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Lupus Nephritis Class II: A Challenging Entity

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Abstract

Most of the literature focused on the proliferative forms of the lupic Glomerulonephritis. Clinicians are increasingly confronted with cases of lupic nephropathy purely mesangial (class II). The aim of our study is to describe the mode of presentation of the class II Lupus nephropathy, evaluate its evolutionary profile, and investigate possible risk factors for therapeutic misresponse, relapse or histological transformation. This is a retrospective descriptive and analytical study conducted in nephrology depratement at the Hassan II university hospital Fez from January 2009 until September 2018. We included 20 patients. The average age was 33.8 ± 7.25 years [22 - 50 years]. Nephropathy was inaugurated in half of the cases. The mean time of onset of nephropathy in relation to the lupic disease was 36.7 ± 45.4 months [1 - 144 months]. The main reason for consultation was non-nephrotic proteinuria (65%). Renal failure revealed diagnosis in three patients. All patients had a positive immunologic assessment. 90% of our patients received oral corticosteroid therapy with immunosuppressive therapy in 3 cases. Remission has been noted in all of our patients. After an average follow-up period of 39 ± 23 months [6 - 92 months], 45% relapsed. A second biopsy was performed in 80% of patients showing histologic transformation in four patients, requiring immunosuppressive therapy. The analytical study showed that the occurrence of relapse was significantly related to the presence of a known Lupus and its seniority. Proteinuria at 12 months was also significantly higher in the relapsed group. One patient died as a result of neurological complications. Another has Evolved into chronic end stage renal failure and has been put on hemodialysis.

Keywords

Lupus Nephritis, Mesangial Nephropathy, Relapse

1. Introduction

Kidney damage during lupus is common and accounts for almost half of lupus patients. It represents an important risk factor for morbidity and mortality [1]. Class II lupus nephritis (LN), known as purely mesangial nephropathy, accounts for 5% to 22% of cases of lupus nephropathies depending on the series Class II is defined by high mesangial cellularity (characterized by at least 3 mesangial cells trois per air in a section of 3 mm) with immune deposit on immunofluorescence and/or electronic microscopy.

It has long been considered a benign variant of LN. However, new data show a significant rate of histological transformation, particularly towards proliferative forms, thus impacting the long-term evolution of these patients [2] [3]. there are disparities in the guidelines on the treatment of class II LN due to a lack of evidence, leaving the clinician with a dilemma concerning, the indications for initial renal biopsy (RB) and re-biopsy, as well as the very poorly codified therapeutic choices.

The aim of this work is to explore the clinical biological and therapeutic features of patients with LN class II in our unit, as well as to assess their evolutionary profile and examine the possible risk factors for poor therapeutic response, relapse or histological transformation.

2. Materials and Methods

This is a retrospective descriptive and analytical study conducted in the Nephrology Department of the Hassan II university hospital of Fez over a period of 9 years that extends from January 2009 to September 2018.

We included in this study all patients who were subject to a first RB during the study period and whose results were in favour of LN class II. Lupus was diagnosed according to the Criteria for Systemic Lupus Erythematosus (SLICC 2012) criteria.

We excluded patients with follow-up less than 6 months, renal biopsies with less than 10 glomeruli, biopsies without immunofluorescence data, RB performed after at least 1 month of immunosuppressive therapy.

Data on the demographic, clinical, biological, therapeutic and evolutionary aspects were collected from patients' medical records and the information system of the Hassan II University Hospital. The different histological parameters were collected from the renal biopsy reports.

The statistical analysis was carried out by the Laboratory of Epidemiology and Clinical Research of the Faculty of Medicine and Pharmacy of Fez. The quantitative variables were expressed as an average ± standard deviation from the mean,

and were compared using Student's test. Qualitative variables were expressed in numbers and percentages and compared by Chi 2 tests. A value of p was considered significant if it is less than 0.05.

