Original Article

Contribution of Clinically Indicated Repeat Renal Biopsy in Indian Patients with Lupus Nephritis

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Abstract

Background: Repeat renal biopsy is usually done for lupus nephritis (LN) flare or resistant disease. We analyzed the changes between first and repeat biopsy and the contribution of repeat biopsy on renal outcome in LN patients. **Methods:** This was a retrospective study carried out at a tertiary care center in India. Sixty-two LN patients who underwent repeat biopsy for clinical indications, between January 2012 to December 2016, were included. Clinical and histological parameters at first and second biopsies were compared. Logistic regression analysis was done to determine parameters on repeat biopsy predicting response at last visit. **Results:** Repeat biopsy was done for relapse in 56% and for resistant disease in 44% patients. Seven (13.7%) out of 51 patients with baseline proliferative histology converted to non-proliferative lesion on second biopsy, while 2 (18.2%) out of 11 with baseline non-proliferative lesion converted to proliferative lesion on second biopsy. On repeat biopsy, the presence of endocapillary proliferation decreased, whereas glomerulosclerosis, interstitial fibrosis/tubular atrophy (IFTA), and glomerular basement membrane thickening increased. At the last visit (median follow-up of 38.6 months after first biopsy and 13.8 months after second biopsy), 79% of patients were in remission and 6.5% needed renal replacement therapy. The presence of IFTA >30% and thrombotic microangiopathy (TMA) on second biopsy independently predicted response at last visit. **Conclusion:** In Indian patients with LN, chronicity markers and superimposed membranous pattern increased on repeat biopsy done for clinical indications. The presence of IFTA and TMA on second biopsy predicted response at last visit.

Keywords: *Glomerulonephritis, IFTA, lupus nephritis, outcome, repeat biopsy*

Introduction

Lupus nephritis (LN) occurs in 25–50% of patients at the onset of systemic lupus erythematosus (SLE) and about 60% develop LN during the course of the disease.[1,2] During a flare, histological pattern is often not predictable by clinical parameters alone, necessitating a repeat biopsy for guiding treatment.[3] Furthermore, histological features on the second renal biopsy such as persistent inflammatory lesions,[4] presence of sub-endothelial deposits,[5] and higher chronicity indices[6,7] have been associated with worse renal prognosis. Most working groups on LN recommend repeat biopsy in cases with worsening proteinuria or renal dysfunction or at relapse.[8] In this manuscript, we describe the histological changes on repeat biopsy done for clinical indications and the contribution of repeat biopsy in predicting clinical outcome in Indian patients with LN.

Methods

This was a retrospective study involving adults with LN who underwent at least one repeat renal biopsy between January 2012 to December 2016 for clinical indications at the Department of Nephrology, Post Graduate Institute of Medical Education and Research, Chandigarh. The study was approved by the Institute Ethics Committee (INT/IEC/2017/436). Criteria for indications of repeat renal biopsy followed at our center are renal relapse or resistant disease as defined below. Patients with incomplete/inadequate clinical or histological records at baseline or at repeat biopsy were excluded. The clinical details of the patients were retrieved from medical records. The renal biopsy details including light microscopic and immunofluorescence (IF) staining results, both at first biopsy and repeat renal biopsy, were noted. LN was classified according to International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 criteria.[9] Glomerular

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activity parameters included endocapillary hypercellularity, cellular crescents, fibrinoid necrosis/karrhyorhexis, glomerular leukocyte infiltration, wire loop lesions, and interstitial inflammation.[10] Chronicity markers included glomerulosclerosis (segmental/global), fibrous crescent, interstitial fibrosis, and tubular atrophy.[10] Vascular lesions were noted as per morphological description.

Statistical analysis

Statistical analysis was done using SPSS. Version 23.0. Armonk, NY: IBM Corp. Continuous variables were expressed as median with interquartile range (IQR) or mean (± standard deviation), and categorical variables were expressed as percentages. McNemar's test was used to compare categorical variables at first and second biopsy. Continuous variables at first and second biopsy were compared using Wilcoxon Signed-Rank test. Univariate analysis followed by multiple logistic regression using histopathological parameters on second biopsy to model response at last visit was done. A P value <0.05 was considered significant.

