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Quantitative analysis of interstitial alterations in lupus nephritis *

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Summary. Ninety-eight patients with lupus nephritis followed up for 3 years or more since initial biopsy were the subject of a qualitative and quantitative study of interstitial lesions. Thirty of the 98 patients showed interstitial cell infiltration and/or fibrosis. The initial and final creatinine clearance (Ccr) values were significantly lower in these 30 patients than in the remaining cases. Hypertension and progressive cases were more frequent in the group with interstitial lesions. Histologically, the severity and activity of glomerular lesions and IgG deposition in tubular basement membranes were more severe in the interstitial disease group. On a quantitative analysis of interstitial volumes (IV) in 20 of the 30 patients, there were significant differences in Δ IV between the two respective groups with Ccr values greater than 80 ml/min and with those less than 80 both at the initial and final observations ($p<0.05$, each). Further, renal function was significantly lower in 11 cases showing Δ IV greater than 17%, than in 9 cases with less than this ($p<0.01$). However, no differences in Δ IV were found between the two groups divided according to the degree of severity and activity of glomerular lesions. Further, there was no correlation between renal function, and the severity and activity of glomerular lesions in the 20 cases with interstitial lesions. These results indicate that quantitative analysis is a very useful tool in the evaluation of the functional and prognostic significance of interstitial alterations in lupus nephritis.

Introduction

Although interstitial alterations in lupus nephritis are well recognized (Klassen et al. 1972; Boelaert et al. 1974; Andres and McCluskey 1975; Brentgens et al. 1975; Lehman et al. 1975; Morel-Maroger et al. 1976), the clinical significance of the lesions is not fully understood. In recent reports, serum creatinine levels were found to correlate well with relative interstitial volumes (Schwartz et al. 1982). Further, the severity of interstitial infiltration correlates well with the level of renal function at the time of biopsy and is related to the prognosis of renal involvement (Park et al. 1986).

In lupus nephritis, however, most patients with apparent interstitial changes have associated glomerular alterations to various degrees. So, the correlation between interstitial lesions and deteriorated renal function is obscured by these concomitant glomerular lesions. It is difficult to assess the relative contribution of each to the renal involvement.

In this study in order to clarify the renal functional and prognostic significance of interstitial alterations, qualitative and quantitative analyses were performed. Firstly, the renal clinical and histological findings in 98 patients with lupus nephritis, divided into those with and without apparent interstitial alterations, were compared. Secondly, 20 patients with interstitial lesions were selected on a random basis and their quantified interstitial volumes were compared with renal function, prognosis and glomerular alterations.

Quantitative analysis of interstitial volumes revealed a close correlation between renal function and prognosis on the one hand, and interstitial alterations on the other. There was no correlation with the severity and activity of glomerular alterations.

Patients and methods

One hundred ninety-eight patients fulfilling the ARA criteria for systemic lupus erythematosus (SLE) (Tan et al. 1982) underwent 228 renal biopsies during a period of 15 years from April 1972 through May 1987. Ninety-eight of these 198 patients were followed up for more than 3 years. In 30 of the 98 patients,

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apparent interstitial cell infiltration and/or fibrosis was observed by light microscopy. In this study, firstly, the clinical features and glomerular alterations of these 30 patients were compared with those of the remaining 68 who did not have apparent interstitial changes. Secondly, of the 30 patients, 20 were randomly selected and their initial biopsy specimens formed the subject of a quantitative study.

Endogenous creatinine clearance (Ccr), 24-h urinary protein excretion, urine sediment erythrocytes, serum creatinine concentration, anti-nuclear antibody titers, anti-DNA antibody titers, C3, C4 and blood pressure were examined during the follow-up period. Hypertension was defined as blood pressure of more than 150/90 mmHg. A progressive course was defined as that which showed a decrease of 15% or more of the initial Ccr values during the observation period. An unchanged course was one with stable renal function and no significant decrease of proteinuria. A course showing stable renal function and a significant reduction in proteinuria was considered to be an improved course. All of the 98 patients were administered 30 to 100 mg/day of prednisolone as an initial treatment dosage. In addition to oral steroid treatment, 7 of these patients received methylprednisolone pulse therapy. According to systemic or renal symptoms, the corticosteroids were tapered on a gradual basis. Most patients were maintained at 10 to 20 mg/day throughout the course of the disease.

