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*Clinical Study*

# Clinical and Morphologic Differences between Class IV-S and Class IV-G Lupus Nephritis

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*Introduction.* The new ISN/RPS classification of lupus nephritis (LN) divides diffuse proliferative LN into two subcategories with predominantly segmental proliferative lesions (class IV-S) and with predominantly global proliferative lesions (class IV-G). This paper explores the validity of this distinction and possible differences between the two types of lesions. Patients and Methods. A retrospective analysis of biopsy-proven cohort of 231 patients with LN was performed. Clinical and laboratory data were available on all patients selected. *Results.* The prevalence of Class IV was 27,27% (41 patients had class IV-S, 22-class IV-G). The serum creatinine levels, proteinuria, and diastolic blood pressure were significantly greater in the IV-G class, but haemoglobin was significantly lower. Histologically combined lesions with segmental endocapillary proliferation and fibrinoid necrosis were more frequent in the class IV-S. No significant difference was detected in outcomes in the two groups after followups of 145,2 ± 76,87 months. *Conclusions.* There are definite clinical and morphologic differences between class IV-S and IV-G lesions. Data suggest that class IV-G lesions behave as an immune complex disease; however, in class IV-S lesions, the presence of proportionally greater glomerular fibrinoid necroses suggests that these lesions may have a different pathogenesis.

## 1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease whose etiology and pathogenesis are incompletely understood. The development of autoimmunity in SLE has been attributed to a loss of self-tolerance due to inadequate central or peripheral deletion or silencing of autoreactive lymphocytes, leading to multiple autoantibody specificities [1]. Although knowledge of the etiology of SLE is incomplete, it is clear from the varied forms of tissue injury that a number of different effector mechanisms may act alone or in concert to produce the pleomorphic patterns of lupus nephritis. Autoantibodies may lead to cell and tissue injury by Fc receptor-mediated inflammation [2] as well as by direct cytotoxicity, which is usually complement dependent, as has been shown for antibody-mediated hemolytic anemia or thrombocytopenia. In the kidney, intrinsic antigens such as extracellular matrix components or cell surface glycoproteins may serve as targets for autoantibody binding. In addition, renal injury in lupus nephritis may result from autoantibodies that bind to circulating antigens, forming circulating preformed immune complexes, or autoantibodies that bind to antigens deposited from the circulation in glomerular and vessel walls, causing in situ immune complex formation, as has been shown for nucleosomes and antidouble stranded DNA autoantibodies [3].

Based on various experimental models of autoimmune and immune complex diseases in the kidney and on observations in human renal biopsies, it is now well established that the glomerular patterns of immune complex-mediated injury are related to the site of accumulation of immunoglobulins, their antigen specificity, their capacity to bind and activate complement and other serine proteases, and their ability to evoke a cellular inflammatory response [4].

The introduction of renal biopsy in the 1950s, the application of immunofluorescence and electron microscopic techniques in the 1960s, and increasing knowledge about mechanisms of immune-mediated glomerular injury derived

from experimental studies on serum sickness and other models formed the basis of the recognition and classification of the various patterns of renal injury in SLE. In order to accommodate the clinicopathologic and pathogenetic insights that have been accumulated since 1982, a new classification of glomerulonephritis in SLE has been recently proposed in 2004 [4].

This classification seeks to rectify some of the problems that have arisen over the years with the World Health Organization classification, dating from 1982 and revised in 1995 [4]. The most important changes came in class IV lupus glomerulonephritis (LN). Class IV LN, formerly called diffuse proliferative lupus nephritis, by definition involving more than 50% of glomeruli, has now been subdivided into two subclasses according to whether the majority of the lesions involve the glomeruli in segmental fashion with some lobules involved and others spared (class IV-S), or in a global fashion with the majority or all of the tuft showing proliferative lesions and deposits (class IV-G). This study explores the validity of this distinction and possible differences in pathogenesis between the two types of lesions.

## 2. Materials and Methods

A retrospective analysis of biopsy-proven cohort of 231 patients (21 males and 210 females, aged 15 to 58 years, mean 34,05 ± 9,63 years) with lupus nephritis using ISN/RPS classification was performed.

