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The clinical relevance of a repeat biopsy in lupus nephritis flares

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Abstract

Background. The clinical utility of performing repeat biopsies during lupus nephritis flares is questionable and data pointing towards frequent class switches are based on the old WHO classification. This retrospective study investigates the hypothesis that clinically relevant switches from proliferative to non-proliferative lesions and vice versa as determined by the new ISN/RPS classification are a rare event and that repeat biopsies are unnecessary in many cases.

Methods. Thirty-five patients with lupus nephritis and one or more repeat renal biopsies were included. Eighty-four biopsies were blindly reassessed according to the ISN/RPS classification.

Results. Twenty-five patients had one repeat biopsy, 6 patients had two and 4 patients had three repeat biopsies. Forty-nine comparisons between reference and repeat biopsies could be made. In 25 cases (54.3%), there was no shift in ISN/RPS class on repeat biopsies. In 41 instances, paired biopsies showed proliferative lesions both on reference and repeat biopsies, whereas five of six cases with non-proliferative lesions on a reference biopsy switched to proliferative lesions on a repeat biopsy. Clinically significant class switches during lupus nephritis flares were more frequent in patients with non-proliferative lesions in their reference biopsy ($P < 0.001$).

Conclusion. The results show that patients with proliferative lesions in the original biopsy rarely switch to a pure non-proliferative nephritis during a flare. Therefore, a repeat biopsy during a lupus nephritis flare is frequently not necessary if proliferative lesions were found in the refer-

ence biopsy. However, in the case of a non-proliferative lesion in the reference biopsy, class switches are frequently found and repeat biopsies are advisable.

Keywords: ISN/RPS classification; kidney biopsy; lupus nephritis; proliferative lesions; SLE

Introduction

A renal biopsy is a pivotal step in determining the nature of renal involvement in patients with lupus nephritis. Up to 60% of patients with systemic lupus erythematosus (SLE) develop lupus nephritis [1]. Six classes of lupus nephritis are distinguished in the current classification of the International Society of Nephrology and the Renal Pathology Society (ISN/RPS). Classification and treatment decisions strongly depend on the findings in the renal biopsy. The diagnosis of lupus nephritis cannot be based on clinical features alone (e.g. proteinuria, rising serum creatinine, active sediment), since the clinical features do not permit a reliable prediction of the type of SLE nephritis [2,3]. Kidney diseases due to other causes than lupus nephritis may also need to be excluded as a cause of renal damage [1].

Relapses occur frequently in patients with lupus nephritis, even after an initial complete remission [4]. To determine the most effective treatment in the case of a lupus nephritis flare, a number of authors advise to perform repeat biopsies [1,5–8]. Based on such findings, it has been hospital policy at the Leiden University Medical Centre (LUMC)

for over 25 years to perform a biopsy before treating renal flares. However, others have suggested that the need for repeat biopsies in renal flares may depend on the type of lupus nephritis in the original biopsy [4]. Conversion from one proliferative form to another (e.g. class III to class IV) will usually not influence the choice of current therapeutic regimens. Recent studies investigating the optimal therapy for proliferative lupus nephritis include classes III and IV nephritis together in the treatment arms [9–13]. Moreover, treatment guidelines usually do not differentiate between classes III and IV nephritis. Therefore, transitions between proliferative classes have no additive value on treatment decisions. Similarly, the addition or disappearance of class V lesions on a second biopsy next to persisting proliferative lesions should not be of great influence on treatment choices, since the prognosis is largely determined by the associated proliferative lesions [14]. Thus, only a switch from proliferative to non-proliferative lesions (e.g. class III to class V) or vice versa will have clear therapeutic consequences, and a reasonable chance to detect such a switch will justify performing a repeat biopsy.

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. Based on the concept that the presence or the absence of proliferative lesions determines therapy in lupus nephritis, it was hypothesized that repeat biopsies would only be helpful if switches between purely non-proliferative to proliferative or vice versa were detected. Since haemorrhage remains a concern in the face of renal biopsies, with major complications requiring blood transfusion or invasive intervention in 0–6.4% of biopsies [1], it is desirable only to perform biopsies that will influence treatment. In addition, the discomfort for the patient and the costs of renal biopsies are important factors.