For light microscopy, biopsy specimens were fixed by 10% buffered formalin and embedded in paraffin. Serial sections were cut at 2 μm and stained with haematoxylin and eosin (HE), periodic acid-Shiff (PAS), periodic acid-methenamine (PAM), and Masson's trichrome. Frozen sections for immunofluorescence were cut at 2 μm in a cryostat and stained by fluoresceined antisera against human IgG, IgA, IgM, C3, Clq, C4 and fibrinogen (Behringer). The glomerular lesions were evaluated according to Tateno's classification (1983). Briefly, the 7 classes consist of minimal lupus nephritis (LN), membranous LN (Mem), mesangial LN (Mes), mild diffuse proliferative LN (DP1), moderate diffuse proliferative LN (DP2), severe diffuse proliferative LN (DP3) and sclerosing LN. The activity of the glomerular lesions on light microscopy was assessed according to the method of Morel-Maroger (1976).

For quantitative measurement of interstitial lesions, all the PAM stained specimens were used, because the margins of the glomeruli and tubules were sharper than those with other stainings, (Fig. 1A). Photomicroscopy of the renal cortex in each specimen was performed and prints were made as large as 42 × 30 cm. All glomeruli, vessels, tubules and the margin of the cortex were demarcated with a fine line (Fig. 1B). The basement membrane of Bowman's capsule, outer elastic layers in vessels and tubular basement membrane were designated as a border. The demarcated areas of each portion were measured with a digitizer (YHP 9874A) linked to a computer (YHP 1000). In order to represent the plotted areas accurately, they were depicted on the display simultaneously (Fig. 1C). Interstitial areas (I) were calculated by subtracting the total areas of glomeruli, vessels and tubules (T) from the area of the cortex. The percentage of interstitial areas occupying the cortex was calculated as $I/(I+T) \times 100$ (interstitial volume: IV). Interstitial areas were also calculated in 4 biopsy specimens without interstitial changes from 4 lupus nephritic patients as a control. Δ IV was then determined in each specimen, subtracting a control area from each subject area.

Student's unpaired *t* test was used to analyze differences in age and creatinine clearance values. The chi-square analysis or Fisher's exact test was used to analyze differences in percentage of hypertension, progressive cases, death cases and cases with IgG deposits in TBM. The Mann-Whitney *U* test was used to analyze the distribution of glomerular lesions, the extent of Δ IV and activity points between the two groups. In these analyses, a *p* value of less than 0.05 was considered as statistically significant.