3. Results

During the period of our study, 1483 RB were performed in total. Of these, 146 were in favour of lupus nephropathy on the first RB, with a prevalence of 10%. Nephropathy was classified as class II in 20% of LN cases (n = 29). Nine patients were excluded due to a follow-up of less than 6 months, renal biopsies with less than 10 glomeruli, biopsies without immunofluorescence data, RB performed after at least 1 month of immunosuppressive therapy (Figure 1).

All our patients were women. The average age was 33.8 ± 7.25 years [22 - 50 years]. We studied the distribution of patients according to 4 age groups: The majority was between 25 and 45 years old (80%) (Table 1).

The first renal sign in our series was non-nephrotic proteinuria (65%). Renal failure revealed the diagnosis in three patients, while macroscopic hematuria was present in only one patient.

Systemic lupus erythematous (SLE) was known in half of our patients, with an average time to diagnosis of renal impairment of 36.7 ± 45.4 months [1 - 144 months].

Regarding the treatments in progress at the time of the discovery of renal involvement, 30% of patients were on low-dose corticosteroids associated with azathioprine in two patients, 20% were on inhibitors of the renin angiotensin aldosterone system and 30% were on synthetic antimalarials.

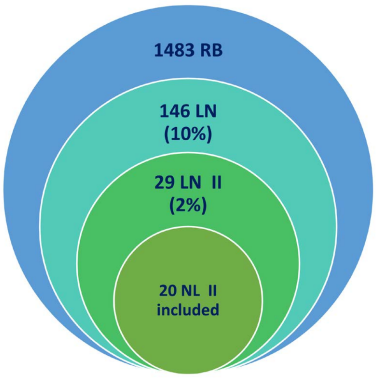

Figure 1. Flow-chart of our study.

Table 1. Distribution of cases by age group.

Age groups	Number of patients	(%)
16 - 24 ans	3	15
25 - 34 ans	8	40
35 - 45 ans	8	40
>45 ans	1	5

Clinical examination revealed high blood pressure in 5 patients, three of whom were not known to be hypertensive. Lower limb edema was present in 35% of patients. The urine dipstick revealed albuminuria in all patients and hematuria in 35% of patients. The mean 24-hour proteinuria was 2.34 ± 1.54 g/d [0.56 - 4.8 g/d]. Nephrotic syndrome was present in 35% of the cases (Figure 2).

For renal function, mean serum creatinine was 10.4 ± 7.5 mg/L [5 - 40 mg/L. The average GFR in our patients was 86.8 ± 37.18 mL/min/1.73m^2 [13 - 153 mL/min/1.73m^2] according to the MDRD (Modification of Diet in Renal Disease) formula. On patient was anuric.

Extrarenal manifestations were dominated by articular, immunological and cutaneous manifestations. The different manifestations are shown in Figure 3.

Renal biopsy was performed after an average time of 31 ± 45 days [1 - 180 days] compared to nephrological consultation. No cases of post-biopsy complications were noted. In addition to glomerular involvement renal biopsy showed interstitial infiltrate in 4 patients. No vascular lesions have been described (Figure 4 and Figure 5).

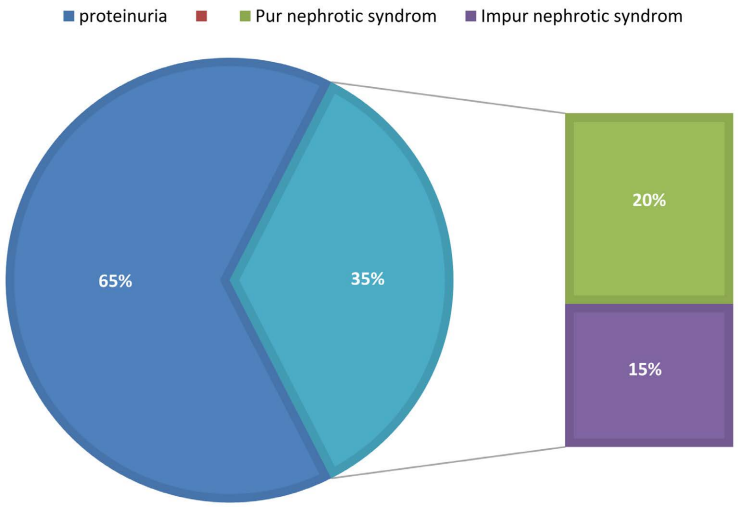

Figure 2. Distribution according to the degree of proteinuria.