Definitions

Complete remission (CR): Normalization of serum creatinine to the baseline, no active urinary sediments plus a decrease in urine protein creatinine ratio <500 mg/g.[11] Partial remission (PR): Stabilization (±25% of baseline) or improvement of serum creatinine, but not to normal with a ≥50% fall in urine protein creatinine ratio (uPCR). For nephrotic range, proteinuria defined as uPCR ≥3000 mg/g, improvement required was ≥50% reduction in uPCR and PCR <3000 mg/g.[11] Renal relapse: Renal relapse was defined as mild if presence of glomerular hematuria (>15 RBCs or 1 acanthocytes per high power field) or urinary RBC cast or WBC cast. Moderate renal relapse was defined as doubling of 24 h urine proteinuria but <5 g/day or increase in serum creatinine by 0.2–1.0 mg/dl if baseline <2 mg/dl or by 0.4–1.5 mg/dl if baseline 2 mg/dl. Severe renal relapse was defined as an absolute increase in proteinuria to >5 g/day or increase in serum creatinine by >1 mg/dl if baseline <2 mg/dl or by >1.5 mg/dl if baseline 2 mg/dl.[11] Resistant disease: not achieved either PR or CR with or without deteriorating renal dysfunction and/or deteriorating proteinuria. Nephrotic syndrome: 24-h protein of 3.5 g/day with serum albumin <3.5 g/dl or 24-h protein of 1.5 g/day with serum albumin <2.5 g/dl, massive edema and hyperlipidemia.[12]

Results

Sixty-two patients who underwent repeat biopsy during the period from January 2012 to December 2016 were included in this study. The median (IQR) age of the patients was 28 (22–36.25) years and male to female ratio is 1:4. Nephrotic syndrome was the most common mode of presentation in 24 (38.7%) patients at first biopsy and 21 (33.9%) patients at second biopsy, respectively. Only 19 (30.6%) patients had proteinuria >4 g/day despite 45 (72.6%) having serum albumin <3 g/dl during first biopsy [Table 1]. The indications for second biopsy were relapse in 34 (54.83%) patients and resistant disease in 28 (45.16%) patients, respectively. Of the 34 patients with renal relapse, 18 (52.94%) had moderate relapse and 16 (47.05%) had severe relapse. Of the 28 patients with resistant disease, 18 (52.94%) were labeled resistant in view of no response (CR/PR) and 10 (35.71%) had deteriorating proteinuria and/or serum creatinine in addition. The median (IQR) time from first to second biopsy was 23.13 (7.92–55.13) months and the median (IQR) time to relapse in the 34 patients was 45.2 (24.9–76) months. Third biopsy was done in 8 patients; 5 patients with resistant disease and 3 patients with relapse. Class IV LN (51.6%) was the most common class on first biopsy and class IV + V LN was the most common class on both second (29.03%) and third biopsy (50%), respectively. Class transformation was seen in 38 (61.3%) patients on second biopsy; 22 (64.7%) in those with relapse and 16 (57.2%) in those with resistant disease. Of 51 patients with proliferative pattern (class III V LN and/or class IV V LN) on first biopsy, 7 (13.7%) showed switch to non-proliferative lesion (class II, V and/or VI LN) on second biopsy and 2 out of 11 (18.2%) patients with non-proliferative pattern on first biopsy switched to proliferative pattern on second biopsy. On comparison of histopathological variables between first and second biopsy, the presence of endocapillary hypercellularity decreased, whereas glomerulosclerosis, glomerular basement membrane thickening, and IFTA >30% increased [Table 1]. Nineteen out of 37 (51.3%) of patients with class III and/or IV LN had superimposed class V pattern on second biopsy. Further subgroup analysis based on indication for repeat biopsy was done. In patients with relapse as the indication for repeat biopsy, glomerulosclerosis (P = 0.031), glomerular basement membrane thickening (P = 0.004), and IFTA ≥25% (P = 0.008) increased on second biopsy compared to first biopsy, however, activity markers were the same. In patients with resistant disease as the indication for repeat biopsy, whereas glomerular basement membrane thickening (P = 0.012) and IFTA ≥25% (P = 0.021) increased, endocapillary hypercellularity (P = 0.016) decreased on second biopsy as compared to first biopsy.

After second biopsy, treatment was changed in 52 (83.9%) patients. Multi-target therapy comprising mycophenolate mofetil, tacrolimus, and oral steroid was started in 15 (24.19%) patients and Rituximab, as add-on therapy, was given in 3 (4.83%) patients after second biopsy, respectively. Five (8.06%) patients were shifted to maintenance immunosuppression (azathioprine) and 4 (6.45%) patients were continued on azathioprine after second biopsy.

