clinical value

Table 5

Transitions from one class to other in 676 well-documented published cases of patients with repeat biopsy performed only on clinical indications. *

Reference biopsy	Repeat biopsy
Class II mesangial LN (N = 81)	4% (3/81) switched to class I
	18.5% (15/81) no shift in pathological class
	77.5% (63/81) switched to higher grade nephritis: 63% (51/81) transformed to proliferative classes (III, IV, III + V, IV + V); 13.5% (11/81) switched to class V; 1% (1/81) switches to class VI
Proliferative classes (pure class III focal LN and class IV diffuse LN) (N = 397)	28.5% (113/397) transformed to nonproliferative classes (I, II, V, VI): 12% (49/397) switched to classes I or II; 16% (62/397) switched to classes V or VI; 0.5% (2/397) switched to class II + V
	61% (243/397) remained in pure proliferative classes (39% of class III patients' switched to class IV and 8% of patients in class IV switched to class III)
	10.5% (41/397) transformed to mixed classes: 7% (28/397) switched to class III + V; 3.5% (13/397) switched to class IV + V
Mixed classes III + V and IV + V (N = 87)	2% (2/87) switched to class II
	21% (18/87) switched to classes V or VI
	77% (67/87) remained in the same mixed class or were reclassified into pure class III or IV
Pure class V mesangial LN (N = 111)	2% (2/111) switched to class II and 1% (1/111) switched to class II + V
	56% (62/111) no shift in pathological class
	40% (45/111) transformed to proliferative classes (III, IV, III + V, IV + V)
	1% (1/111) progressed to class VI

LN = lupus nephritis.

* Due to the low number of cases with classes I or VI in the reference biopsy, they were excluded in the table.

of repeat biopsy vary greatly depending on the LN class from the initial biopsy.

Current evidence demonstrates that histological transformation is common in nonproliferative lesions. The great majority of patients with class II (78% in our series and 77.5% in the literature revision) progressed to a higher grade of nephritis, resulting in worse renal prognosis. Most of these patients progressed to a proliferative class (III, IV, or a combination of III/IV + V), and less frequently to a class V.

The frequency of pathological conversion in class V is lower (33% in our series and 43% in the literature) but equally clinically relevant, since in almost all cases these patients switched to a proliferative class. Therefore, nonproliferative II or V LN class diagnosed at baseline biopsy can benefit from a repeat biopsy, because these patients have a reasonable possibility of switching to a proliferative LN that may require more aggressive immunosuppression.

In contrast, the great majority of patients (82% in our series and 73% in the literature revision) with proliferative classes in the reference biopsy (III, IV, or mixed III/IV + V), remained into proliferative class on the repeat biopsy, although the transition from class III to class IV or vice versa, or the switch from a mixed class to pure class III or IV or vice versa, were common. Theoretically, the detection of these transformations within the proliferative group generally does not have clear therapeutic consequences, since treatment guidelines usually do not differentiate between classes III and IV nephritis.[1,3,5] Similarly, the addition or disappearance of class V lesions on a second biopsy next to persisting proliferative lesions should not significantly influence treatment choices, since the prognosis is largely determined by the associated proliferative lesions.[1,3,5] However, data from the literature do not seem to confirm this approach.[4,68,70,71,74,75] Although the proliferative classes were the majority in the reference biopsy in nearly all of the reviewed series (484/676; 72%), the results of the repeat biopsy led to a change in the immunosuppressive treatment in 18% to 79% of the patients (mean 57% of cases), intensifying it in the majority of the cases (between 18% and 60.5%; mean 39%). These data suggest that in daily clinical practice, in some cases with clear progression of proliferative lesions in the second biopsy despite the initial treatment, the immunosuppressive treatment was intensified to avoid the progression of renal damage and the development of sclerosing lesions. Another important question to consider when deciding if it is worthwhile to rebiopsy this group of patients is that a considerable percentage of cases (18% in our series and 27% in the literature review) switched to a nonproliferative class, being much more frequent the progression to a class V or VI, than the improvement to a classes I or II. The switch from proliferative to nonproliferative lesions has clear therapeutic consequences that justify performing a repeat biopsy.

No clinical or biochemical predictor of transformation have been identified.[71,72] In diffuse proliferative lupus nephropathy, some histological parameters at the initial biopsy (higher glomerular activity and larger interstitial volume density) can predict the progression of renal pathology or function at the second biopsy.[77]

Whether repeat renal biopsies have a prognostic value was not addressed in the present study. Although the immediate clinical relevance of the serial renal biopsy may be limited, repeat biopsies could have a prognostic value. Recently, Arriens et al have demonstrated that a repeat renal biopsy demonstrating histopathologic worsening and a short time between biopsies is associated with significantly increased risk for end-stage renal disease and death.[78] Only 2 known studies investigated the prognostic value of repeat biopsies in the face of a LN flare and both report a predictive association of high chronic index scores and poor renal outcome.[75,76] In addition, having a higher serum creatinine and a high activity index at the second biopsy was also associated with a worse renal prognosis.[63,68,75,76]

When interpreting the results of our study, one needs to consider the potential limitations derived from its retrospective nature and the small sample size. Not all of the biopsies were evaluated with activity and chronicity indices, and they were evaluated by different pathologists with different classifications according to the year when they were performed, as mentioned. In addition, we cannot ignore the pitfalls inherent in any systematic review, including the relatively small number of identified patients, the retrospective design, and incomplete follow-up data in some cases.

In conclusion, histological transformations are common during a LN flare, and they occurred when the previous biopsy had nonproliferative lesions as well as when lesions were proliferative. However, the prevalence of transitions varied when they were analyzed according to proliferative or nonproliferative lesions. In cases of a nonproliferative lesion in the reference biopsy (classes II or V), switches to a proliferative class are frequently found and repeat biopsy is highly advisable. In most but not all cases with originally proliferative LN, the repeat biopsy confirmed ongoing or recurrent proliferative LN. Although rebiopsy in this group does not seem as necessary, it is also advisable since it will allow us to identify the 18% to 20% of patients that switch to a nonproliferative class. In addition, consistent with the reported clinical experience, repeat biopsy might also be helpful to identify selected cases with clear progression of proliferative lesions despite the initial treatment, for whom it is advisable to intensify immunosuppression. Thus, our experience and the literature data support that repeat biopsy also brings more advantages than threats in this group.

Although there is still a need for new randomized, prospective studies to confirm clinical observations, in daily practice kidney repeat biopsies are useful in guiding treatment of LN flares. The results of the repeat biopsy led to a change in the immunosuppressive treatment in more than half of the patients on average, leading to not only its intensification in the majority of the cases, but also its reduction in 5% to 30%

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