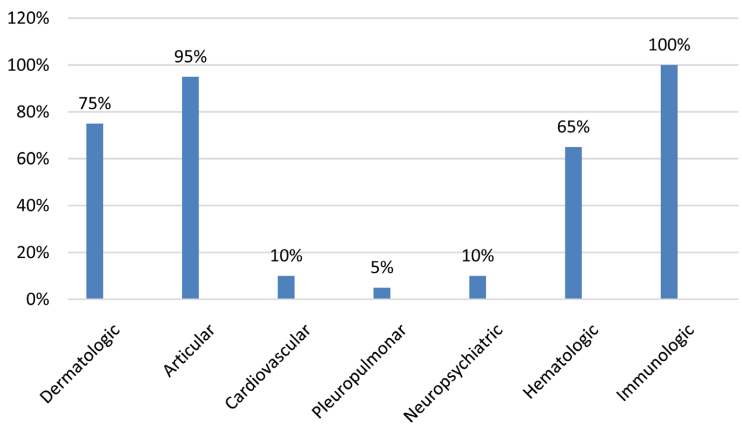

Figure 3. Prevalence of extra-renal manifestations.

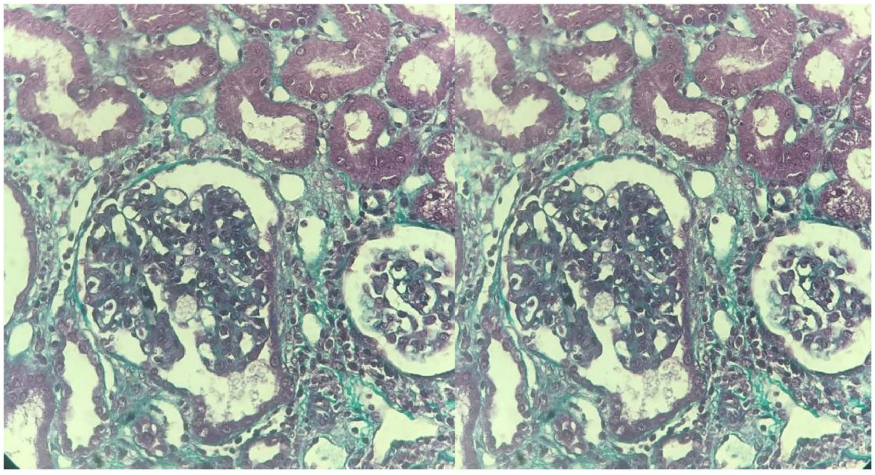

Figure 4. Histological sections of a RB showing in optical microscopy with Masson trichrome a mesangial proliferation without endo or extra-capillary proliferation.