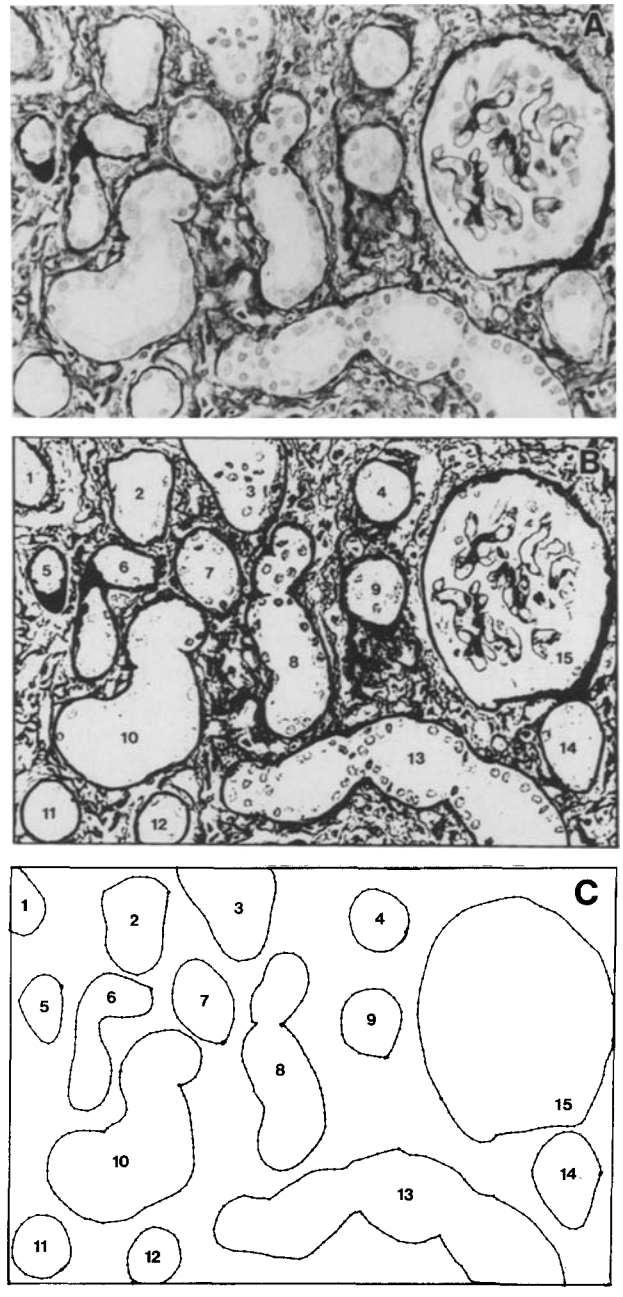

Fig. 1. (**A**) A representative photomicrograph of a portion of renal cortex. PAM, × 120. (**B**) The same portion of renal cortex as in **A**. Outer margin of a Bowman's capsule and tubular basement membranes are demarcated with fine lines. (**C**) The same outlines as in **B** are depicted by a plotter

Results

Table 1 shows a comparison of clinical features between the two groups (with and without intersti-

Table 1. Comparison of clinical features between two groups, with and without interstitial lesions

	Positive group	Negative group
Number of cases	30	68
Sex (M/F)	3/27	0/68
Age at initial biopsy (years)	34±12	33± 9
Duration from onset to biopsy (months)	43±45	72±73
Follow-up period (months)	66±43	83±41
Ccr (ml/min)		
initial	78±26	106±19***
final	64±38	104±23***
Initial hypertension (cases)	7 (23.2%)	3 (4.4%)**
Progressive cases	7 (23.3%)	3 (4.4%)**
Hemodialysis cases	4 (13.3%)	1 (1.5%)*
Death cases	7 (23.3%)	5 (7.3%)*

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Table 2. Comparison of histological findings between two groups, with and without interstitial lesions

	Positive group Cases (%)	Negative group Cases (%)
Number of cases	30	68
Minimal LN	0 (0)	4 (5.9)**
Membranous LN	1 (3.3)	16 (23.5)**
Mesangial LN	4 (13.3)	17 (25.0)**
Mild diffuse proliferative LN	3 (10.0)	22 (32.4)**
Moderate diffuse proliferative LN	11 (36.7)	8 (11.8)**
Severe diffuse proliferative LN	11 (36.7)	1 (1.5)**
Activity points	9.4±6.1	1.5±2.1**
IgG depositions in TBM	18 (60.0)	25 (37.0)*

* $p<0.05$, ** $p<0.01$. TBM: tubular basement membrane; LN: lupus nephritis

tial lesions) both at the time of renal biopsy and at final observation. The mean ages of the two groups were comparable. The mean duration of the disease before the initial biopsy was longer in the negative group than in the positive one. The mean follow-up periods were similar. The mean initial Ccr value in the positive group was 78 ml/min, lower than the 106 ml/min in the negative group ($p<0.01$). The mean final Ccr value in the positive group was 64 ml/min, also lower than the 104 ml/min in the negative cases ($p<0.01$). Hypertension at the time of biopsy, progression, haemodialysis and death were all more frequent in the positive group.