Sixty-three (27,27%) cases had initially been diagnosed as diffuse proliferative lupus nephritis and then divided into diffuse segmental (IV-S) and diffuse global (IV-G) lupus glomerulonephritis. Specimens were processed by standard histologic and immunofluorescence techniques. Clinical and laboratory data were available on all patients selected.

All data were analyzed using SPSS 15.0.1. Differences between groups were evaluated by *t*-test. Univariate analysis was used in the determination of morphologic variables significantly associated with and predictive of class IV-S and class IV-G LN. Comparisons of survival were done by the Kaplan-Meier method. $P < 0,05$ was considered to indicate statistical significance.

## 3. Results

The prevalence of Class IV LN was 27,27%. Of 63 patients with class IV lupus nephritis (6 males and 57 females, aged 15 to 60 years, mean 33,87 ± 10,39 years, mean SLEDAI 21,76 ± 5,97, SLICC 1,56 ± 1,51), 41 had class IV-S and 22 had class IV-G (Table 1). There were no significant differences in ages and sex between the two groups. Duration of systemic lupus erythematosus before renal biopsy were similar in the two groups (mean 45,73 ± 22,13 months).

There were several important differences between patients with segmental and global proliferative lesions (Table 2). The percentage of viable glomeruli affected was much higher among the global proliferative lesions, roughly 91,85% versus 76,78%. Segmental lesions never involved all viable glomeruli whereas global lesions not infrequently did (81,82% of patients). In the segmental proliferative group, 37,93% of fibrinoid necroses were unaccompanied by any endocapillary proliferation, as opposed to 0% in the global proliferative group. The percentage of affected glomeruli having fibrinoid necroses was much higher among the segmental proliferative group (32,63% versus 20,78%). Membranoproliferative features were found in 40,91% of patients with global proliferative lesions and in 2,44% of patients with segmental lesions. Crescents were equally distributed between the two types of lesions (31,82% in class IV-S and 34,55% in class IV-G). There were more sclerotic glomeruli among the segmental proliferative cases (28,24% versus 23,88%). Hyaline deposits by light microscopy were greater in the global proliferative group (in 21,95% of glomeruli in class IV-S versus 34,55% of glomeruli in class IV-S). Subendothelial deposits were much higher in the class IV-G lupus nephritis and mesangial deposits—in the class IV-S lupus nephritis. Subepithelial lesions did not differ between the groups. The percentage of glomeruli with cellular crescents also was greater in the class IV-S LN (28,24% versus 23,88%), but the difference was not significant.

At the time of renal biopsy (Table 3), there were established mucocutaneous manifestations in 40 (63,49%) patients (28 class IV-S, 12 class IV-G), musculoskeletal in 31 (49,21%) patients (16 class IV-S, 15 Class IV-G), pyrexia in 30 (51,72%) patients (11 class IV-S, 19 class IV-G LN), gastrointestinal symptoms (lupus hepatitis or pancreatitis) in 3 (4,48%) patients (2 class IV-S, 1 class IV-G), ascites in 5 (7,94%) patients (2 class IV-S and 3 class IV-G), pneumonitis in 4 (6,35%) patients (2 class IV-S, 2 class IV-G), pleural effusion with dyspnoea in 11 (17,46%) patients (4 class IV-S, 7 class IV-G), cardiovascular symptoms (endocarditis/myocarditis/aortitis) in 9 (14,28%) patients (5 class IV-S, 4 class IV-G), pericarditis in 14 (22,22%) patients (4 class IV-S, 10 class IV-G), psychosis in 4 (6,35%) patients (1 class IV-S, 3 class IV-G), epilepsy in 4 (6,35%) patients (2 class IV-S, 2 class IV-G), and primary ocular manifestations (retinal vasculitis/optic neuritis) in 16 (25,4%) patients (6 class IV-S, 10 class IV-G). Anemia (mean hemoglobin levels 111,3 ± 14,32 g/L) was established in 40 (63,49%) patients (24 class IV-S, 16 class IV-G), thrombocytopenia in 44 (69,84%) patients (25 class IV-S, 19 class IV-G), leukopenia in 23 (36,51%) patients (12 class IV-S, 11 class IV-G), and lymphopenia in 38 (60,32%) patients (22 class IV-S, 16 class IV-G).