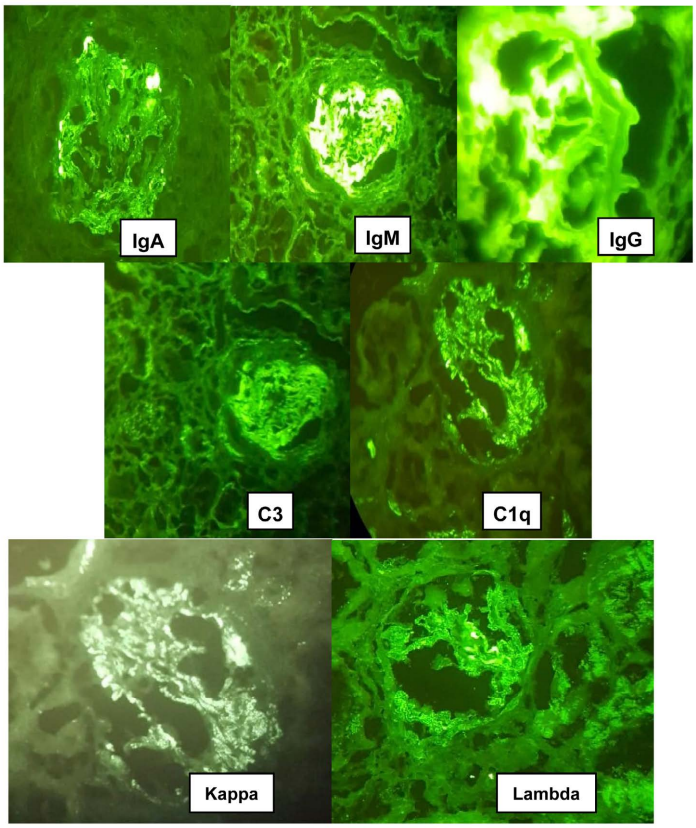

Figure 5. Histological sections of a RB showing LN II immunofluorescence deposits of IgA, IgM, IgG, C3 and C1q with a so-called "Full house" appearance.

Assessment of LED activity revealed a SLEDAI score at nephrology admission of 11 ± 3.7 [8 - 18 g/dL] on average. Half of the patients had high activity; the other half had medium activity. No patient had a very high activity score.

Regarding treatment, almost all of our patients received oral corticosteroid therapy (90%), combined with immunosuppressive therapy in 3 cases. Indica-

tions for immunosuppressive therapy were the presence of neurological impairment in two cases, and renal impairment at admission in only one case. Two patients received only antiproteinuric therapy based on an inhibitor of the renin system angiotensin aldosterone. All our patients were put on synthetic antimalarials at the time of diagnosis; six of them were already taking it before the discovery of kidney injury.

All our patients received an anti-protein treatment based on IEC and/or ARA as well as an adjuvant treatment of corticosteroid therapy in particular vitamin D and calcium orally. The average duration of follow-up was 39 ± 23 months [6 - 92 months]. One patient died a few days after renal diagnosis as a result of neurological complications. All other patients achieved remission under treatment: 70% in complete remission with an average time of 2.6 ± 2 months [1 - 6 months].

The evolution of proteinuria levels at 6 months, 12 months, and at the latest news is represented in (Table 2). Of our patients, 45% relapsed after an average delay of 13 ± 6 months [6 - 24 months]. Of these, 80% were rebiopsied. The indication for rebiopsy was worsening of proteinuria in all our patients, associated with hematuria in three patients and worsening of renal function in only one patient. The second biopsy showed histological transformation in four patients, three of whom were proliferative (Figure 4).

Patients who did not undergo histological transformation were treated with oral corticosteroid therapy alone. Those who switched to a proliferative form received in addition, treatment by cyclophosphamide. A single biopsy revealed a transformation to class V and was treated with mycophenolate mofetil.

Remission was achieved in almost all patients after an average time of 2.3 ± 1.5 months [1 - 4 months]. Only one patient who had a class IV on the second biopsy did show only partial remission and was then lost to follow-up for four years. She then returned with advanced renal failure, the third biopsy showed a NL class IV, and she was put on Rituximab. The evolution was marked by persistence of renal failure. A fourth biopsy performed 5 months later showed a histological transformation to LN class VI. The patient is currently undergoing chronic hemodialysis.

Table 2. Evolution of proteinuria and risk of relapse.

