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REVIEW ARTICLE

Very Late Onset Lupus Nephritis: Single-Centre Experience and A Review of the Literature

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ABSTRACT

Background: In the majority of lupus patients, lupus nephritis (LN) develops within the first five years of diagnosis. Here we evaluated patients treated in our department during the past 40 years distinguishing those with very early onset [within one year of diagnosis]; early onset [two to five years post diagnosis]; medium-term onset [between six to ten years after diagnosis]; late onset [presenting six to 15 years after diagnosis] and very late onset LN [presenting 16 years or later after diagnosis]. Early onset [two to five years post diagnosis]; medium-term onset [between six to ten years after diagnosis]; late onset [presenting six to 15 years after diagnosis] and very late onset LN [presenting 16 years or later after diagnosis].early onset [within two years of diagnosis]; medium-term onset [between two and five years after diagnosis]; late onset [presenting five to ten years after diagnosis] and very late onset LN [presenting ten years after diagnosis].

Aim: To compare the differences in demography, clinical data, serological profile and follow up of patients with LN of early, medium, late and very late onset.

Methods: This was a retrospective study of 226 systemic lupus erythematosus (SLE) patients with biopsy proven nephritis. We focused on a comparison of their epidemiology, serology, clinical and follow-up data.

Results: We identified 97 (43%) very early-onset patients; 69 (31%) early-onset; 28 (12%) medium onset; 22 (10%) late-onset and 10 (4%) very late-onset LN patients. Comparing those patients whose LN was delayed by> 10 years post their lupus diagnosis compared to those with LN onset <10 years we found that these patients were statistically significantly more likely to be Caucasian [p=0.04]; to have arthritis [p=0.001] and to be leucopaenic [p=0.004]. There were no other difference between the groups. Among the 10 patients with very late onset LN there was an increase trend towards them having higher ANA titer (>1:640) [p=0,044] and having biopsy-proven combined type of LN (III+V, IV+V) [p=0.034].

Conclusion: Although the majority of SLE patients who get LN do so within 10 years of diagnosis in our experience 14% [approximately 1:7] developed renal involvement 10 years or more after SLE diagnosis. The observation emphasis the need to be vigilant when caring for SLE patients long term.

INTRODUCTION:

Approximately 30-50% of patients with systemic lupus erythematosus [SLE] develop nephritis [LN].[1] As we and others have reported, [2,3,4] LN is a serious and potentially sinister manifestation of lupus and it remains important to be mindful of its potential development in patients who present with any of the myriad other clinical features of the disease, not least because unlike its most common clinical manifestations, notably skin rashes and arthritis, it is "clinically silent". It is mandatory to monitor both blood pressure and the presence of proteinuria on a regular basis.

In the majority of lupus patients, LN develops within the first five years of diagnosis.

The SLE Clinic at University College Hospital/the Middlesex Hospital was established in January 1978 and since then approximately 850 patients have been under our long-term care. We have now carefully reviewed the available data on these patients and, restricting our analysis to those who have biopsy-proven LN, have distinguished those patients with very early onset [within one year of diagnosis]; those with early onset [between two and five years after diagnosis]; medium onset [presenting six to ten years after diagnosis]; those with late onset disease [presenting eleven to 15 years after diagnosis] and those with very late onset (> 16 years post diagnosis). We have focused on those presenting with very late onset disease since they are less well-described, and have sought to determine whether there are any identifying features, which might help to characterise this group of patients and to distinguish them, both from LN patients developing their nephritis earlier in the course of the disease or those who never seem to develop LN at all.

METHODS

This was a retrospective observational study comprising a total of 226 patients with biopsy-proven LN treated between 1978 and 2022 at SLE Clinic at University College Hospital/the Middlesex Hospital. The diagnosis of SLE in all patients was made according to the 1997 American College of Rheumatology (ACR) revised criteria.[5] The biopsy specimens were assessed using the classification system of on the International Society of Nephrology/ Renal Pathology (ISN/RPS).[6] Among those patients with repeated histopathological results, the first result was used in this study.