Table 2 depicts a comparison of histological findings in the two groups. Membranous lupus nephritis (LN) was more frequent in the negative group. Mesangial LN and mild diffuse proliferative LN, both mild in respect to mesangial hypercellularity, were also more frequent in the negative group. However, moderate and severe diffuse proliferative LN were apparently higher in frequency in the positive than in the negative group. The difference in these glomerular lesions between the two groups was significant ($p<0.01$). The frequency of IgG depositions in tubular basement membranes (TBM) and activity points was also significantly higher in the positive group.

Table 3 demonstrates the clinical features at the initial and final observations, with histological findings and final outcome in the 20 cases and 4 control cases. The mean age of the subjects was 34 years. The mean duration of the disease before biopsy was 40 months. The mean follow-up period was 69 months. The mean initial Ccr value was 77 ml/min and the final 71 ml/min. Heavy proteinuria greater than 2.0 g/day was seen in 7 cases. Haematuria was observed in 11. Hypertension was noted in 5.

Histologically, moderate and severe diffuse proliferative LN were revealed to be common at the rate of 75%. The mean activity point was also high at 10.4 counts. IgG depositions in TBM were found in 11 patients (55%).

The results of quantitative measurement of interstitial volumes (IV) are also shown in Table 3. The mean interstitial volume was 31.4% in the subjects and 13.4% in the control. In Fig. 2, comparisons of Δ IV are demonstrated according to the values of initial and final renal functions, presence or absence of hypertension and the degree of proteinuria. The mean Δ IV of 24.1% in 9 cases with initial Ccr value of less than 80 ml/min was significantly larger than that of 13.0% in 11 cases with Ccr value of 80 ml/min or more ($p<0.05$). There was also a significant difference in the mean Δ IV, 23.8 and 13.3%, between the cases grouped according to final Ccr values of 80 ml/min or more, and those less than 80 ml/min ($p<0.05$). However, there were no differences of Δ IV in the incidence of hypertension and in the amounts of urine protein excretion. Figure 3 compares Δ IV according to the severity and activity of glomerular lesions, and IgG depositions in TBM. There were no significant differences between the group pairings for each parameter.

Table 3. Clinical features, histological findings and outcome in 20 patients with interstitial lesions

Patient number	Age (years)	Sex	Duration to biopsy (months)	Follow-up (months)	Ccr (ml/min)		Proteinuria (g/day)		Hematuria		Hypertension (>150/90 mmHg)	
					I	F	I	F	I	F	I	F
1	26	M	37	70	55	0	3.6	2.8	+++	−	+	+
2	22	F	12	106	81	95	0.4	−	+	−	−	−
3	33	F	78	131	90	101	1.8	−	+	−	−	−
4	42	F	105	105	105	90	0.2	−	−	−	−	−
5	43	M	48	69	114	125	1.0	−	−	−	−	−
6	47	F	14	117	81	97	0.6	−	+	−	−	−
7	41	F	13	37	94	0	2.8	3.3	+++	+++	−	+
8	31	F	9	42	92	92	1.5	−	++	−	−	−
9	19	F	17	55	96	95	2.1	1.3	+++	−	−	+
10	27	F	12	113	101	91	3.6	−	−	−	−	−
11	37	F	204	2	26	16	0.5	0.5	+	+	+	+
12	16	M	6	4	50	39	6.4	4.2	+++	+++	−	−
13	51	F	21	134	80	88	−	−	−	−	−	−
14	30	F	2	4	25	40	1.0	0.8	−	−	+	+
15	58	F	21	74	49	22	−	1.8	−	−	+	−
16	42	F	13	70	74	35	5.4	3.8	−	−	−	−
17	30	F	71	1	69	69	1.6	1.6	−	−	−	−
18	15	F	4	68	123	123	1.1	0.2	+++	+	−	−
19	31	F	108	68	62	129	4.1	0.5	+++	−	+	+
20	42	F	6	103	75	75	−	−	−	−	−	−
	34±11		40±50	69±42	77±26	71±40	1.8±1.8	1.0±1.3				
Control												
1	36	F	72	29	111	111	−	−	−	−	−	−
2	51	F	96	27	100	100	0.6	−	+	−	−	−
3	50	F	8	26	137	137	−	−	−	−	−	−
4	29	F	3	28	97	102	−	−	−	−	−	−
	34±11		45±40	28±1	111±16	112±15						