First and successive biopsies were compared for classification according to the new ISN/RPS revision, therapy regimen and clinical manifestation (e.g. proteinuria and serum creatinine).

Subjects and methods

Study population

Patients were selected from the electronic database of the patient registration at the LUMC. Inclusion criteria were a diagnosis of SLE and two or more renal biopsies. Thirty-eight patients were included on the basis of these criteria. Thirty patients are under treatment at LUMC for their SLE, 4 are currently treated elsewhere and 4 patients are deceased (1 male and 3 females).

Materials and procedure

Ninety-four biopsies were retrieved from the archive and blindly reassessed by two renal pathologists (IMB and NNTG) by light microscopy. The Renal Biopsy Scoring Form of the Dutch Lupus Nephritis Study [11] was used to record ISN/RPS-classification, activity index and chronicity index. After reassessment, the new classifications were compared with those in the old pathology reports. In the case of notable deviations between the former and new assessment (e.g. a class III on original diagnosis and a class IV on reassessment), the assessment was repeated. Hence, these second assessments were not blinded. If important electron microscopy (EM) or immunofluorescence (IF) findings were mentioned in the reports, these were added to the classification.

ISN/RPS classifications between first and second biopsy were compared. If patients had more than two biopsies, the second and third and

Table 1. ISN/RPS classifications on repeat biopsy

| | Reference biopsy | | | | | | | | |
|---------------|------------------|----|-----|----|---|----|--------|---------|--------|
| | I | II | III | IV | V | VI | II + V | III + V | IV + V |
| Repeat biopsy | | | | | | | | | |
| I | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| II | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| III | 0 | 0 | 1 | 5 | 0 | 0 | 0 | 0 | 1 |
| IV | 0 | 1 | 5 | 19 | 2 | 0 | 0 | 2 | 0 |
| V | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| VI | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| II + V | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| III + V | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 3 | 0 |
| IV + V | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| Other | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

third and fourth biopsies were paired. Thus, the last biopsy performed before the repeat biopsy served as the reference biopsy.

Paper files and the electronic database were consulted to register clinical parameters. Serum creatinine and proteinuria at the time of biopsy were recorded. Hospital correspondence retrieved from the paper files and the electronic database was used to collect date of diagnosis and medical regime following the biopsy.

Statistical analysis

Data were analysed using the SPSS Version 15.0 software. A Fisher exact test for categorical variables was applied to determine if class switch occurred more often in patients with non-proliferative versus proliferative lesions. Two-sided *P*-values of <0.05 were considered statistically significant.

Results

Ten biopsies were excluded from the study after reassessment. Four biopsy specimens contained no useful material (e.g. solely renal medulla) or inadequate material so judgement was not possible. Two repeat biopsies were performed as protocol biopsies in the setting of a clinical trial and were excluded. One biopsy performed in a hospital other than the LUMC could not be traced. As a result, three patients and their original biopsies were excluded. The 84 remaining biopsies were included in the analysis.

Material from three biopsies could not be recovered from the archives. Classification of these biopsies was based on careful examination of the old pathology reports.

In six cases, IF results, as mentioned in the pathology reports, led to the addition of class V to the classification. After comparing the results from the biopsy evaluations of the two pathologists with the original reports, discrepancies were found in only four cases. These only involved minor issues, which were solved by plenary discussion in order to reach a final scoring.

The patient group consisted of 26 females and 9 males. The mean age of the total group was 41.5 (SD 10.9). The patients were on average 26.0 years (SD 9.6) when SLE was diagnosed, and the mean disease duration at the time of reassessment of biopsies was 15.5 (SD 6.0) years. Twenty-five patients had one repeat biopsy, 6 patients had two and 4 patients had three repeat biopsies. The mean time period between reference and repeat biopsies was 4.1 years (SD 3.6).