Response (CR and/or PR) was achieved in 46 (74.19%) patients and 16 (25.8%) patients had resistant disease at 6 months of treatment following second biopsy. At the last

Table 1: Change in clinical and histological variables between first and second biopsy

Clinical variable	Biopsy 1	Biopsy 2	*P*
Hypertension (%)	15 (24.2%)	21 (33.9%)	0.180
Serum creatinine (median; IQR) mg/dl	0.9 (0.7-2.01)	1.32 (0.8-2.1)	0.596
Serum creatinine >3 mg/dl (%)	10 (16.1%)	9 (14.5%)	1.00
Serum albumin (median; IQR) g/dl	2.6 (2.1-3.0)	2.82 (2.1-3.3)	0.047
Hypoalbuminemia <3 g/dl (%)	45 (72.6%)	33 (53.2%)	0.038
24 h urine protein (median; IQR) g/day	2.8 (1.95-4.2)	2.8 (1.88-4.85)	0.736
24 h urine protein >4 g/day (%)	19 (30.6%)	19 (30.6%)	1.00
Low C3 (%)	51 (82.3%)	33 (53.2%)	<0.001
Low C4 (%)	34 (54.8%)	14 (22.6%)	<0.001
Hemoglobin (median; IQR) g/dl	9.2 (8.2-10.2)	9.65 (8.87-11)	0.014
Histological variable			
Glomerulosclerosis (%)	15 (24.2%)	29 (46.8%)	0.018
Endocapillary proliferation (%)	50 (80.6%)	40 (64.5%)	0.013
Glomerular basement membrane thickening (%)	22 (35.5%)	40 (64.5%)	<0.001
Wireloop lesion (%)	14 (22.6%)	19 (30.6%)	0.359
Crescents >50% of glomeruli (%)	10 (16.1%)	10 (16.1%)	1.00
Fibrinoid necrosis (%)	9 (14.5%)	3 (4.8%)	0.070
Glomerular leucocyte infiltration (%)	4 (6.5%)	4 (6.5%)	1.00
Interstitial inflammation (%)	38 (61.3%)	42 (67.7%)	0.571
Fibrous crescent (%)	8 (12.9%)	11 (17.7%)	0.581
IFTA >30% of cortex (%)	2 (3.2%)	10 (16.1%)	0.021
ATN (%)	15 (24.2%)	21 (33.9%)	0.307
Arteriosclerosis (%)	14 (22.6%)	23 (37.1%)	0.078
TMA (vascular±glomerular) (%)	6 (9.7%)	10 (16.1%)	0.388
IgG intensity ≥3+ (%)	43 (69.4%)	39 (62.9%)	0.164
C1q intensity ≥3+ (%)	24 (38.7%)	20 (32.5%)	0.571
C3 intensity ≥3+ (%)	34 (54.8%)	24 (38.7%)	0.089

visit of 38.6 (22.2–76) months, 49 (79.03%) patients were in remission (CR in 17 and PR in 32) and 13 (21%) patients had resistant disease (4 on renal replacement therapy). Of the 28 patients with resistant disease as the indication for second biopsy, 20 (71.42%) were in remission (CR in 8 and PR in 12) and 8 (28.57%) patients remained resistant at last visit. Of the 34 patients with relapse as the indication for second biopsy, 29 (85.29%) were in remission (CR in 11 and PR in 18) and 5 (14.7%) patients had resistant disease at last visit. On univariate analysis of histopathological parameters on second biopsy, the presence of IFTA >30% (OR: 0.18 95% CI: 0.04–0.77, $P = 0.021$), arteriosclerosis (OR: 0.17 95% CI: 0.04–0.67, $P = 0.011$), and thrombotic microangiopathy (TMA) (OR: 0.18 95% CI: 0.04–0.77, $P = 0.021$) was found to predict response at the median (IQR) last visit of 13.8 (7.6–22.8) months from second biopsy. On multiple logistic regression using these variables, the presence of IFTA >30% (OR: 0.12 95% CI: 0.02–0.7, $P = 0.018$) and TMA (OR: 0.17 95% CI: 0.03–0.98, $P = 0.048$) independently predicted response at last visit.

Discussion

We report low rates (<20%) of clinically significant class switch on repeat biopsy done for renal relapse or resistant disease in patients with LN. Histological activity in the form of endocapillary hypercellularity was noted to decrease and chronicity markers (glomerulosclerosis and IFTA) along with superimposed membranous pattern were found to be increased on repeat biopsy. With a median follow-up of 38.6 months, 79% patients were in remission. The presence of IFTA >30% and TMA on second biopsy, independently predicted response at last visit (13.8 months).

The overall rate of class transformation on second biopsy was 61.3% in our study. However, clinically significant switch was seen infrequently (13.7% with proliferative lesion switched to non-proliferative; 18.2% switched from non-proliferative to proliferative), which is similar to that described by Daleboudt *et al.*[13] but differs from others reporting high transformation rates.[6,14]