I: initial data; F: final data; IV: interstitial volume; TMB: tubular basement membrane; pulse: pulse methylprednisolone therapy; PSL: prednisolone; CY: cyclophosphamide; AZ: azathioprine; P: progressive course; I: improved course; U: unchanged course; HD: hemodialysis; Tbc: tuberculosis

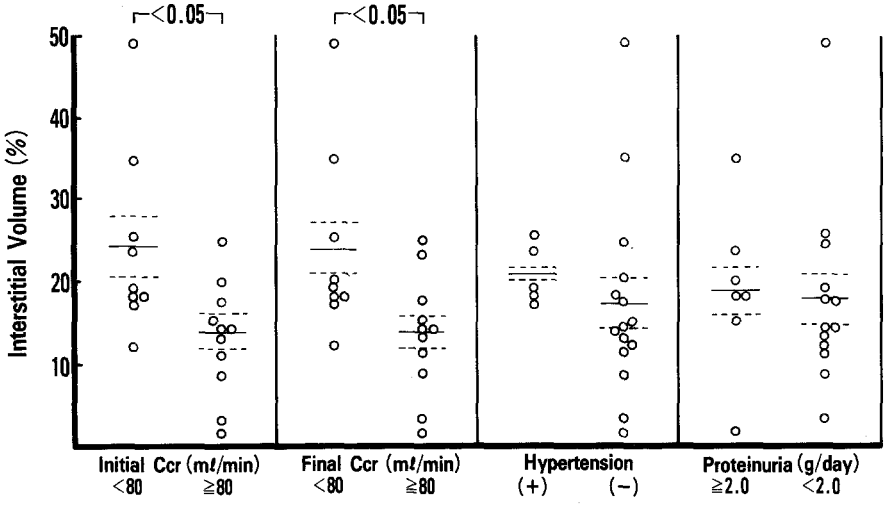

Fig. 2. Comparisons of Δ IV between four pairs of groups divided according to the initial and final values of renal functions, presence or absence of hypertension and the degree of proteinuria (Mann-Whitney *U* test)

Figure 4 demonstrates comparisons of Ccr values between four pairs of groups divided according to the extent of Δ IV, the severity and activity of glomerular lesions. The mean initial Ccr value of 61 ml/min in 11 cases showing Δ IV greater than 17% was significantly lower than that of 96 ml/min in 9 cases showing Δ IV of less than 17% ($p<0.01$). The mean final Ccr values of the

