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Original Article

Change Seen in Histological Pattern in Patients with Lupus Nephritis with Positive Antiphospholipid Serology

Faisal Naseeb[1], Khalid Parvez[1], Muhammad Afzal Hamdani[1], Abdul Rehman Alarfaj[1], Hala Kfoury[2], Josep Hope Cal[3]
Department of Rheumatology[1], Department of Pathology[2], Department of Medicine[3], King Saud University Medical City, Riyadh, Saudi Arabia.

Abstract

Background: It is debatable whether a repeat renal biopsy during lupus nephritis (LN) flare is helpful in guiding the treatment and predicting prognosis.
Objective: To determine the value of serial renal biopsies in detecting histological changes in patients with lupus nephritis with APL antibodies.
Study design, settings and Duration: This Cross sectional retrospective study was conducted at King Saud University Medical City Riyadh Kingdom of Saudi Arabia (KSA) during May 2013 to August 2017.
Patients and Methods: Patients having diagnosis of SLE with positive APL antibodies and who underwent two or more renal biopsies for various indications were included into the study. The histological features of serial renal biopsies were compared. Renal biopsies were reassessed with light microscopy, immunofluorescence and electron microscopic studies and were categorized according to ISN/RPS 2004 classification. Data was analyzed using Chi-square test to assess the differences between categorical study variables.
Results: A total of 15 patients with LN having positive APL antibodies were included. The mean age of the patients was 38±10.5 years, and the disease duration was 160±9 months. The Interval between the two biopsies was 73.5±48 months. Antiphospholipid syndrome nephropathy (APSN) was noted in 4 (26%) patients at time of the first renal biopsy and in 9 (60%) on repeat biopsies. Thrombotic microangiopathy (TMA) which is the hallmark of APSN was detected in the repeat biopsy in two patients Change in the histological class was frequent and was seen in 12 out of the 15 patients while patients with proliferative LN class switching to non-proliferative class was rare.
Conclusion: Histological changes are common in serial biopsies in patients with lupus nephritis with positive APL serology. Repeat renal biopsies led to change in immunosuppression treatment in more than half of patients on average.
Key words: Renal biopsy, antiphospholipid syndrome nephropathy, lupus nephritis, thrombotic microangiopathy, systemic lupus erythematosus.

Introduction

Renal involvement is a major cause of morbidity and hospital admissions in patients with systemic lupus erythematosus (SLE) and occurs in up to 60% of lupus patients during course of disease.[1]The SLE patients with lupus nephritis (LN) who has APL antibodies have even poorer prognosis. Clinical presentation of LN and, Antiphospholipid syndrome nephropathy (APSN)is similar and thus renal biopsy becomes mandatory to differentiate between two conditions.[2] LN and APS nephropathy is significant problem because repeated flares may cause cumulative damage that can lead to chronic kidney injury even after adequate therapy.

Experts recommended baseline renal biopsy in patients with clinical and laboratory evidence of active lupus nephritis ,before starting immunosuppression (IS) therapy.[3,4] Renal histology

Corresponding Author:
Faisal Naseeb
Department of Rheumatology
King Saud University Medical City, Riyadh, Saudi Arabia.
Email: faisalnaseeb1973@gmail.com

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Authors Contribution

FN & ARA conceptualized the project. FN, KP & MAH did the data collection and literature search. FN & JHC performed the statistical analysis. Drafting, revision and writing of manuscript were done by FN, KP, HK & JHC. HK also reviewed the histology slides.

in patients of SLE can change especially during flare, particularly in terms of LN class, activity index, chronicity index. Indications of repeating renal biopsy are controversial and vary between experts. Although evidence is sparse in literature, repeat renal biopsy is done if there is persistent hematuria or nephritic range proteinuria or impairment in renal functions, in spite of adequate treatment. Repeat renal biopsy is also helpful in detecting additional pathologies in lupus patients like APS nephropathy which is poorly responsive to immunosuppressive therapy.[5] Serial Renal biopsies are also effective way of determining the efficacy of different immunosuppressive therapies in clinical trials. Histological findings can also guide the physicians about treatment changes.[6,7] Additional benefit of repeating renal biopsy is Identification of quiescent disease which may help to avoid the use of unnecessary immunosuppressive therapy with its deleterious side effects.[8]

Our objective was to review retrospectively patients of lupus nephritis with APL positive antibodies who had more than one renal biopsy performed on clinical indications, and to analyze histological changes after successive biopsies.