On analyzing the change in histological parameters between first and second biopsies, we found significant increase in the presence of glomerulosclerosis, diffuse glomerular basement membrane thickening, and IFTA, whereas, significant decrease in endocapillary proliferation was noted. We found that 51.3% (19 out of 37) of patients with class III and/or IV LN developed superimposed membranous pattern on second biopsy. Esdaile *et al.*[5] studied 42 patients with LN who underwent per protocol repeat biopsy at the

end of 2 years of therapy. Membranous (WHO class V) and mesangial (WHO class II) patterns increased, whereas class III and IV LN decreased. However, the authors used WHO classification of LN and the distribution of pure and mixed membranous pattern at repeat biopsy was not clear. We noted significant increase in IFTA on repeat biopsies. This increase in tubulointerstitial scarring, also seen by others[10,15] may reflect inefficacy of therapy in ameliorating tubulointerstitial lesions or a pathogenesis different from glomerular lesion. Endocapillary hypercellularity decreased and other activity markers did not change on repeat biopsy done after a median of 23.13 months despite clinical activity. This is in synchrony with other studies on repeat biopsy for LN.[6,13,16,17] Moroni *et al.*[6] found the median NIH activity index to be reduced or unchanged on repeat biopsies done after a median follow-up of around 3 years despite clinical worsening. Furthermore, significant clinico-pathological discordance was noted in an Hispanic cohort of 25 patients who underwent repeat biopsy after 2 years of maintenance therapy with 25% of complete responders having chronicity index ≥5 on repeat biopsy and 60% of patients with clinically active disease having no activity on biopsy.[18] Although we examined only clinically indicated repeat biopsies, disparity between histological activity markers and clinical status in our patients could be a reflection of clinico-pathological discordance seen in treated LN patients.

While Austin *et al.*[19] popularized the activity (AI) and chronicity (CI) indices, Schwartz *et al.*[20] found poor correlation and reproducibility of AI and CI between renal pathologists. In a retrospective analysis of 105 patients with LN by Rijnink *et al.*,[21] renal flare was predicted by fibrinoid necrosis and non-white race, whereas, ESRD was predicted by fibrinoid necrosis, fibrous crescents, interstitial fibrosis/tubular atrophy (IF/TA) ≥25%, eGFR at baseline and non-white race. The authors suggested independent scoring of histological parameters such as fibrinoid necrosis, fibrous crescents, and IFTA ≥25% for prognostic relevance. Similar to the study by Rijnink *et al.*,[21] the presence of IFTA >30% predicted response at last visit in our patients. Vascular involvement in LN is considered a poor predictor of renal outcome. In a previous study at our center,[22] those with TMA had higher rates of treatment failure compared to the group without TMA at the end of 6 months of induction therapy. We found TMA on second biopsy to be a predictor of response at last visit. Although various histological parameters on repeat biopsy done per protocol after induction/maintenance therapy are known to be predictors of renal outcome, few studies[6,14,23] have looked into prognostic factors on repeat biopsy done during LN flare [Table 2].

The major limitation of our study is its retrospective nature and the lack of a control group preventing comparison between those with resistant/relapsing disease versus those with sustained response. However, we were able to analyze the change in all histological parameters between first and second biopsies and association of these variables with clinical outcome.

Conclusion

To conclude, repeat biopsy done after 23.13 (median) months from first biopsy for relapse or resistant disease in Indian patients with LN showed that significant class switch was infrequent. The prevalence of endocapillary hypercellularity decreased and that of glomerulosclerosis and IFTA increased on repeat biopsy despite patients

Table 2: Comparison of various studies on histologic parameters on repeat biopsy affecting long-term clinical outcome

Author, year	Indication for repeat biopsy	Parameter	Outcome
Moroni *et al*., 1999[6]	Persistent, worsening or relapsing proteinuria and/or renal dysfunction	Crescents in>30% of glomeruli Chronicity index (CI) ≥5	Doubling of serum creatinine
Greloni *et al*., 2014[14]	Persistent, worsening or relapsing proteinuria and/or renal dysfunction	Chronicity index≥6.5	Doubling of serum creatinine and/or end-stage renal disease (ESRD)
Zickert *et al*., 2014[24]	Per protocol (after induction therapy)	Chronicity index	ESRD and/or estimated glomerular filtration rate <60 ml/min
Alsuwaida *et al*., 2011[25]	Per protocol (after maintenance therapy)	Activity index Persistent endocapillary proliferation Persistent interstitial inflammation	Doubling of serum creatinine
Hill *et al*., 2001[26]	Per protocol (after induction therapy)	Glomerular activity index, immunofluorescence index, and biopsy index Membranoproliferative pattern Glomerular/tubular macrophages	Doubling of serum creatinine
Tannor *et al*., 2018[23]	Per protocol after induction therapy (24.4%) Disease flare (75.6%)	Chronicity index	Non-response
Present study	Renal relapse or resistant disease	Interstitial fibrosis/tubular atrophy >30% Thrombotic microangiopathy	Response (complete or partial)

having clinically active disease. Superimposed membranous pattern was seen in more than half (51.3%) of the patients with baseline class III and/or IV LN. The presence of IFTA >30% and TMA on second biopsy predicted response at the median last visit of 13.8 months from the second biopsy.

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Conflicts of interest

There are no conflicts of interest.

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