Table 3. Continued

C3 (mg/dl)		Anti-DNA Ab (μ/ml)		IV	Δ IV	Glomerular severity	Glomerular activity	IgG deposition in TBM	Therapy	Outcome	Comment
I	F	I	F								
15	82	26	7	31.6	18.2	DP-3	13	+	pulse, PSL, CY	P	HD
21	67	2750	10	16.5	3.1	DP-2	18	+	pulse, PSL	I	
32	70	4	9	26.4	13.0	DP-3	18	+	PSL, AZ	I	
135	114	7	12	21.9	8.5	DP-2	4	−	PSL	I	
74	91	1184	10	27.7	14.3	DP-2	11	−	PSL	I	
24	75	504	16	31.0	17.6	DP-2	8	+	PSL	I	
41	78	816	78	33.6	20.2	DP-3	16	+	pulse, PSL	P	HD
30	68	108	24	38.0	24.6	DP-2	14	+	PSL	I	
44	64	15	8	28.4	15.0	Mem	2	+	PSL	U	
54	80	52	13	14.9	1.5	DP-2	5	−	PSL	I	
47	64	90	52	30.8	17.4	DP-1	1	+	pulse, PSL, AZ	P	death (pneumonia)
21	83	−	−	31.3	17.9	DP-3	17	−	PSL, AZ	P	death (pneumonia)
22	91	17	16	24.6	11.2	DP-2	4	+	PSL	U	
28	74	92	23	38.8	25.4	DP-3	17	−	pulse, PSL	U	death (Tbc)
90	94	26	16	32.5	19.1	Mes	2	−	PSL	P	death (cerebral
131	100	23	4	48.2	34.8	DP-3	12	−	PSL	P	bleeding)
66	135	128	3	62.2	48.8	Mes	4	+	pulse, PSL, CY	U	death (heart
30	89	850	39	27.6	14.2	DP-3	18	+	pulse, PSL	I	failure)
38	71	103	15	37.0	23.6	DP-3	22	−	PSL	I	
64	106	24	5	25.5	12.1	Mes	2	−	PSL	U	
				31.4±10.2	18.0±10.2		10.4±6.7				
143	96	13	10	15.6		DP-1	1	−	PSL	U	
80	138	29	20	13.0		DP-1	1	−	PSL	I	
42	81	54	24	14.1		Mem	1	−	PSL	U	
24	37	210	21	11.1		Mes	1	−	PSL	U	
				13.4±1.6							

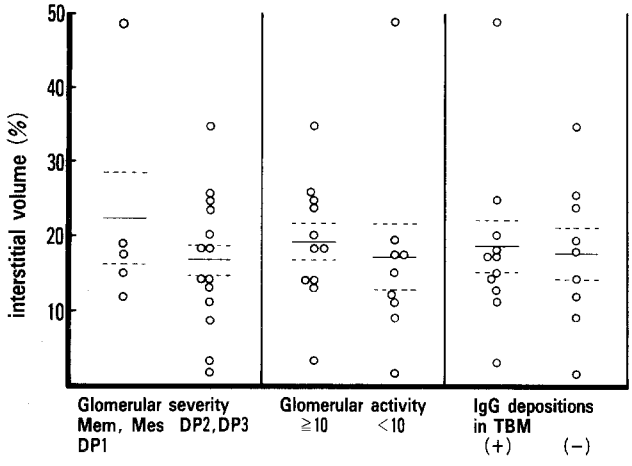

Fig. 3. Comparisons of Δ IV between three pairs of groups divided according to the severity and activity of glomerular lesions, and presence or absence of IgG depositions in TBM (Mann-Whitney *U* test)

two groups, 43 and 96 ml/min, were also significantly different from each other ($p<0.01$). However, there were no differences in Ccr values between the two respective groups divided according to the severity and activity of glomerular lesions.

Table 4 compares clinical features and glomerular activities between one group with Δ IV of 17% or more and the other with Δ IV of less than 17%. Ccr values at the initial and final observations in the former group were significantly lower than those in the latter. Further, hypertension, progression and death were all more frequent in the former; no such cases were seen in the latter. No difference between the two groups was observed in the extent of glomerular changes.

Discussion

In the present study, interstitial lesions were noted in 30 of the 98 initial renal biopsy specimens (30.6%). This incidence was lower than those of recent reports showing 66.7 to 93.0% (Schwartz et al. 1982; Magil and Tyler 1984; Park et al. 1986). This low incidence seems to be partly due to the fact that 33 patients with no urinary abnormalities at the time of biopsy were included in the 98 cases and to the fact that specimens showing mild patchy interstitial cell infiltration or fibrosis were excluded from the positive group.