Patients and Methods

Study was approved by Institutional Review Board (IRB) of King Saud University, Medical City Riyadh KSA. This retrospective cross-sectional study was carried out at King Saud University Medical City, Riyadh, Saudi Arabia who have more than one renal biopsies during 1994 and 2017. The patients who underwent renal biopsy and were positive for APL antibodies were identified. From medical record results of their biopsies were reviewed from renal histopathology. Renal biopsies were re-examined with light microscopy immunofluorescence and electron microscopy and were categorized according to ISN/RPS 2004 classification. The activity and chronicity indices were determined as suggested by Austin et al.[9]

Specific histological features such as interstitial fibrosis, tubular atrophy were quantified semi quantitatively on scale of 0-3 indicating none, mild, moderate or severe respectively. The reasons for obtaining the biopsies were documented and the therapeutic decisions after first biopsy and following the second biopsy were tabulated. International Society of Thrombosis and Haemostasis (ISTH) guidelines were followed to test Anticardiolipin antibodies, beta-2 glycoprotein I antibodies and lupus anticoagulant.[10]

The decisions of treatment changes after renal biopsies were at the discretion of the individual nephrologist and rheumatologist. Changing in the treatment defined when the immunosuppressive drug was suspended, changed to another drug, or new drug was added to present regime.

The diagnosis of APSN was made when at least one of the lesions suggestive of APSN was found.

Lesions identified on biopsy were pigeon holed as acute or chronic according to the following

Criteria: (I) Acute APSN: Presence of thrombotic microangiopathy (TMA), consisting of fibrin thrombi in arteries, arterioles and/or glomeruli. (II) Chronic APSN: presence of fibrous intimal hyperplasia (FIH) consisting of myofibroblastic cellular proliferation in the intima of the arterioles, fibro-cellular arterial occlusion (FAO) consisting of arterial fibrous occlusion of small interstitial arteries and Focal cortical atrophy(FCA) involving the subcapsular cortex with or without tubular thyroidisation.[11]

Patients having diagnosis of SLE with positive APL antibodies and who underwent two or more renal biopsies in our hospital between 1994 to 2017 were included into the study. All patients had met at least four of American college of Rheumatology (ACR) 1982 revised classification criteria for Systemic Lupus Erythematosus (SLE). Patients who had renal impairment or proteinuria due to other causes were excluded.

Statistical software SPSS (version 18.0; SPSS Inc., Chicago, IL, USA) was used to analyze all data. Chi-square test was used to assess the differences between categorical study variables. A two-sided *p* value ≤0.05 was considered statistically significant.

The study was approved by Institutional Review Board (IRB) of King Saud University, Medical City, Riyadh, Kingdom of Saudi Arabia.

Results

A total of 15 female patients with LN having positive APS antibodies were included in the study. At the time of the kidney biopsy, the mean age of 15 SLE patients was 38±10.5 years, and the disease duration was 160±9 months. The Interval between the two biopsies was 73.5±48 months (Table-1).

Table 1: Demographic data and lab data.

	Mean
Age at time of first biopsy	38±10.5 years
Duration of SLE	160±9 months
Creatinine at first biopsy	71.1±16.7 mmole/L
Creatinine at cecond biopsy	166.6±120 mmole/L

Clinical indications for repeat biopsies were persistent proteinuria in 9 (53%) and worsening of renal function in 6 (47%).

APS manifestations such as arterial or venous thrombosis were found in 4 (26%) patients, and 4 (26%) females had a history of recurrent abortions. Lupus anticoagulant was positive in 6 (40%) whereas anticardiolipin (IgG and /or IgM) were positive in 13 (86%) and beta-2 glycoprotein I anti-bodies were positive in 8 (53%).

Hypertension was present in 9 (60%) of patients. Renin angiotensin blockade therapy was given in 14 (90%) of the patients.

Table 2: Evolution of histological lesions on sequential biopsy

Histological Lesions	*First Renal Biopsy*	*Second Renal Biopsy*	*p-value*
APS nephropathy	4	9	0.107
Thrombotic microangiopathy	0	2	0.480
Arterial sclerosis	2	11	0.001
Arterial hyalinosis	2	7	0.109
Focal cortical atrophy	0	5	0.042
Fibrous intimal hyperplasia	2	2	1.000
Global sclerosis	4	10	0.028
Glomerular fibrocellular crescents	2	5	0.390
Glomerular endocapillary proliferation	6	4	0.439
Glomerular double wall contour	5	4	1.000
Glomerular capillary wall wrinkling	1	1	1.000
SLE Class			0.651
SLE Class I	1	0	
SLE Class II	3	2	
SLE Class III	5	3	
SLE Class IV	3	3	
SLE Class IV and V	2	5	
SLE Class III and V	1	2	
Activity index			0.842
0 – 5	9	9	
6 – 9	2	3	
10 - 12	4	3	
Chronicity index			0.022
0 – 3	10	2	
4 – 12	5	11	
More than 12	0	1	
Interstitial fibrosis			0.230
Mild	2	4	
Moderate	0	2	
Severe	0	1	
Tubular atrophy			0.415
Mild	5	5	
Moderate	3	3	
Severe	0	2	

