Seasonal Variation of Lupus Nephritis: High Prevalence of Class V Lupus Nephritis During the Winter and Spring

NAOMI SCHLESINGER, MICHAEL SCHLESINGER, and SURYA V. SESHAN

ABSTRACT. ***Objective.*** Systemic lupus erythematosus is a multisystem disease with many clinical variations, including renal involvement. Our aim was to determine whether lupus nephritis (LN) has a specific seasonality.

Methods. Reports of renal biopsies performed from 1990 to 2002 were reviewed. Three hundred and seventy-three patients with class II, III, IV, and V LN were identified. Using the modified WHO classification of LN, diagnoses were tabulated and the seasonality (season of diagnosis) of LN was statistically analyzed.

Results. Class IV LN was detected in 179 patients (48%), class II in 63 patients (16.9%), class III in 73 patients (19.57%), and class V in 74 patients (19.9%). No difference could be detected in the number of patients diagnosed in each season when all 373 patients were analyzed as one group. The number of patients with class IV LN was higher during summer and fall than during the winter and spring. In contrast, a higher number of patients with class V LN were observed during the winter and spring seasons than during the summer and fall seasons. The percentage of patients with class V LN was significantly higher during winter and spring than during summer and fall. A similar, though non-significant, trend was seen for class III LN. A striking parallelism was found between the month of occurrence of class III and class V LN. The monthly distribution of the percentage of patients in each month with class III and V LN showed a significant correlation. The monthly distribution of patients with class IV LN was different from those with either class III or V LN.

Conclusion. We found that the prevalence of class V LN was significantly higher and that of class III LN non-significantly higher in winter and spring. Parallelism between the monthly occurrences of class III and class V may suggest a common trigger. Analysis of the seasonality of LN may contribute to the understanding of the pathogenesis of LN, which may be multifactorial, as the different classes of LN represent different types of glomerular injury. Further studies are needed to clarify this potentially important observation. (J Rheumatol 2005;32:1053–7)

Key Indexing Terms:
LUPUS NEPHRITIS SEASONAL SYSTEMIC LUPUS ERYTHEMATOSUS

Seasonal variation has been shown in a number of rheumatic diseases. The incidence of acute gouty attacks is highest in the spring[1-4]. The onset or exacerbation of rheumatoid arthritis[5], the onset of Wegener's granulomatosis[6], and antineutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis and systemic vasculitis are seen more commonly in the winter[7]. There is a significant increase in incidence of positive biopsies in giant cell arteritis in late winter and autumn[8].

Systemic lupus erythematosus (SLE) is a multisystemic disease with a wide variety of clinical manifestations. SLE is characterized by exacerbations and remissions. Previous attempts to find a seasonal pattern for the onset and activity of SLE were largely inconclusive. Clear seasonality was found only for photosensitive rashes characteristic of SLE patients[9-11]. Increased incidence of photosensitive rashes occurred predominantly in summer[9,10]. A survey study found SLE patients to have more joint pain in winter and spring[11]. No seasonal variation was seen in other disease manifestations[9,10].

It is possible that there may be a tendency for different organs to be affected in SLE during different seasons. Renal involvement constitutes one of the major criteria in the revised ARA criteria in the diagnosis of SLE[12]. Our aim was to determine whether lupus nephritis (LN) might have a unique, characteristic seasonality.

From the Department of Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, New Jersey; Hubert H. Humphrey Center for Experimental Medicine and Cancer Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel; and the Department of Pathology, Weill Medical College of Cornell University, New York, NY.

N. Schlesinger, MD, Director, Clinical Rheumatology, Department of Medicine, UMDNJ/RWJ; M. Schlesinger, MD, Hubert H. Humphrey Center for Experimental Medicine and Cancer Research, The Hebrew University; S.V. Seshan, MD, Chief, Renal Pathology, Department of Pathology, Weill Medical College of Cornell University.

Address reprint requests to Dr. N. Schlesinger, Department of Medicine, UMDNJ-Robert Wood Johnson Medical School, One Robert Wood Johnson Pl., P.O. Box 19, New Brunswick, NJ, 08903-0019. E-mail: schlesna@umdnj.edu

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MATERIALS AND METHODS

Reports of consecutive percutaneous native renal biopsies (n = 5650) performed for the last 13 years (1990-2002) were reviewed from our files (SVS). A total of 373 patients with class II, III, IV, and V LN were identified.