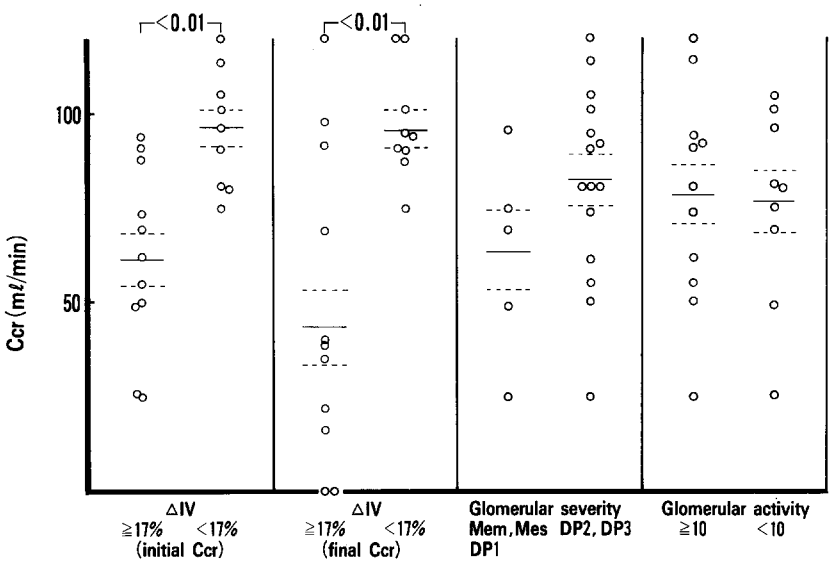

Fig. 4. Comparisons of Ccr values between four pairs of groups divided according to the extent of Δ IV, the severity and activity of glomerular lesions (Mann-Whitney *U* test)

Table 4. Comparison of clinical features and activity points between two groups, Δ interstitial volumes of 17% or more and less than 17%

	Δ IV	
	≧17%	<17%
Number of cases	11	9
Age at the biopsy (years)	35±11	33±12
Follow-up period (months)	45±37	98±27
Ccr (ml/min)		
initial	61±24	96±16**
final	43±33	96±15**
Initial hypertension (cases)	5 (45)	0*
Progressive cases	6 (54%)	0**
Hemodialysis cases	2 (18%)	0
Death cases	5 (45%)	0**
Activity points	11.4±6.5	9.1±6.7

* $p<0.05$, ** $p<0.01$

In the group with these interstitial lesions, renal clinical features such as a decrease of renal function and hypertension were seen more frequently. Moreover, the percentages of progression cases, haemodialysis and death were significantly higher in this group. In the histological study, the severity and activity of glomerular lesions as well as IgG deposition in TBM were also significantly higher. The results from our qualitative analysis of interstitial alterations in lupus nephritis suggested that these lesions were of great importance in defining the severity of renal involvement from both the clinical and histological points of view. They are in accord with a recent report in which the severity of interstitial lesions correlated well with the severity and activity of glomerular lesions and were said to be a reliable prognostic indicator (Part et al. 1986). From the present qualitative investigation, however, since the patients with apparent interstitial lesions exhibited remarkable glomerular lesions concurrently, it was not clear whether the interstitial alterations themselves could be responsible for these effects, independent of the glomerular alterations. Therefore, in order to investigate how the extent of interstitial lesions influences renal function, prognosis and glomerular lesions, interstitial volumes were measured quantitatively in 20 renal biopsy specimens showing interstitial lesions.

In our previous report, the coefficient of variation in the measurement of glomerular mesangial areas in IgA nephropathy using the same method was very small, from 0.2 to 1.8%. The method is accurate enough for quantitative measurement and makes it possible to measure the area in a short time (Tateno and Kobayashi 1987). In the present study, PAM stained sections were used because this staining made it easy to determine each fraction in the renal cortex.