Proteinuria g/day	Mean proteinuria in patient with complete remission n = 10	Mean proteinuria in Patients with partial remission n = 9	p
At admission	1.6	2.17	0.7
At 6 months	0.2	0.94	0.25
A 12 months	**0.16**	**1.35**	**0.02**
To the latest news	0.2	0.28	0.55

In our study, we compared two groups according to the occurrence or not of a relapse. We excluded the deceased patient. Patients who relapsed were younger, with a longer mean time between the renal biopsy and the first nephrological consultation, greater proteinuria on admission, and had more anemia and thrombocytopenia. However, not all of these parameters were significant.

When comparing the two groups (patients who relapsed versus those who did not relapse), The analytical study showed that the occurrence of relapse was significantly related to the presence of known lupus as well as its seniority, however, a high SLEDAI score, the presence of a nephrotic syndrom, hematuria, kidney injury, hematological abnormalities, the treatment by corticosteroids or renin angiotensin inhibitors was not related to the occurrence of a relapse.

Proteinuria at 12 months was also significantly higher in the group that relapsed (Table 3).

We also compared patients who had histological transformation with those who did not. No factor was significantly related to histological transformation.

Table 3. Risk factors for relapse.

	No relapse (n = 10)	Relapse (n = 9)	p
Age (years)	36	30	0.07
Time to biopsie (days)	12	20	0.6
Lupus seniority (months)	**0**	**12**	**0.04**
SLEDAI at admission	12	8	0.9
Inaugural lupus	**80%**	**20%**	**0.025**
High blood pressure	30%	20%	1
Proteinuria (g/d)	1.6	2.1	0.7
Nephrotic syndrom	30%	40%	1
Hematuria	50%	20%	0.32
Kidney injury	30%	10%	0.5
Anemia	50%	70%	0.65
Lymphopenia	37.5%	62.5%	0.6
thrombopenia	40%	10%	0.3
Corticosteroids	67%	90%	0.58
Renin angiotensin inhibitors	14%	0%	0.4
Immunosuppressive therapy	25%	10%	0.55
Antimalarial treatment	80%	77%	0.9

4. Discussion

Renal involvement is common in lupus and determines the prognosis. It is seen in about half of patients. It appears in 10% to 40% of cases during the first year of the disease and can sometimes be inaugural [1]. Until today, there is a limited number of publications that have focused on the particularities and evolution of class II lupus nephropathy [2]. In our study, Class II LN represents 20% in our study, compared to 4.9% and 22% in the literature [3] [4].

Although there is no anatomo-clinical correlation between renal presentation and histological type, the most reported clinical presentations in the literature are microscopic hematuria with subnephrotic proteinuria and normal renal function [5] [6]. However, other reports have shown that many class II LN can initially present as a nephrotic syndrome [7]. High proteinuria may be related to podocytopathy since histological changes are not severe enough to explain this degree of proteinuria. In our study, 35% of patients had nephrotic proteinuria, compared to 20% in the Argentine series [2].

Renal failure is less frequently described in NL class II and was found at the time of diagnosis in 20% of cases in our series versus 7% to 22% in other series [2] [6].

The treatment of NL Class II is not very well codified. The KDIGO 2021 similar to KDIGO 2012 suggests treating patients based on the level of proteinuria and the severity of extrarenal manifestations [8] [9]. Although corticosteroid therapy is often recommended only for highly proteinuric forms or those that do not respond to antiproteinuric therapy initially, the fact remains that the majority of published series report wider us [2] [6]. In our series, all patients were treated with corticosteroid therapy combined in 3 cases with immunosuppressive therapy, when extrarenal manifestations required it. Despite this wider use of corticosteroid therapy, this treatment could not prevent relapses in almost half of our patients, or the long-term adverse results in almost half of the patients in the Argentina series [2], this risk is shown to be more significant when tapering the steroids treatment [10]. In the absence of randomized controlled trials, observational studies showed that over 90% of patients given glucocorticoid monotherapy achieved remission within a median time of 4 weeks [11] [12].