The mean serum creatinine was (71.1±16.7) mmole/L at time of first biopsy while it was 166.6±120 mmole/L (p value =0.005) at time of second biopsy. Eight patients (53%) out of 15 had high serum creatinine (more than 110mmole/L) at time of second renal biopsy, except one all other had proliferative class of LN (III and IV).

APS nephropathy was noted in 4 (26%) patients at time of the first renal biopsy and in 9 (60%) repeat biopsies (*p* value =0.121). Thrombotic microangiopathy which is the hallmark of APS nephropathy was detected in the repeat biopsy in two patients as shown in Figure-1. Focal cortical atrophy another feature of diagnostic importance of APS nephropathy was noted in 5 patients (33%) in subsequent biopsy (Table-2).

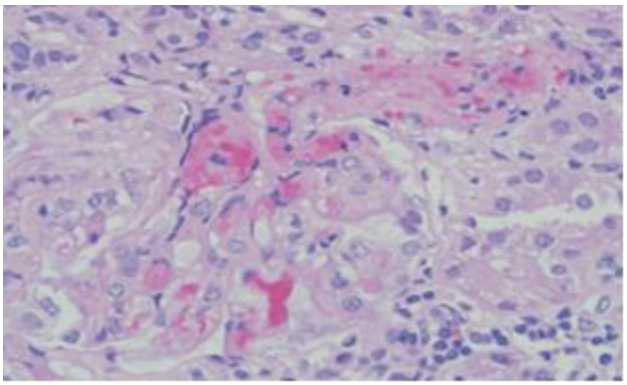

Figure 1: Photomicrograph showing afferent arteriole and glomelular capillary loops with intraluminal thrombi (HNE multiply 400).

Glomerular sclerosis is an important feature of chronicity (shown in Figure-2). When serial biopsies were compared, repeat biopsies demonstrated a higher incidence of glomerular sclerosis 4 (26%) in initial biopsy and 10 (66%) in repeat biopsy. Tubular atrophy is another feature of chronicity. Moderate to severe tubular atrophy was present 3 (20%) initial biopsies and 5 (33%) patients in subsequent biopsies.

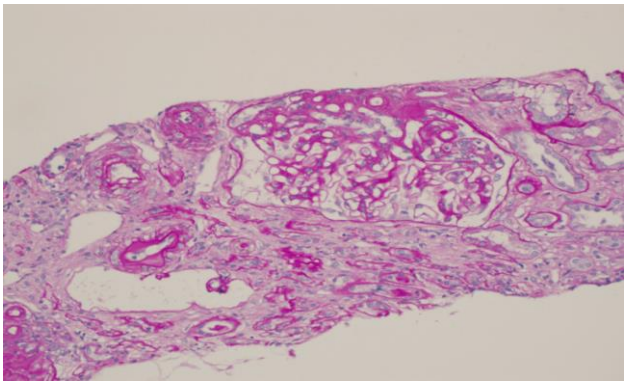

Figure 2: Figure-2-Photomicrograph showing one glomerulus with segmental sclerosis and arterioles with hyaline arteriosclerosis (PASx200).

Interstitial fibrosis is a sign of chronicity, only 2 patients in the initial biopsy has mild fibrosis while serial renal biopsies revealed underneath mild interstitial fibrosis in 4 patients, moderate fibrosis in 2 and severe interstitial fibrosis in biopsies in one patient.

LN class switch was common and was seen in 12 out of the 15 patients. In other patients LN class remained the same but they developed features suggestive of greater chronicity (2 patients class IV-A LN changed to class IV-C and one patient of class IV-A/C progressed to class IV-C).

Patient with proliferative LN class switching to non-proliferative class was rare and was noted only in one patient (class III LN changed to class II LN).

The second biopsy showed persistence of endocapillary proliferation in the majority of patients 4 out of 6 patients (26%).

Double wall contour, which was evident on electrons microscopy, was seen in 5 patients in initial biopsies and was also noted in 4 patient in repeat biopsies (26%) (Figure-3).