All clinical and laboratory data were assessed at the time of kidney biopsy.

The demographic data included age, sex, origin, date of SLE diagnosis, duration of SLE (from the diagnosis of SLE to renal biopsy) and comorbidities including Sjögren's syndrome (SS)/anti-phospholipid syndrome (APS).

Laboratory data collected were white blood cell count, platelet count, lymphocyte count, hemoglobin level, rheumatoid factor (RF), anti-Ro/SSA, anti-La/SSA, complement 3 (C3), lupus anticoagulant, anticardiolipin antibody, anti-nuclear antibody (ANA), anti-double-stranded DNA antibody (anti-dsDNA), anti-Smith (anti-Sm) antibody, and anti-ribonucleoprotein (anti-RNP) antibody.

We assessed those clinical manifestations which comprise the 1997 ACR revised classification criteria, including skin rash, photosensitivity, oral ulcer, arthritis, serositis and neurologic, hematologic and immunologic disorders.

We divided the 226 patients into five groups: first group was defined as the development of LN within 1 year of the patient's SLE diagnosis, second group - 2-5 years, third - 6-10 years, fourth - 11-15 years, fifth - more than 15 years.

The follow-up duration was determined as the time from the diagnosis of lupus nephritis to the last visit for those patients who survived, to death for the deceased patients, and to the initiation of dialysis for the patients with end-stage renal disease (ESRD).

Comparisons between the groups were performed using the Chi-square test for categorical variables The significance level was set at $p < 0.05$.

RESULTS

Demographic data

The majority of patients, n= 97(43%), developed lupus nephritis within a year of being diagnosed with systemic lupus erythematosus (Table 1). There were 69 patients - whose disease developed after 2-5 years; the so-called medium-onset LN group comprised 28 patients 12%. Late onset LN occurred in 22 patients andvery late onset disease in 10 patients.

Table 1. Demographic characteristics of the patients

	Time of LN diagnosis in years after SLE diagnosis				
	0-1 years	**2-5 years**	**6-10 years**	**11-15 years**	**>16 years**
Number of patients, n (%)	97 (43%)	69 (31%)	28 (12%)	22 (10%)	10 (4%)
Female, n (%)	88 (90%)	62 (89%)	25 (89%)	21 (96%)	8 (80%)
Ethnicity: Caucasian, n (%)	40 (41%)	26 (38%)	14 (50%)	13 (59%)	7 (70%)
Black, n (%)	29 (30%)	19 (28%)	6 (21%)	6 (27%)	1 (10%)
Asian, n (%)	17 (18%)	11 (16%)	7 (25%)	2 (9%)	0
Mixed, n (%)	11 (11%)	13 (19%)	1 (4%)	1 (5%)	2 (20%)
Follow up, n (%) **Death** **Continued follow-up** **Moved away from follow up**	 11 (11%) 80 (83%) 6 (6%)	 17 (25%) 43 (62%) 9 (13%)	 3 (11%) 23 (82%) 2 (7%)	 2 (9%) 20 (91%) 0	 1(10%) 7 (70%) 2 (20%)
End stage renal disease, n (%)	9 (9%)	17 (25%)	2 (7%)	4 (18%)	1(10%)

Female population dominate in all groups, and the majority of patients in all groups were Caucasian.

The percentage of patients of mixed origin was relatively similar in the groups of patients with early and very late onset of LN, and fewest in the patients with medium and late onset.

There was also no difference in the long-term outcomes (the mortality, development of terminal renal failure) between groups.

Clinical manifestations

The most common clinical manifestations in all patients were arthritis and rash (Table 2).

Oral ulcers and serositis were more common in the late-onset and very late-onset LN groups.

Nervous system involvement in contrast, was almost identical in all groups except in the very late onset LN group, where this feature was not recorded.

We observed Sjögren's syndrome in 4 patients in the early onset group, 2 in the late onset group, and 2 in the very late onset group.