Demographic and clinical information. Most of the 373 patients were residents of the New York/New Jersey metropolitan area. The M:F ratio was 47:326, with ages ranging from 10 to 70 years, but the majority were in their third and fourth decades of life. The patient population comprised African-Americans (102), Asians (14), Caucasians (120), and Hispanics (137). Disease duration ranged from less than a month up to 10 years. SLE diagnosis was established either before or after renal biopsy.

Renal biopsies. All native renal biopsies from these patients were assessed systematically by at least 2 or all 3 modalities of examination: light (LM), electron (EM), and immunofluorescence microscopy (IF). Biopsies were read and reported by one pathologist (SVS), ensuring uniformity of the reporting process. Histopathological findings were reported according to the modified WHO classification of LN for glomerular lesions[13], which includes the following 6 major categories: Class I: normal kidney, normal by LM, but deposits seen by either EM or IF; Class II: pure mesangial proliferation; Class III: focal segmental glomerulonephritis affecting < 50% of the glomeruli; Class IV: diffuse glomerulonephritis affecting > 50% of the glomeruli; Class V: diffuse membranous glomerulonephritis; and Class VI: advanced sclerosing glomerulonephritis.

Seasons. The 4 seasons were defined as follows: winter: December 22 to March 21; spring: March 22 to June 21; summer: June 22 to September 21; and fall: September 22 to December 21. From renal biopsy data, the numbers of patients with the various WHO classes of LN were tabulated against the 4 seasons, based on the date of the confirmatory renal biopsy.

Statistical methods. Statistical methods included regression analysis and Pearson correlation, and 2-tailed t test. Bonferroni modification of Student's t test was used with $p < 0.05$ indicating significance.

Changes in the seasonal prevalence of various classes of LN in SLE patients throughout the year were assessed in 2 ways. For each of the 13 years, number of patients in the various classes was determined for each season and the mean annual number was calculated.

For each year, the proportion of patients in the various classes was calculated, taking the total annual number of patients in each category as 100%. The percentage of patients for each season or month of that year was determined. Finally, the average annual percentage was calculated.

RESULTS

Lupus glomerulonephritis in SLE patients. Kidney biopsies of 373 SLE patients with class II, III, IV, and V were identified over a time period of 13 years (1990-2002). The most frequent form of lupus nephritis (LN), detected in 179 patients (48% of the patients) was class IV, representing diffuse proliferative lupus nephritis (Table 1). The numbers of patients with other classes of LN were as follows: class II in 63 patients (16.9% of the patients); class III in 73 patients (19.57%), and class V in 74 patients (19.9%). Among these, 16 patients had mixed forms (III + V, IV + V). Class I was seen in 2 patients and class VI was seen in 6 additional patients.

Distribution of glomerular lesions in SLE patients in various seasons. No differences were detected in number of patients in each season when all 373 patients, comprising various classes of LN, were analyzed as one group (Table 1). The number of patients with class IV LN was slightly higher during summer and fall than during the winter and spring. Higher numbers of patients with class V LN were observed during the winter and spring seasons than during the summer and fall seasons.

Table 1. Seasonal occurrence of lupus nephritis (LN) in all patients and in each class of LN as assessed by 3 data sets. Values are mean (± SE) percentage.