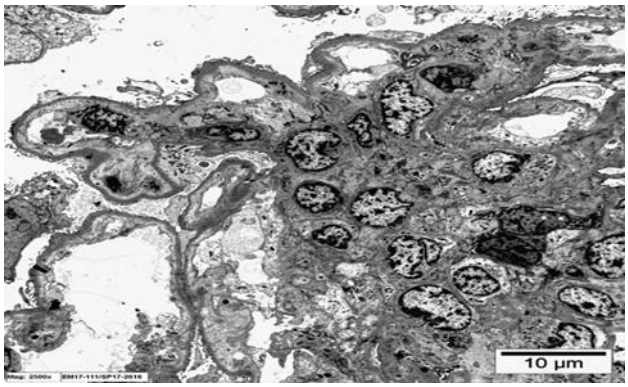

Figure 3: Electron microscopy study photomicrograph highlighting the focal double contour formation and the thickening of the glomerular basement membranes. (Uranyl acetate, Lead citrate x2500).

Just after the repeated renal biopsy, 8 patients (53%) were started on new therapy or additional immunosuppressive therapy (IST), 5 (33%) remained with the same complementary IST, and one patient (6%) on IST had discontinuation of treatment.

Discussion

Usefulness of serial renal biopsy in SLE patients is debatable issue. On one hand its effects on treatment decisions are variable while on other hand being an invasive procedure, it has risks of complications. In study current study, all patient were females, which is comparable to finding of Greloni in which 90% patients were females.[8]

Prevalence of APS nephropathy, including acute and chronic changes, in this study was 4/15 (26.6%) and in first biopsy which reached upto 9/15 (60%) in second biopsy. It was also noted by Silvariño et al.[11] Thus heterogenecity of APS nephropathy lesions can be observed not only between patients but also in same patient when the the biopsy is repeated.

Interestingly previous studies on APS antibodies and lupus nephritis revealed positive relationship between presence of APS antibodies and class V LN 12. Current study found class V

LN in combination with proliferative LN in 3 patients in initial biopsy and 7 patients in second biopsy.

In serial kidney biopsies, it was possible to find both acute and chronic lesion of APS nephropathy. Thus, serial biopsies have more chances of detecting APS nephropathy lesion, which may have therapeutic implications.[13] Although historically TMA was mentioned as hallmark of APS nephropathy, but similar lesions are also found in thrombotic thrombocytopenic purpura and scleroderma renal crises. When making diagnosis of APS nephropathy clinical scenario should be considered, rather than just depending only on histological criteria.[14]

Chronic lesions such as interstitial fibrosis and tubular atrophy were more common in second biopsies and if present in first biopsy, it did not improve with treatment and which can progress to chronic renal failure.[15,16] FIH was noted in 2 patient in initial biopsy ,in one patient it persisted while in other patient it disappeared in second biopsy. So the repeated biopsies give us chance to observe the natural evolution of APS nephrotpathy.[15]

Double wall contour due to glomerular ischemia is another important features of APS nephropathy mentioned in our previous study.[17] It persisted in serial biopsies in most patients as also mentioned by Gerhardsson (2015).[18] We observed that patients who had proliferative lesions on original biopsy seldom converts to non-proliferative lesions on second biopsy while generally class switch is common. It was also mentioned by Dalebout et al.[19] This finding supports the argument by some experts that repeating renal biopsy in patients with proliferative LN on initial biopsy is not helpful. On the other hand, non-proliferative classes like II or V LN diagnosed at baseline can benefit from repeat biopsy, because if these patient develop proliferative LN ,they may need more aggressive IS therapy.

It was previously mentioned that wrinkled basement membrane may be characteristic of APS nephropathy, was noted only in one patient in initial biopsy which persisted in second biopsy. Thus electron microscope did not seem to add in diagnostic evaluation in this respect.[19] With respect to management of patients with lupus nephritis this study has shown clinical relevance of doing second biopsy as there was change in treatment regimen after the second biopsy in most of patients while remaining patients were saved from harmful effects of additional immunosuppression therapy. It was also observed by other Alvarado (2014).[20] who mentioned that in 64% of patients Immunosuppressive (IS) therapy was tapered off and while in 34% IS therapy was continued. Current study has some limitations. Owing to retrospective design of our analysis, some points such as effect of anticoagulation on progression of APS lesions cannot be predicted.

The present study suggests that the histological changes are common in serial biopsies especially in form of class Switch and appearance and disappearance of APS lesions. Treatments are modified after the repeat renal biopsy in the majority of patients. Thus, repeat kidney biopsies were found to be useful in guiding treatment of LN flares.

Conflict of interest: None declared.

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