Table 2. Clinical characteristics of the patients

	Time of LN diagnosis in years after SLE diagnosis				
	0-1 years	**2-5 years**	**6-10 years**	**11-15 years**	**>16 years**
Rash, n (%)	58 (60%)	42 (61%)	21 (75%)	16 (72%)	6 (60%)
Photosensitivity, n (%)	32 (33%)	26 (38%)	14 (50%)	10 (46%)	4 (40%)
Alopecia, n (%)	32 (33%)	19 (28%)	10 (36%)	6 (29%)	1 (10%)
Oral ulcers, n (%)	20 (21%)	18 (26%)	14 (50%)	9 (40%)	3 (30%)
Arthritis, n (%)	82 (84%)	63 (91%)	27 (96%)	21 (96%)	9 (90%)
Serositis, n (%)	35 (36%)	27 (39%)	10 (36%)	10 (46%)	3 (30%)
Central nervous system (CNS), n (%)	18 (18%)	14 (20%)	5 (18%)	4 (18%)	0%
Sjogren's syndrome, n (%)	4 (4%)	0%	2 (7%)	1 (5%)	1 (10%)

Laboratory data

Summary data on laboratory studies, including immunology, are presented in the table 3.

Patients in the very late-onset LN group, were more likely to have high an ANA titre (>1:640) [p=0.044]

Differences in the ISN/RPS classification

The distribution of patients by class of LN is presented in the Fig.1. LN VI class was not present in any patient in our case.

Table 3. Laboratory characteristics

	Time of LN diagnosis in years after SLE diagnosis				
	0-1 years	**2-5 years**	**6-10 years**	**11-15 years**	**>16 years**
Haemolytic anemia, n (%)	2 (2%)	5 (7%)	0%	0%	1 (10%)
Leucopenia, n (%)	17 (17%)	23 (33%)	8 (29%)	11 (50%)	5 (50%)
Lympopenia, n (%)	73 (75%)	62 (90%)	22 (79%)	17 (77%)	10 (100%)
Thrombocytopenia, n (%)	9 (9%)	12 (17%)	5 (18%)	2 (9%)	1 (10%)
ANA, n (%)	95 (98%)	68 (99%)	28 (100%)	22 (100%)	9 (90%)
RF, n (%)	14 (14%)	14 (20%)	7 (25%)	6 (27%)	2 (20%)
anti-Sm, n (%)	28 (29%)	14 (20%)	6 (21%)	6 (27%)	1 (10%)
anti-RNP, n (%)	32 (33%)	28 (41%)	8 (29%)	11 (50%)	3 (30%)
anti-Ro, n (%)	45 (46%)	26 (38%)	7 (25%)	8 (36%)	3 (30%)
anti-La, n (%)	18 (18%)	10 (15%)	3 (11%)	5 (23%)	0%
anti-dsDNA, n (%)	79 (81%)	54 (78%)	24 (85%)	17 (77%)	9 (90%)
Decreased C3, n (%)	76 (78%)	52 (75%)	21 (75%)	17 (77%)	7 (70%)
Lupus anticoagulant, n (%)	15 (15%)	11 (16%)	6 (21%)	5 (24%)	1 (10%)
Anticardiolipin, n (%)	17 (17%)	21 (31%)	5 (18%)	5 (23%)	3 (30%)