Nephrotic syndrome at the time of biopsy was present in 26 (41,27%) patients (13 class IV-S and 16 class IV-G), hypoalbuminaemia in 35 (55,56%) patients, elevated serum creatinine in 18 (28,57%) patients, hematuria in 26 (41,26%) patients (20 class IV, 6 class IV-G) with predominance of patients with intermittent (11) microscopic haematuria.

The serum creatinine levels (185,2 ± 138,7 $\mu$moL/L versus 114,0 ± 64,14 $\mu$moL/L), proteinuria (5,54 ± 4,69 g/24 h versus 3,22 ± 2,26 g/24 h), and diastolic blood pressures (104,12 ± 10,45 mmHg versus 96,42 ± 13,12 mmHg) were significantly greater in the IV-G group, but haemoglobin was significantly lower (102,8 ± 13,64 g/L versus 115,9 ± 12,48 g/L); (Table 4).

ANA were positive in all patients at the time of biopsy, a-dsDNA antibodies were found in 54 (85,71%) patients

Table 1: Distribution of patients with class IV lupus nephritis (LN) according to the results of renal biopsy.

| Class IV (diffuse) LN | Class IV LN with active lesions (A) | Class IV LN with active and chronic lesions (A/C) | Class IV LN with chronic inactive lesions with scars (C) |
|---|---|---|---|
| Class IV-S (diffuse segmental proliferative) LN | 18 | 10 | 13 |
| Class IV-G (diffuse global proliferative) LN | 6 | 15 | 1 |
| Total | 24 | 25 | 14 |

Table 2: Comparison between parameters related to class IV segmental (S) versus global (G) proliferative lupus nephritis (LN).

| Parameter | Class IV-S LN ($n = 41$) | Class IV-G LN ($n = 22$) |
|---|---|---|
| Cases with all glomeruli affected | No | 81,82% (18 biopsies); ($P < 0,0001$) |
| Number (%) of affected glomeruli | 473 (76,78%) | 327 (91,85%); ($P < 0,05$) |
| Number (%) of cases with membranoproliferative features | 1 of 41 (2,44%) | 9 of 22 (40,91%); ($P < 0,0001$) |
| Percentage of affected glomeruli with fibrinoid necrosis | 32, 63% (201 glomeruli) | 20, 78% (74 glomeruli); ($P < 0,01$) |
| Number (%) of biopsies with fibrinoid necrosis in absence of endocapillary proliferation | 11 of 29 (37,93%) | 0 of 22 (0%) |
| Number (%) of biopsies with capillary hyaline deposits | 9 of 41 (21,95%) | 20 of 29 (68,96%); ($P < 0,01$) |
| Percentage of affected glomeruli with crescents | 31,82% | 34,55% ($P > 0,05$) |
| Number (%) of sclerotic glomeruli | 174 (28,24%) | 85 (23,88%); ($P < 0,05$) |