The optimal duration is not known; maintenance with low-dose glucocorticoid plus an additional agent such as a Mycophenolic acid analog, azathioprine, or calcineurin inhibitors is suggested, especially in patients with a history of relapse [9].

Optimal control of blood pressure by blocking RAAS is a cornerstone of conservative treatment of all forms of LN. The KDIGO recommend the introduction of an I or ARB II as first-line antihypertensive therapy for the treatment of proteinuric kidney diseases such as LN [9]. These drugs decrease intraglomerular pressure, lower systemic blood pressure, reduce urinary protein excretion and delay the progression of chronic kidney disease to end-stage renal failure. Other

studies have shown that RAAS and its pharmacological blockade may play a role in the pathogenesis and prognosis of SLE regardless of its effects on systemic blood pressure and glomerular hemodynamics [13]. Animal studies have focused on the inflammatory components of RAAS and the potential benefits of blocking RAAS in reducing inflammation in non-proliferative forms of NL [14].

Although mesangial nephropathy is considered a mild variant of NL, one-fifth of patients have severe outcomes [2] [4]. In our study, of the 45% (9 patients) who relapsed, 80% were rebiopsied. The second biopsy showed histological transformation in four patients, three of whom were proliferative. The biopsies were redone within an earlier period of 13 ± 6 months [6 - 24 months], this could be explained by the expansion of ACB indications in our unit.

The frequency of histological transformations reported by the other authors varies between 14.8% and 47.4% with an average rebiospie time of 33 to 58 months [3] [7]. Since most subsequent biopsies were performed nearly 3 years after the first biopsy, histological transformation is considered a late event. This transformation is sometimes described as the consequence of different stages of a single continuum, which begins in the mesangium with deposits of immune complexes and complements and progresses to more severe classes when the phagocytic capacities of mesangial cells are burned out [15]. Predictors of unfavorable outcome in the long term were the persistence of proteinuria with values greater than 0.5 g/d, and the persistance of proteinuria at 6 months [2] [16].

In our series, patients who required a second biopsy were younger, but the age criterion was not significant. In other series, younger patients were significantly more at risk of relapse, perhaps as follow-up would be more prolonged. Indeed, in the Argentine series, patients who received a second RB were significantly younger, proteinuria at 1 year was significantly higher in this group [2].

This study showed also, that a short time between the diagnosis of lupus and the occurrence of renal injury was significantly linked to the risk of relapse. In our study, it was rather about the age of the lupus disease that was related to relapse [2].

Then, as might be expected, taking a synthetic antimalarial or a RAAS inhibitor was more of a protective factor [17]. Several other studies have looked at the interest of clinical or biological markers that would predict the occurrence of relapse in lupus nephropathy; the various markers essentially help us to confirm a lupus flare-up. An increase in anti-DNA titer has often been associated with a relapse of LN and retrospective studies even show up to 89% relapse within ten weeks of an increase in anti-DNA titer, but this marker can also remain elevated regardless of any recurrence [18]. On the other hand, Studies of treated mice identified a type II (M2b)-activated macrophage as a marker of remission induction and impending relapse and suggest that therapy for systemic lupus erythematosus nephritis should include strategies that prevent both activation of monocytes and their migration to the kidney [18]. However, to date, no blood or urinary marker is able to provide as much information as a kidney biopsy.

In a study by Wang *et al.*, they analyzed 125 biopsies of lupus nephritis patients divided into podocytopathy group and mesangial group where the foot process effacement was less than 50% with a risk of renal relapse greater in the podocytopathy group.

5. Conclusions

Our results as well as those published for lupus nephropathy class II show a fairly high rate of histological transformation, especially when lupus disease is old and proteinuria at one year is high. The indication to perform a new biopsy should always be discussed in order to note these transformations requiring immunosuppressive treatment.

However, this study has inherent limitations to its retrospective nature, as well as the size of the sample. This is why it is necessary to conduct prospective studies with a higher number of patients to reinforce these results.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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