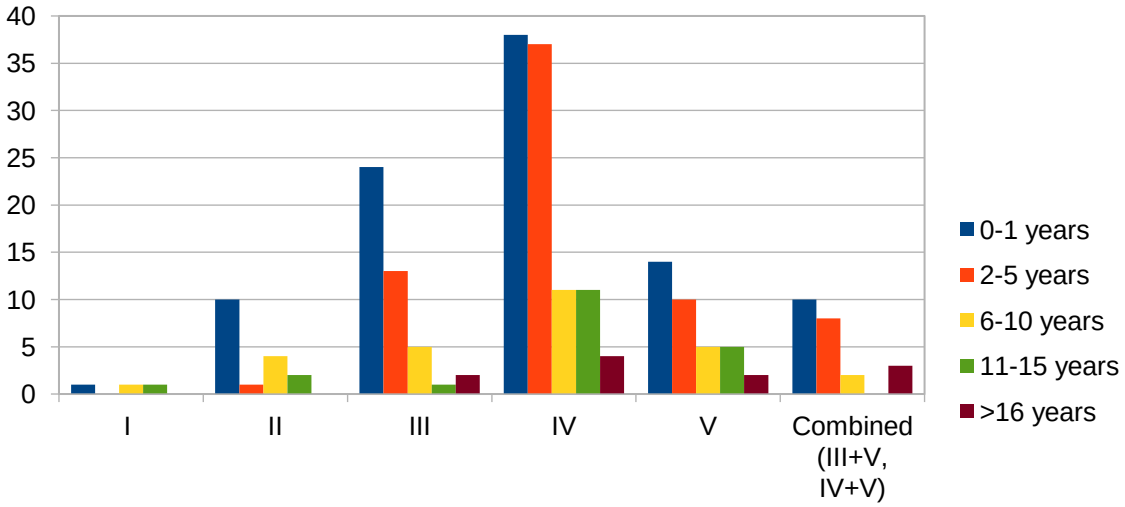

Fig.1 ISN/RPS class of LN

By chi-square analysis we compared a variety of clinical and serological features of those LN patients whose disease developed within 10 years of their lupus diagnosis and those whose LN developed >10 years after diagnosis (Table 4). The only statistically significantly different results indicate that those patients whose renal disease started >10 years post diagnosis were more likely to be Caucasian [p=0.04], to have arthritis [p=0.001], to be leucopaenic [p=0.004] and have combined classes of LN [p=0.034].

In the group of 10 patients whose LN began >16 years post diagnosis we noted that they were more likely to have high ANA titre [p=0.044] and have combined class of LN [p=0,034] (Table 5).

Table 4. Comparison of clinical and serological features between LN patients whose onset was <10 years or >10 years after SLE diagnosis

	<10 years n=194	>10 years n=32	p-value
Female	175	29	NS
Ethnicity: **Caucasian**	80	20	p=0,04
Black	55	7	NS
Asian	35	2	NS
Mixed	25	3	NS
Follow up **Death** **Continued follow-up** **Moved away from follow up**	31 146 17	3 27 2	NS NS NS
End stage renal disease	28	5	NS
Rash	121	22	NS
Photosensitivity	72	14	NS
Alopecia	61	7	NS
Oral ulcers	52	12	NS
Arthritis	172	20	P=0.001
Serositis	72	13	NS
Central nervous system (CNS)	37	4	NS
Sjogren's syndrome	6	2	NS
Haemolytic anemia	7	1	NS
Leucopenia	48	16	P=0.004
Lympopenia	157	27	NS
Thrombocytopenia	26	3	NS
ANA	191	31	NS
RF	35	8	NS
anti-Sm	48	7	NS
anti-RNP	68	14	NS
anti-Ro	78	11	NS
anti-La	31	5	NS
anti-dsDNA	157	26	NS
Decreased C3	149	24	NS
Lupus anticoagulant	32	6	NS
Anticardiolipin	32	8	NS

WHO Class kidney biopsy			
I	**2**	**1**	**NS**
II	**15**	**2**	**NS**
III	**42**	**3**	**NS**
IV	**86**	**15**	**NS**
V	**29**	**7**	**NS**
VI	**0**	**0**	
Combined (III+V, IV+V)	**20**	**3**	**0,034**

Table 5 Comparison of clinical and serological features between LN patients whose onset was <16 years or >16 years after SLE diagnosis