(32 class IV-S, 22 class IV-G), a-ssDNA antibodies in 19 (9 class IV-S, 10 class IV-G) of 48 (39,58%) tested, a-Sm antibodies in 24 (8 class IV-S, 16 class IV-G) of 56 (42,86%) patients, anti-C1q antibodies in 20 (8 class IV-S, 12 class IV-G) of 21 (95,24%) tested, a-RNP antibodies in 11 (5 class IV-S, 6 class IV-G) of 40 (27,5%) tested, a-Ro antibodies in 15 (6 class IV-S, 9 class IV-G) of 44 (34,09%) investigated, a-La antibodies in 7 (3 class IV-S, 4 Class IV-G) of 44 (15,9%) tested, antiribosomal-P antibodies in 30 (14 class IV-S, 16 class IV-G) of 33 (90,91%) patients, p-ANCA in 5 of 21 (23.81%) tested (4 of 12 patients with class IV-S and 1 of 9 patients with class IV-G), cryoglobulins in 46 (28 class IV-S, 18 class IV-G) of 59 (73,02%) patients, antiphospholipid antibodies in 26 (13 class IV-S,13 class IV-G) of 48 (54,17%) patients, anticardiolipin antibodies in 23 (8 class IV-S, 15 class IV-G) of 48 (47,92%) patients, antibodies against $\beta 2$ glycoprotein I in 18 (8 class IV-S, 10 class IV-G) of 48 patients (35,7%), and LAC in 16 (7 class IV-S, 9 class IV-G) of 48 (33,33%) patients. C3 complement was decreased in 61 (96,82%) patients (39 class IV-S, 22 with class IV-G). The values of C3 complement were significantly lower ($P < 0,001$) in patients with class IV-G LN (0,77 $\pm$ 0,06 g/L) compared with class IV-S LN (0,88 $\pm$ 0,12). The average values of C4 complement were 0,24 $\pm$ 0,09 g/L. Hypocomplementemia C4 was present in 28 (12 class IV-S, 16 class IV-G) of 51 (54,9%) tested. Mean values of IgG were 7,45 $\pm$ 3,68 g/L, of IgA—1,72 $\pm$ 2,01 g/L, of IgM—1,34 $\pm$ 1,01 g/L (it was not statistically significant differences between the two classes of diffuse lupus nephritis). Patients with LN were followed for an average period of 145,2 $\pm$ 76,87 months (from 10 to 289 months). At the date of last visit with doubled serum creatinine values compared with values before biopsy were 51 (80,95%) patients. For the observation period of 25 years (1984–2009) 35 (55,56%) patients died (23 with class IV-S and 12 with class IV-G LN) with an average age 40,26 $\pm$ 10,53 years (from 21 to 61 years). The most common causes of death were events of respiratory (40%) and cardiovascular systems (34,28%). Five-, 10-, 15-, and 20-year survival, respectively, were 96,72%, 89,8%, 48,9% and 14,29%. In our experience there is no statistically significant difference in survival between patients with segmental and global proliferative lupus nephritis.

## 4. Discussion and Conclusion

There are 4 studies to which our data may be more or less directly compared:

(1) Najafi et al. [5] found (2001) that cases with "severe segmental" glomerular lesions, involving greater than 50% of glomeruli (the equivalent of class IV-S) actually had a worse outcome at 10 years than those with those with diffuse proliferative lesions involving the entire glomerular tuft (the equivalent of class IV-G);

(2) Mittal et al. [6], using the new classification, performed a retrospective analysis (2004) of a biopsy in patients with lupus nephritis;

(3) Yokoyama et al. [7] offering outcome data (2004) in 23 patients with lupus nephritis (6 with class IV-S and 17 with class IV-G);

(4) Hill et al. [8] evaluated the distinction between classes IV-S and IV-G LN (2005) reviewing the material from a previously studied group of patients having initial and systematic 6-month posttreatment induction biopsies. The cases were reclassified according to the new classification (15 patients with class IV-S and 31 patients with class IV-G) and the previously gathered

Table 3: Comparison between some clinical manifestation in patients with class IV segmental (S) versus global (G) proliferative lupus nephritis (LN) at the time of renal biopsy.

| *Clinical manifestation* number (%) of cases | Class IV-S LN ($n = 41$) | Class IV-G LN ($n = 22$) |
|---|---|---|
| *Mucocutaneous manifestations* 40 (63,49%) patients | 28 (68,29%) | 12 (54,54%) |
| *Pyrexia* 30 (51,72%) patients | 11 (39,02%) | 19 (68,18%) |
| *Musculoskeletal manifestations* 31 (49,21%) patients | 16 (26,83%) | 15 (86,36%) |
| *Gastrointestinal symptoms (lupus hepatitis or pancreatitis)* 3 (4,48%) patients | 2 (4,88%) | 1 (4,54%) |
| *Ascites* 5 (7,94%) patients | 2 (4,88%) | 3 (13,64%) |
| *Pneumonitis* 4 (6,35%) patients | 2 (4,88%) | 2 (9,09%) |
| *Pleural effusion with dyspnoea* 11 (17,46%) patients | 4 (9,76%) | 7 (31,82%) |
| *Cardiovascular symptoms (endocarditis/myocarditis/aortitis)* 9 (14,28%) patients | 5 (12,195%) | 4 (18,18%) |
| *Pericarditis* 14 (22,22%) patients | 4 (9,76%) | 10 (45,45%) |
| *Psychosis* 4 (6,35%) patients | 1 (2,44%) | 3 (13,64%) |
| *Epilepsy* 4 (6,35%) patients | 2 (4,88%) | 2 (9,09%) |
| *Primary ocular manifestations (retinal vasculitis/optic neuritis)* 16 (25,4%) patients | 6 (14,63%) | 10 (45,45%) |
| *Anemia* 40 (63,49%) patients | 24 (58,53%) | 16 (72,73%) |
| *Thrombocytopenia* 44 (69,84%) patients | 25 (60,98%) | 19 (86,36%) |
| *Leukopenia* 23 (36,51%) patients | 12 (29,29%) | 11 (50%) |
| *Lymphopenia* 38 (60,32%) patients | 22 (53,68%) | 16 (72,73%) |
| *Nephrotic syndrome* 26 (41,27%) patients | 13 (31,71%) | 16 (72,73%) |