Class of patients	Overall No. (13 yrs)	Winter Dec 22–Mar 21	Spring Mar 22–June 21	Summer June 22–Sept 21	Fall Sept 22–Dec 21
All classes of SLE patients					
Total no.	373	94	93	95	91
Mean ± SE no. per season		7.23 ± 0.90	7.15 ± 0.81	7.31 ± 1.33	7.00 ± 0.77
Mean ± SE percentage per season		25.39 ± 2.22	26.09 ± 3.02	24.00 ± 3.30	23.26 ± 2.38
Class II					
No. of patients	63	16	15	16	16
Mean ± SE no. per season		1.23 ± 0.41	1.15 ± 0.36	1.23 ± 0.32	1.23 ± 0.23
Mean ± SE percentage per season		21.94 ± 5.89	26.02 ± 7.98	23.54 ± 6.18	28.49 ± 5.17
Class III					
No. of patients	73	18	19	19	17
Mean ± SE no. per season		1.38 ± 0.43	1.46 ± 0.28	1.46 ± 0.51	1.31 ± 0.43
Mean ± SE percentage per season		33.42 ± 9.05	25.82 ± 5.44	21.83 ± 2.94	18.94 ± 6.46
Class IV					
No. of patients	179	42	40	51	46
Mean ± SE no. per season		3.23 ± 0.48	3.08 ± 0.48	3.92 ± 0.83	3.54 ± 0.56
Mean ± SE percentage per season		23.85 ± 3.42	23.92 ± 3.57	25.39 ± 4.64	26.84 ± 3.76
Class V					
No. of patients	74	23	23	11	17
Mean ± SE no. per season		1.77 ± 0.48	1.77 ± 0.45	0.85 ± 0.32	1.31 ± 0.37
Mean ± SE percentage per season		35.91 ± 7.26	31.99 ± 5.79	12.79 ± 5.19[a]	19.31 ± 4.40[b]

While the total number of patients with LN classes II, III, IV and V was 373, sixteen patients had mixed forms. [a] The percentage of patients with class V renal changes was significantly lower in the summer than in both winter ($p < 0.02$) and spring ($p < 0.05$). [b] The proportion of patients with class V LN was significantly lower in the fall than in both winter and spring ($p < 0.02$).

If season did not have an effect on the prevalence of LN in SLE, the percentage of patients with each of the classes of LN would constitute 25% for each of the 4 seasons. The highest percentage of patients with class III LN was found in the winter, lower percentages were obtained in the spring and summer, and the lowest in the fall season (Table 1). These differences were, however, not statistically significant.

Significant seasonal differences were found among patients with class V LN. The highest percentages of patients with class V LN were found in the winter and spring, the lowest in the summer, and an intermediate percentage in the fall. The proportion of patients with class V LN was significantly lower in the summer than in both winter ($p < 0.02$) and spring ($p < 0.05$). Similarly, the proportion of patients with class V LN was significantly lower in the fall than in both winter and spring ($p < 0.02$).

Monthly prevalence of classes of lupus nephritis. Monthly occurrence of various classes of LN was determined by calculating the percentage of patients detected in each month, when the total number of cases of each class per year was taken as 100%. A random distribution for each month would theoretically yield each month 8.33% of the total annual number of patients.

Analysis of SLE patients with all classes of LN showed that the highest percentage occurred in the month of June (Table 2). The percentage of cases for the month of June was significantly higher than for September ($p < 0.01$), November ($p < 0.05$), and December ($p < 0.02$). The high percentage of patients with LN detected in June was contributed mainly by patients with class II and III LN.

The percentage of patients with class V LN was strikingly elevated during the months of January and March. The percentage of class V LN patients detected in January was significantly higher than those detected in April ($p < 0.05$), July ($p < 0.01$), September ($p < 0.05$), and December ($p < 0.05$). Likewise the percentage of class V LN patients detected in March was significantly higher than those detected in April ($p < 0.02$), July ($p < 0.01$), August ($p < 0.05$), September ($p < 0.02$), and December ($p < 0.02$).

The percentage of patients with class V LN found in various months paralleled the monthly occurrence of class III LN in SLE patients. The percentage of class III and IV LN for each month showed a significant correlation ($r = 0.6188$, $p = 0.038$). In contrast, the monthly distribution of class V LN differed from that of class II, III, or IV LN.

DISCUSSION

Previous attempts to find a seasonal pattern for the onset and activity of SLE have been largely inconclusive. Clear seasonality has been found only for photosensitive rashes characteristic of SLE patients[9-11]. Large retrospective studies have suggested kidney involvement in greater than 80% of patients, occurring sometime during the course of SLE[14]. Our study provided evidence for seasonal variation in the manifestation of class V renal changes. Among 373 cases of LN over 13 years, no seasonal pattern was detected when all classes of LN were combined. In contrast, a significantly higher prevalence in the winter and spring was observed among SLE patients with class V LN, as compared to summer and fall. This distinctive pattern was seen when the mean percentage of patients with class V LN was calculated for these seasons. A similar, though non-significant, trend was seen for seasonal variation of the percentage of class III LN patients. The seasonal variation of class V LN is supported by the finding that the percentage of class V LN was significantly elevated in January and March. This is the first demonstration of seasonal variation in the occurrence of distinct classes of LN. In this study, seasonality of renal changes was established by correlation of pathological

Table 2. Patients with diagnosis of lupus nephritis, studied over 13 years, according to month of confirmatory biopsy and class of LN.