	<16 years n=216	>16 years n=10	p-value
Female	196	8	NS
Ethnicity: **Caucasian**	93	7	NS
Black	60	1	NS
Asian	37	0	NS
Mixed	26	2	NS
Follow up **Death** **Continued follow-up** **Moved away from follow up**	31 146 17	3 27 2	NS NS NS
End stage renal disease	28	5	NS
Rash	137	6	NS
Photosensitivity	82	4	NS
Alopecia	67	1	NS
Oral ulcers	61	3	NS
Arthritis	193	9	NS
Serositis	82	3	NS
Central nervous system (CNS)	41	0	NS
Sjogren's syndrome	7	1	NS
Haemolytic anemia	7	1	NS
Leucopenia	59	5	NS
Lympopenia	174	10	NS
Thrombocytopenia	28	1	NS
High ANA	213	9	P=0,044
RF	41	2	NS
anti-Sm	54	1	NS
anti-RNP	79	3	NS
anti-Ro	86	3	NS
anti-La	36	0	NS
anti-dsDNA	174	9	NS
Decreased C3	166	7	NS
Lupus anticoagulant	37	1	NS
Anticardiolipin	48	3	NS

WHO Class kidney biopsy			
I	3	0	NS
II	17	0	NS
III	43	2	NS
IV	97	4	NS
V	34	2	NS
VI	0	0	
Combined (III+V, IV+V)	20	3	p=0.034

DISCUSSION

To our knowledge, this is the first study to assess, in detail, the differences between lupus nephritis patients who developed renal involvement before and 16 years after SLE diagnosis.

There is a lack of knowledge about LN which starts more than 16 years after SLE diagnosis. This is explained mainly by its scarcity; its delayed presentation confirming the importance of long follow-up of patients with SLE. With the increasing life expectancy of patients with SLE, it is likely that more cases of very late-onset LN will emerge.

We report a group of 10 patients whose lupus nephritis was diagnosed more than 15 years after the onset of their SLE. As far as we are aware, this is the largest group of very late onset lupus nephritis cases reported to date. This is part of a much larger cohort [n = 226] who have been followed up in our centre since 1978. Notably we report that 14% of our patients [approximately 1 in 7] develop their disease more than 10 years after diagnosis. It thus remains important to be vigilant and monitor both for late onset hypertension and proteinuria more than 10 years after SLE is diagnosed. This group of patients was also, incidentally, more likely to be Caucasian, to have arthritis, to be leucopenic and, interestingly to have, more than 1 class of LN present on their biopsy.

The latest developing case of LN after an SLE diagnosis that we have been able to identify in the literature occurred 34 years after the original lupus diagnosis.[7] Table 6 highlights a number of reports describing the onset of lupus some years after the original diagnosis of lupus. In Table 6a we identify those reports where the nephritis occurred more than 5 years after the diagnosis of lupus and Table 6b [which includes our original report] those groups reporting onset more than 10 years after diagnosis. Perhaps not surprisingly there are a number of differences amongst the previously reported series and in our experience. Tian et al [8] found no difference in terms of "kidney outcome comparing their early onset [less than 5 years] and late onset [more than 5 years] cases and these findings were reproduced by Ugoleni Lopez et al [9] and Ahn et al [10]. These data are broadly in line with our own results although the trend to end-stage renal disease in those whose nephritis diagnosis began more than 15 years after diagnosis was high [5 out of 10, 50%] compared to those whose nephritis began earlier [28 out of 216, 13%]. In addition, the number of deaths [3 out of 10, 30%) was higher in the more delayed onset group compared to 31 out of 216 (14.3%) in the earlier onset patients. This result suggests that later onset nephritis patients may not do as well. In support of this view The reports of Yap et al[11] and Faurschou et al[12] showed that patients with very-late LN have high risk of ESRD and mortality.

Table 6A. Cases of late-onset LN > 5 years after diagnosis Literature review.