There are several reports on quantitative measurement of interstitial lesions in various renal diseases including membranous nephropathy, acute glomerulonephritis, focal glomerulosclerosis, li-

poid nephrosis, membranoproliferative glomerulonephritis and IgA nephropathy (Bohle et al. 1977a, b, c; Fischbach et al. 1977; Riemenschneider et al. 1980; Bennett et al. 1982). These studies indicated that the extent of interstitial lesions had an inverse relation to renal function. In lupus nephritis, however, there are only two reports in which interstitial volumes were measured (Schwartz et al. 1982; Magil and Tyler 1984). Schwartz et al. measured interstitial volumes by using a point-counting method and demonstrated the presence of an inverse correlation between serum creatinine concentration and interstitial volume (Schwartz et al. 1982). Another report found no correlation between interstitial volumes and immune deposits in TBM, using a similar method (Magil and Tyler 1984). However, neither of these two reports were concerned with the prognosis of the patients or any correlation with glomerular lesions.

In the present study, significant correlations between the interstitial volumes and the degree of renal function in Ccr values were found, although there were no correlations between the interstitial volume and the severity and activity of glomerular lesions, nor between the renal function and the severity and activity of glomerular lesions. Furthermore, progressive cases were seen to be more frequent in the group with high interstitial volumes. These results indicate that in lupus nephritis accompanying interstitial lesions, renal function and prognosis correlate well with the extent of interstitial changes rather than with the severity or activity of coexisting glomerular lesions.

The mechanisms responsible for a decrease of glomerular filtration rate (GFR) in interstitial lesions remains unclear. Bohle et al. (1981) proposed that an increase in interstitial fibrosis led to an increased resistance in post-glomerular capillary networks, resulting in impairment of glomerular flow. Mackensen-Haen et al. (1981) also considered that tubular damage might involve GFR by a tubuloglomerular feed-back mechanism. We postulate two possible mechanisms of impairment of GFR: firstly, the extent of interstitial change may be related to that of tubular damage, leading to nephron destruction. This loss of nephrons would result in impairment of GFR. Secondly, interstitial oedema, cell infiltration and fibrosis may reduce the peritubular capillary blood flow and cause impairment of GFR.

Tubulointerstitial immune deposits are frequent findings in patients with lupus nephritis (Klassen et al. 1972; Andres and McCluskey 1975; Brentgens et al. 1975; Lehman et al. 1975; Morel-Maroger et al. 1976; Orfila et al. 1979; Biesecker et al. 1981; Park et al. 1986). These deposits are thought to be part of the pathogenesis of lupus interstitial nephritis. In the present study, IgG depositions in TBM were observed in 44% of a total of 98 patients and in 60% of those with interstitial lesions. However, there was no correlation between the extent of interstitial volumes and the presence of TBM depositions. Park et al. (1986) also reported that there was no correlation between the prevalence of tubulointerstitial deposits and the prevalence and severity of interstitial infiltration. These disagreements over interstitial lesions and TBM depositions may be due to the fact that TBM deposition is not seen in all tubules and it is likely that a small block used for immunofluorescence may not include positive areas. Further, when interstitial lesions become inactive, resulting in fibrotic changes, they may disappear. However, cell-mediated immunity may be important in the occurrence of tubulointerstitial lesions (Rich et al. 1981; McCluskey and Bhan 1982).

In this study, the patients with Δ IV greater than 17% showed a deterioration of renal function both at the time of biopsy and at the final observation. In addition, a subsequent decrease of Ccr values was conspicious in this group during the follow-up period. Moreover, all progressive cases and death cases were seen in this group. These results indicate that 17% in Δ IV seems to be a critical value in predicting subsequent deterioration of renal function or prognosis in lupus nephritis with interstitial lesions.

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