Table 1 shows the ISN/RPS classification in the 84 biopsies that were reassessed. Forty-nine comparisons between

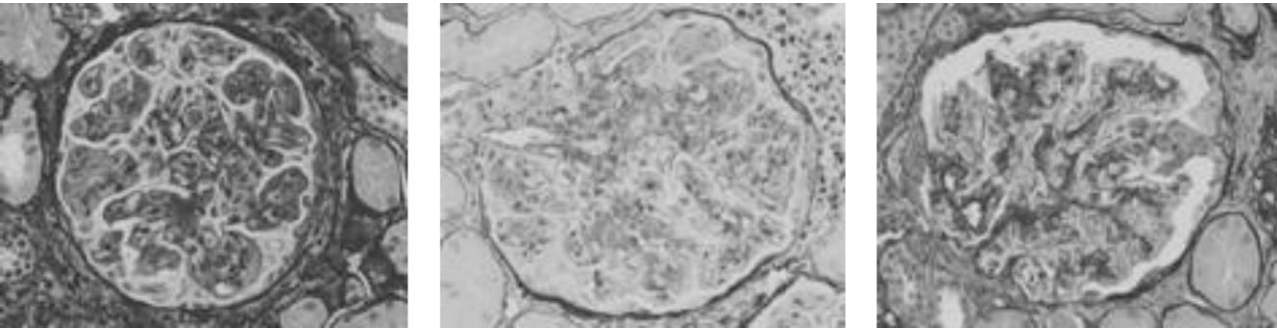


Fig. 1. Example of a patient with proliferative lesions in three successive biopsies (classes IV, IV and III, respectively).

Table 2. Proliferative versus non-proliferative

| | Reference biopsy | |
|--------------------|------------------|-------------------|
| | Proliferative | Non-proliferative |
| Repeat biopsy | | |
| Proliferative | 41 | 5 |
| Non-proliferative | 1 | 1 |
| Glomerulosclerosis | 1 | 0 |

$P < 0.001$.

reference and repeat biopsies could be made. In 25 instances (51.0%), there was no shift in ISN/RPS class on repeat biopsy. This concerned 19 cases of class IV (35.7%), 3 of class III + V (7.1%), 1 of class III (2.4%), 1 class of VI (2.4%) and 1 of class IV + V (2.4%).

The most frequent transitions occurred between classes IV and III (54.2%), with five transitions in both directions, two shifts of class III + V to class IV and one from class IV + V to class III.

Table 2 shows the changes from proliferative to non-proliferative lesions and vice versa between the reference and repeat biopsies. In 41 instances (84%), the reference biopsy as well as the repeat biopsy showed proliferative lesions. Figure 1 illustrates the presence of proliferative lesions in three successive biopsies from a representative patient. Five cases (10%) with pure non-proliferative lesions on reference biopsy switched to proliferative lesions on repeat biopsy. This indicates that clinically relevant class switches were more frequent in patients with non-proliferative lesions in the reference biopsy ($P < 0.001$).

One patient with proliferative lesions in the reference biopsy showed extensive glomerular amyloid depositions in the repeat biopsy.

The mean renal activity index on first biopsy was 6.18 (SD 4.43) and on repeat biopsy was 5.27 (SD 3.84) ($P = .315$). The mean chronicity index for the first biopsy was 2.62 (SD 2.53) and for the repeat biopsy was 4.20 (SD 2.39) ($P < .001$).

Data on serum creatinine and proteinuria at the time of the biopsy could be retrieved for 45 out of the 49 instances of reference as well as the repeat biopsy. Because of the missing values, the presence of a high creatinine and/or the extent of proteinuria could be determined in 43 instances

Table 3. Clinical manifestation at the time of the reference versus repeat biopsy

| | Reference biopsy | Repeat biopsy |
|---|------------------|---------------|
| Proteinuria > 3.5 g/24 h | 10 | 7 |
| Proteinuria > 3.5 g/24 h + serum creatinine > 106 μ mol/L | 20 | 19 |
| Proteinuria < 3.5 g/24 h | 10 | 7 |
| Proteinuria < 3.5 g/24 h + serum creatinine > 106 μ mol/L | 4 | 9 |
| Total | 43 | 42 |