Number of patients with late-onset LN	Time after diagnosis of SLE	Histology	Other comments	Reference
71	> 5 years	Class III or IV (III/IV) and mixed classes III + V and IV + V were significantly more prevalent Higher index of chronicity	Higher WBC count, a smaller ANA titer , higher CH50 and C3 levels	Ichinose et al [14]
21	> 5 years	Class IV is more frequent	No differences in epidemiological, clinical, serological profile, SLICC and SLEDAI, except that late onset nephritis patients were older at nephritis diagnosis	Delfino et al [15]
35	>5 years	Classes IV, V, IV + V were common	Lower prevalence of malar rash, a higher leukopenia and skin vasculitis, hypertension ANCA and SSA positivity were more common More severity of the disease	Tang Z et al [21]
102	>5 years	Class IV + V is more common Milder active lesions but severer chronic lesions	Patient survival of late-onset LN population was poorer Kidney outcome was comparable than that of patients with early-onset LN Higher blood pressure, worse kidney function	Tian et al [8]
18	>5	Class III, IV, V are more common	Clinical, laboratorial and histological features of late-onset and early-onset nephritis are similar	Ugolini-Lopes et al. [9]
65	>5	Class III, IV, V are more frequent Higher renal chronicity index	Less disease activity No difference regarding ESRD and mortality Clinical outcomes of early and delayed lupus nephritis are not significantly different	Ahn et al. [10]
48	>5	Class III, IV, V were more common Histopathological patterns were similar as in early-onset	Associated with Sjögren's syndrome, lung involvement and antiphospholipid syndrome	Varela D et al.[16]
70	>2	Class III, IV, V were more common	More renal flares	Nakano et al.[17]

Table 6B. Cases of very late-onset LN > 10 years after diagnosis Literature review.

Number of patients with late-onset LN	Time after diagnosis of SLE	Histology	Other comments	Reference
30	> 10 years	Milder active lesions and more severe chronic lesions	Lower female predominance	Xu et al [13]
3	>15	Class IV is more common No chronic component	High ANA, anti-dsDNA and anti-Ro Abs, decreased C3 Multiple SLE flares	Alexandre A et al.[18]
24	> 10 years	Class III, IV were common	High risk of ESRD	Yap D et al. [11]
23	> 10 years	-	Increased mortality	Faurschou M et al. [12]
30	> 10 years	Diffuse proliferative glomerulonephritis is more common	Hypertension, nephrotic-range proteinuria	Kobkitcharoen M. et al. [19]
25	> 10 years	Higher scores of glomerular sclerosis, fibrous crescents, tubular atrophy, interstitial fibrosis	Prevalence of hypertension Higher serum creatinine levels, lower rates of positive anti-dsDNA	Huang J. et al. [20]

Some authors have found an increased frequency of ANCA and anti-SSA antibody positivity in late onset nephritis [13]; in the main however relatively few differences have emerged those patients whose nephritis develops more than 5 years post-lupus diagnosis compared to those whose disease started earlier.

The results of our analysis demonstrated that most patients with very late-onset LN were female and of Caucasian origin. This is most likely due to the clinic being based in London with relatively smaller numbers of Asian and Black patients..

Almost all the previous reports confirmed the high frequency of III, IV and V classes of LN in late-onset LN.[8-11,15]

Our analysis of the clinical and laboratorial features of our 226 LN biopsy proven patients demonstrated that whether the nephritis onset is very early, early, medium, late and very late onset, these groups broadly share same clinical and serological characteristics although as above, Caucasian origin; arthritis and leucopaenia, seem to be more common in those patients whose renal disease becomes evident > 10 years after diagnosis.

We are aware of some limitations of this study: its retrospective nature and the relatively small number of patients in the late-onset group reduce the statistical power of the analysis. However, despite the small number of patients in the late group, this percentage of the late onset is comparable to previous studies.[12-14,19-21] Our study is also unique in that we identified a separate group of patients who developed lupus nephritis 16 years after the onset of SLE, who are more likely to have higher ANA titer (>1:640) and biopsy-proven combined types of LN.

CONCLUSION

We retrospectively compared the very early, early, medium, late and very late onset cases of lupus nephritis identified in our cohort of SLE patients which we have followed up since 1978. Our results highlight the importance of long term follow up in SLE keeping in mind that approximately one SLE patient in seven develops overt nephritis 10 years or more after diagnosis. Clinicians should be aware of the possibility of late onset of lupus nephritis and continue to test for proteinuria and the possibility that late onset hypertension might be due to previously dormant nephritis becoming active.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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