Table 4: Comparison of some laboratory and clinical parameters in patients with class IV segmental (S) versus global (G) proliferative lupus nephritis (LN).

| Parameter | Class IV-S LN | Class IV-G LN | $P$ |
|---|---|---|---|
| Proteinuria (g/24 h) | 3,22 ± 2,26 (0,41–10,50) | 5,54 ± 4,69 (0,32–15,54) | $P < 0,05$ |
| Serum albumin (g/L) | 35,07 ± 7,27 (19–47) | 29,82 ± 6,25 (21–44) | $P < 0,01$ |
| Serum total protein (g/L) | 63,08 ± 8,46 (28–75) | 56,27 ± 8,52 (38–73) | $P < 0,05$ |
| Serum creatinine ($\mu$moL/L) | 114,0 ± 64,14 (67–348) | 185,2 ± 138,7 (70–540) | $P < 0,05$ |
| Haemoglobin (g/L) | 115,9 ± 12,48 (78–136) | 102,8 ± 13,64 (84–130) | $P < 0,001$ |
| C3 complement (g/L) | 0,88 ± 0,12 (0,67–1,25) | 0,77 ± 0,06 (0,64–0,89) | $P > 0,05$ |
| Number (%) of patients with arterial hypertension | 24 (58,54%) | 22 (100%) | $P < 0,05$ |
| Diastolic blood pressure (mean values) | 96,42 ± 13,12 mmHg | 104,12 ± 10,45 mmHg | $P < 0,02$ |

clinical and morphologic data was reevaluated in light of the new classification. They found that at the control biopsy after treatment, persistence of class IV-G lesions appeared to be associated with a much worse survival than that for patients who manifested class IV-S lesions at the second biopsy.

In these studies there is consensus that the clinical manifestations are worse with global proliferative lesions and that hyaline deposits/wire loops and subendothelial deposits are worse with global lesions, whereas fibrinoid necroses/fibrin thrombi are worse with segmental lesions [8]. It is probably fair to say that activity and chronicity indices are generally worse with global proliferative lesions, a notable exception being the greater chronicity index in segmental lesions in the series of Najafi et al. [5]. A question of perhaps more interest is whether the segmental proliferative lesions have a different pathogenesis than the global proliferative lesions, as has indeed been proposed by previous authors [4, 6–8]. The global proliferative lesions behave as an immune complex glomerulonephritis, as we have traditionally conceived of lupus glomerulonephritis as a whole. The segmental proliferative lesions tended to show a negative correlation with glomerular subendothelial deposits and had a definite predominance of mesangial staining over capillary wall staining. We showed no correlation with serum C3 levels. Fibrinoid necrosis was much more prominent among the segmental proliferative lesions and fibrinoid necroses without associated endocapillary proliferation occurred with some frequency in segmental proliferative cases, but never in global proliferative cases. The percentage of affected glomeruli with fibrinoid necroses was markedly higher among class IV-S lupus nephritis. There are definite clinical and morphologic differences between class IV-S and IV-G lesions.

All of these findings cast doubt on the pathogenesis of the segmental proliferative lesions as a classic immune complex disease. These cases behave much like ANCA-related and anti-GBM glomerulonephritides, which begin focally although they may eventually come to involve all the glomeruli. Only Chin et al. [9] have specifically looked at class IV lesions (their study finding a positive correlation with p-ANCA), and no study has subdivided class IV lesions into segmental versus global proliferative lesions, so the jury is still out as to a possible connection between ANCA and segmental proliferative lesions. We found p-ANCA in 33,33 of patients with class IV-S LN and in 11,11% patients with class IV-G LN. The question may be raised as to what might be the pathogenesis of these segmental lesions.

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