Table 4. Alterations in immunosuppressive therapy after a biopsy

| | After reference biopsy | After repeat biopsy |
|-------------------------------------|------------------------|---------------------|
| Increased immunosuppression | 19 | 21 |
| Decreased/stopped immunosuppression | 1 | 8 |
| No change | 3 | 8 |
| Other | 5 | 3 |
| Unknown | 7 | 9 |
| Total | 35 | 49 |

of the reference biopsy and in 42 cases of the repeat biopsy. The most frequent clinical manifestation of nephritis at the time of the biopsy consisted of nephrotic range proteinuria in combination with a progression of renal failure, in 20 instances (46.5%) at the time of the reference biopsy and in 19 cases (45.2%) of the repeat biopsy (Table 3).

Forty-one comparisons of clinical presentation on reference versus repeat biopsy could be made. In 24 instances (58.5%), a change in presentation was seen, whereas in 17 (41.5%) cases the clinical manifestation at repeat biopsy had not changed.

Data on therapy could not be retrieved for six patients before biopsy, in three cases of reference biopsy and in eight instances of repeat biopsy. As a result, comparison of treatment regimen before and after the reference biopsy and on reference versus repeat biopsy could not be made in seven and nine cases, respectively.

Nineteen patients received an increase in immunosuppression after a reference biopsy (Table 4). In three instances, therapy remained unchanged and in one case immunosuppressive therapy was decreased or stopped. After the repeat biopsy, a comparable number of patients received

Table 5. Treatment regimens

| | Pre-biopsy | After reference biopsy | After repeated biopsy |
|------------------------------|------------|------------------------|-----------------------|
| Steroids alone | 16 (55.2%) | 5 (10.9%) | 3 (7.3%) |
| Steroids + immunosuppression | 5 (17.2%) | 37 (80.4%) | 33 (80.5%) |
| Steroids + AZA | 3 (10.3%) | 25 (54.3%) | 15 (36.6%) |
| Steroids + AZA + Other | 1 (3.4%) | 2 (4.3%) | 1 (2.4%) |
| Steroids + Other | 1 (3.4%) | 1 (2.2%) | 0 (0) |
| Steroids + CYC | 0 (0) | 8 (17.4%) | 10 (24.4%) |
| Steroids + MMF | 0 (0) | 0 (0) | 3 (7.3%) |
| Steroids + CYC + MMF | 0 (0) | 1 (0) | 4 (9.8%) |
| Other | 6 (20.7%) | 1 (2.2%) | 3 (7.3%) |
| None | 2 (6.9%) | 3 (6.5%) | 2 (4.9%) |
| Total | 29 | 46 | 41 |

an increase in immunosuppression, but immunosuppression was decreased or stopped more often than after the reference biopsy.

A clear shift from single steroid use before the biopsy (55.2%) to a combination of steroids and immunosuppression after the reference biopsy (80.4%) was found (Table 5). In two instances of the reference biopsy and in two cases of the repeat biopsy, no immunosuppressive therapy was initiated on the basis of the biopsy results. As for the reference biopsies, this comprised two cases of class III. A repeat biopsy that was reassessed as class IV in the present study was originally misdiagnosed as lupus nephritis in remission. The second repeat biopsy that did not result in therapy concerned a class VI nephritis.

Discussion

This retrospective study investigated the hypothesis that clinically relevant switches in lupus nephritis from proliferative to non-proliferative lesions and vice versa as determined by the new ISN/RPS classification are a rare event and that repeat biopsies during flares are unnecessary in many cases. The results show that patients with proliferative lesions on their original biopsy rarely switch to a pure non-proliferative nephritis during a flare. However, in the case of a non-proliferative lesion in the reference biopsy, class switches are frequently found.