Month	Total (All patients)	Class II	Class III	Class IV	Class V
January	8.19 ± 1.90	5.93 ± 2.50	16.41 ± 7.46	8.06 ± 2.06	16.53 ± 5.03[b]
February	9.44 ± 1.73	6.29 ± 3.26	12.39 ± 7.93	9.61 ± 2.14	8.96 ± 3.93
March	9.33 ± 1.29	13.89 ± 6.16	7.78 ± 3.12	6.04 ± 2.30	18.90 ± 5.33[c]
April	7.29 ± 2.41	4.51 ± 3.16	3.85 ± 2.66	7.20 ± 2.83	3.75 ± 2.34
May	8.45 ± 1.55	4.26 ± 2.21	11.61 ± 3.41	7.79 ± 1.76	11.86 ± 4.93
June	11.66 ± 1.32[a]	20.12 ± 8.30	14.10 ± 4.57	8.37 ± 2.04	11.45 ± 4.07
July	7.83 ± 1.76	8.52 ± 3.75	7.61 ± 3.49	10.26 ± 2.09	1.04 ± 0.86
August	7.37 ± 1.61	4.26 ± 3.23	7.72 ± 2.14	9.61 ± 2.38	6.02 ± 2.53
September	6.19 ± 1.03	5.30 ± 2.27	4.26 ± 1.87	6.50 ± 2.38	3.75 ± 1.87
October	9.07 ± 1.13	5.14 ± 2.62	6.91 ± 2.82	11.55 ± 2.27	7.40 ± 2.92
November	7.53 ± 1.43	9.65 ± 3.67	3.83 ± 1.79	6.91 ± 2.56	7.40 ± 2.57
December	6.49 ± 1.41	12.13 ± 4.48	6.15 ± 4.56	7.32 ± 1.68	2.95 ± 1.54

[a] The percentage of cases for June for all classes of renal change is significantly higher than for September ($p < 0.01$), November ($p < 0.05$), and December ($p < 0.02$). [b] The percentage of patients with class V LN for January is significantly higher than for April ($p < 0.05$), July ($p < 0.01$), September ($p < 0.05$), and December ($p < 0.05$). [c] The percentage of patients with class V LN for March is significantly higher than for April ($p < 0.02$), July ($p < 0.01$), August ($p < 0.05$), September ($p < 0.02$), and December ($p < 0.02$).

changes in the kidney with the time of the needle biopsy. It could be argued that the delay between biopsy and onset of illness may differ among various patient groups. Obviously it would be ideal to correlate the time of pathological tests with the time of appearance of symptoms and laboratory findings. It should be pointed out, however, that no seasonality was detected in studies based on clinical and laboratory findings in SLE patients. It is possible that lack of seasonality of class IV LN, characterized by severe and diffuse forms of proliferative lupus nephritis may reflect a delay in biopsy compared with the onset of renal disease. Possibly, seasonality could be shown only for lesions detected early in disease progression. Indeed, in contrast to class IV LN, there was some indication for seasonality of class III LN in which focal segmental glomerulonephritis affects less than 50% of the glomeruli.

It could be argued that performance of needle biopsies of the kidney of lupus patients introduces a selection bias since in some patients renal biopsy was not performed. The inclusion of a relatively large number of lupus patients with renal biopsy in our study would tend to minimize such a selective bias.

There is a possibility that the disparity of the monthly and seasonal distribution of various classes of LN may reflect different underlying pathogenic mechanisms that participate in the development of various forms of LN. Indirect support for different pathogenic mechanisms in various LN classes was found in a recent study of HLA allotypes in SLE patients. Marchini, *et al*[15] found that the presence or absence of HLA-DR15 was associated with different histological subtypes of LN. Class V LN, which in our study showed seasonal variation, displayed a striking though not exclusive correlation with the HLA-DR15 negative allotype.