A number of studies report a high degree of transformation from one WHO class to another on repeat biopsy [5–8,15–20]. Class switch is thought to be a characteristic of lupus nephritis [4]. Studies that assessed biopsy specimens according to the old WHO classification showed a class switch in 26–50% of repeated renal biopsies [8]. The present study used the new ISN/RPS classification in the assessment of the renal biopsies, but similar results were found with a class switch in 49% of instances. A switch between classes III and IV (with or without an additional class V) was the most frequent (54.2%). A predominance of transitions between classes III and IV (with or without an additional class V) has been reported in several studies [8,15,17]. In a study by Moroni *et al.* (1999) [8], 42.9% of transitions occurred between classes III and IV. Another study found four transitions from classes III to IV, which comprised 36.4% of all shifts [15].

Transitions in WHO class in other studies on repeat biopsies are variable, but the direction of the majority of transitions in five studies is remarkable. Two studies found the most frequent switches from class IV to class II or V, in 50% [16] and 65.2% [6] of cases, and two other studies showed the most shifts from class III or IV to class II or V (60.7% [7] and 61.1%) [19]. In a fifth study with only class IV on first biopsy, 56% of patients had switched to a class III on repeat biopsy [20]. The high frequency of transitions from class III or IV to class II or III could be the result of the fact that repeat biopsies were not performed for clinical reasons but according to the protocol [6,7,19,20] or postmortem [16]. As the present study only pertains to repeat biopsies on account of a clinical manifestation of a lupus nephritis flare, we cannot address the role of protocol biopsies in the management of patients with lupus nephritis.

Numerous authors advise a serial renal biopsy in the management of lupus nephritis [5–8]. Bajaj *et al.* [5] reported that all therapeutic decisions were influenced by the repeat biopsy results, with no change in therapy in 23% of patients and either an increase or decrease in therapy in the remaining 77% of patients. However, repeat biopsies are performed because of the presence of the clinical manifestation of a lupus nephritis flare. Without a repeat biopsy, patients may have been treated on clinical grounds alone. The biopsy results could only help to choose or confirm therapy choice. Therapy change itself after the biopsy does not prove that the therapy would not have been changed without a biopsy.

Eighty-four percent of transitions in this study consisted of a switch from one proliferative form to another. The detection of these transformations within the proliferative group does not have clear therapeutic consequences and does not justify the performance of a repeat biopsy during a flare. The application of similar therapeutic schedules for all proliferative forms of lupus nephritis is justified by recent studies investigating the efficacy of therapy in proliferative lupus nephritis. In these studies, no distinction between the different proliferative classes is made [9–13]. In addition, the recent lupus nephritis European consensus statement does not differentiate in the treatment of classes III and IV lupus nephritis [21]. Moreover, it has been proposed that transitions from focal to diffuse proliferative nephritis might indicate a progression of the same type of nephritis rather than a true transition [15,17,22,23]. Additionally, since the difference between classes III and IV lupus nephritis is defined as < or >50% of the glomeruli having proliferative lesions, a class switch may also be explained by sampling error in borderline cases. Clearly, more studies are necessary to define whether significant pathophysiological and clinical differences between classes III and IV lupus nephritis exist.

If the majority of patients remain in the same proliferative class or switch to another proliferative form and assuming that proliferative lesions are treated alike, no difference between therapy regimen after an initial biopsy and after a successive biopsy would be expected. However, in 77.5% of cases, treatment schedule differed after the reference versus repeat biopsy in the present study. The mean time between initial and repeat biopsies was 4.1 years, which can explain the lack of consistency in treatment policy in

the case of successive proliferative lesions. Pharmaceutical developments could have led to new insights in treatment strategy and new alternatives. Therapy schedules were often difficult to recover, accounting for the amount of missing data (nine comparisons could not be made) and could have resulted in incomplete data.

Interestingly, only one case of class II nephritis was diagnosed in our group of patients who had repeat biopsies. This is probably the result of a conservative biopsy policy at LUMC. Since some mesangial abnormality is present in all patients with SLE [7,15,16], the earlier in the course of lupus nephritis the biopsy is taken the more cases of class II nephritis will be found.

Although the immediate clinical relevance of the serial renal biopsy may be limited, repeat biopsies could have a prognostic value [6,8,11,24,25]. One study allocated a good predictive power to systematic repeat biopsies at 6 months after the start of treatment for proliferative lupus nephritis since they provided a measure of the response to therapy [24]. The patients who did not respond fully to treatment, as reflected by continuing inflammatory lesions at 6 months, were more likely to show a worse response on treatment for a lupus nephritis flare and showed more accumulation of chronic damage. Esdaile *et al.* (1993) [6] state that the amount of electron-dense deposits, especially subendothelial deposits, at protocolized repeat biopsy 2 years after the start of treatment for all classes of lupus nephritis is the best predictor of renal outcome as well as mortality. In addition, a prognostic association between the chronicity index (CI) and mortality was found.

In contrast, a randomized controlled trial found that repeat biopsies were not predictive of outcome [11]. Although the CI was significantly increased on repeat protocolized biopsy 2 years after initiating treatment for proliferative lupus nephritis, it could not predict outcome. The authors suggest that clinical parameters in patients with lupus nephritis are more informative than are findings on repeat renal biopsy.

Only two known studies investigated the prognostic value of repeat biopsies in the face of a flare and both report a predictive association of high CI scores and poor renal outcome [8,25]. Moroni *et al.* [8] found an association between a CI of 5 or greater and a doubling plasma creatinine level in the long term. In addition, they state that the presence of extracapillary proliferation demands aggressive treatment to prevent irreversible renal failure.

Whether repeat renal biopsies have a prognostic value was not addressed in the present study. The two known studies do indicate an association, especially with regard to the CI, but data are too scarce to make a definite conclusion. Moreover, the application of the CI as a measure of outcome seems questionable, since the reproducibility of the CI remains moderate [26–28].

The most frequently mentioned and most important reason to perform a repeat biopsy is to decide on a treatment strategy in the case of a lupus nephritis flare. However, if evaluation of the biopsy specimen will show transition to another proliferative form in the majority of cases and if these forms receive the same treatment, a repeat biopsy becomes unnecessary in these instances. This study did find a significant class switch to proliferative forms in

patients with non-proliferative lesions in their reference biopsy. Based on these results, it seems that patients with a class V nephritis should be followed up closely. If these patients flare or show a progression in renal failure, a re-biopsy may be indicated to exclude the development of proliferative lesions.

On choosing a policy in which repeat biopsies are only performed in patients who flare and had non-proliferative lesions on initial biopsy, it remains uncertain what strategy to follow in the case of prolonged mild deviations. When a patient maintains mild but substantial proteinuria, which does not improve on therapy, it can be difficult to uncover if this reflects chronic damage or activity. In these selected cases, a renal biopsy should be considered. Although pure sclerotic lesions were only found in one repeat biopsy in our series, it may be difficult to clinically distinguish a mild flare from proteinurea and worsening renal function due to glomerulosclerosis in some patients. In these cases, a biopsy will be necessary to guide appropriate treatment and prevent inappropriate immunosuppression. Similarly, a biopsy may be helpful in patients with very poor renal function where severe chronic damage may contribute to the decision to withhold aggressive treatment.

It should be noted that the results of this study might not be applicable to every patient group. The participant group in this study consisted mostly of individuals of Caucasian descent. It is well known that patients with SLE of African descent have a more aggressive course of disease and poorer outcomes [29]. A similar study with this patient group should be performed before a recommendation about biopsy policy can be given.

In conclusion, the clinical relevance of a repeat biopsy in lupus nephritis seems to be limited. In the case of non-proliferative lesions on reference biopsy, a repeat biopsy is advisable in the presence of clinical deterioration since a switch to more proliferative lesions is often found. If a patient with proliferative lesions on a previous biopsy presents with a renal flare, appropriate induction treatment can be initiated without additional biopsies, since a repeat biopsy will show similar lesions in most cases.

Conflict of interest statement. None declared.

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Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids

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Abstract

Background. Lupus nephritis is a life-threatening complication of SLE. Treatment regimes include steroids and cyclophosphamide, both associated with significant mor-

bidity. Newer regimes include mycophenolate mofetil (MMF). We report our outcomes in a prospectively monitored cohort of patients receiving our new standard treatment protocol, comprising rituximab induction therapy and