SLE is an autoimmune disease characterized by the formation of various autoantibodies, predominantly against nuclear antigens, such as double and single stranded DNA and membrane phospholipids. Lupus anti-DNA autoantibodies react with α-actinin, a glomerular structural protein located on the podocyte[16]. A pathogenic, lupus-like autoantibody response could be induced by a peptide antigen, and α-actinin seems to constitute a cross-reactive renal target for the pathogenic anti-dsDNA autoantibody response in lupus mice[17]. Anti-DNA autoantibodies may produce distinguishable immune deposit patterns in specific glomerular locations and elicit different phenotypic changes[18]. Seasonal variations were reported for a number of autoantibodies. Different seasonal patterns were observed in adult idiopathic inflammatory myopathy: in patients with anti-Jo-1 autoantibodies, a high incidence of disease onset was observed in the month of April; in patients with anti-signal recognition particle autoantibodies the onset was mainly in the month of November[19]. Patients with diabetes mellitus displayed seasonal variation in the production of autoantibodies against either islet cell antigens[20] or pancreatic tyrosine phosphatase (IA2-ab)[21]. In normal individuals the level of anti-phospholipid antibodies was lowest in the summer[22]. No information is available on any seasonal variation of autoantibodies in SLE.

The high prevalence of class V LN during the winter and spring could mean that during these seasons this class of nephropathy is precipitated either by infection or by activation of endogenous retroviruses. It is not clear to what extent interactions with environmental stimuli, whether infectious or dietary, are necessary for the initiation and/or continuation of autoimmunity. No difference in autoantibody level was found between MRL-lpr mice prone to SLE-like phenomena kept under germfree versus antigen-free environments[23]. The production of autoantibodies might be regulated by endogenous antigens. It has been suggested that human endogenous retroviruses (HERV) play a role in SLE[24]. A large proportion of patients with SLE produce antibodies against HERV[25] and against the p24 component of HIV-1 retrovirus[26]. In addition, some SLE patients show increased production of mRNA coding for various HERV[27]. It is possible, therefore, that in SLE patients an autoimmune process is triggered following exposure to infectious agents, which could elicit antibodies against HERV antigens, and in turn cross-react with self-antigens.

The pathogenesis of membranous nephropathy in SLE is not known. Many agents can initiate this process in susceptible individuals including patients with diabetes mellitus and infections such as hepatitis B and C, syphilis, filariasis, hydatid disease, schistosomiasis, malaria, and leprosy[28]. The similarity of membranous nephropathy to the lesions induced in rats with antibody to antigens expressed on the surface of glomerular epithelial cell (GEC) (Heymann nephritis) suggests that membranous nephropathy is caused by deposits of antibody to components of GEC membranes[29].

An alternative interpretation of the seasonality of autoimmune processes is that there are inherent seasonal fluctuations in the activity of the immune system[30]. The number of lymphocytes undergoes seasonal changes, reaching a peak in the winter months[31]. This may partially reflect the serum level of melatonin, which is highest in the winter months in normal individuals and in SLE patients[10,32]. Melatonin, in turn, constitutes a strong activator of the immune system[32]. Previously, seasonal variations in the host susceptibility to various infectious diseases were attributed to changes in atmospheric conditions, the prevalence or virulence of the pathogen, or the behavior of the host. Dowell[33] suggested that many features of infectious disease seasonality may be mediated by the pattern of melatonin secretion.

While analysis of the seasonality of renal changes in lupus could be improved, our observations are the first to indicate that it would be worthwhile to invest an effort into such a study. In view of all the difficulties involved in the performance of this study it is remarkable that some renal changes in lupus showed seasonal variation.

Investigation of the seasonality of LN may contribute to understanding of its pathogenesis, which may be multifactorial, as the different classes of LN represent different types of glomerular injury. Possible contributing factors include infectious organisms, activation of endogenous retroviruses, inherent seasonal changes in the activity of the immune system, melatonin or other hormonal influences, and genetic effects, among others. Further studies are needed to clarify this potentially important observation.

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