Mesangial Proliferative Glomerulonephritis. Natural History and Effects of Dextran Sulfate

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We evaluated 246 cases having clinically primary chronic glomerulonephritis and histologically mesangial proliferative glomerulonephritis of varying degrees. 190 patients conservatively followed with serial measurements of GFR served as delineating the natural history. The remaining, randomly selected 56 subjects were treated with Dextran sulfate, a mild anticoagulant, for 7 to 56 months (average, 25.4). 55 cases underwent repeated renal biopsy at the mean interval of 3.3 years. It became evident clinically and morphologically that the severity of diffuse mesangial proliferation and the presence of focal and segmental lesions in more than 20% were two critical determinants of the natural history. All cases with mild mesangial proliferative alteration alone survived more than 10 years, but none of the patients with global sclerosis in more than 50% in the initial biopsy did. 10-year survival rates in mild, and moderate or greater mesangial proliferation with the focal-segmental lesions were 45.0% and 19.3%, respectively. In the treated group, renal function improved or was maintained, along with histologic confirmation in some, during the follow-up period. Moreover, the survival rate of subjects with global sclerosis in more than 50% ameliorated beyond the natural history. Thus, Dextran sulfate appeared promising for a possible suppression of the coagulatory process associated with the focal-segmental lesions.

Key Words: Chronic glomerulonephritis, Focal and segmental lesions, IgA nephritis, Intraglomerular coagulation, Anticoagulants.

In recent years, some progress has been attained in the therapeutical field of glomerulonephritis. The combined therapy of glucocorticosteroids, cytotoxics, anticoagulants and antithrombotics,¹⁻³⁾ steroid pulse therapy⁴⁾ and plasmapheresis⁵⁾ have shown beneficial effects on rapidly progressive or crescentic glomerulonephritis of the primary and secondary variety. However, these aggressive treatments are essentially unsuitable for a slowly progressive glomerulonephritis following a chronic course over many years. For this latter group, those medications which can be prescribed safely for longer periods on the outpatient basis are rather preferable. Since chronic glomerulonephritis is a syndrome including membranous nephropathy, membrano-

proliferative glomerulonephritis, mesangial proliferative glomerulonephritis and IgA nephritis,⁶⁾ the efficacy of any treatment should be evaluated according to their individual morphological or pathogenetic classification. Pioneer works have demonstrated that a combination of cytotoxics and antithrombotics for one year⁷⁾ or alternate-day steroids for 3 to 9 years⁸⁾ resulted in the resolution of circumferential mesangial interposition characteristic of membranoproliferative glomerulonephritis. It has been shown in a controlled study that alternate-day steroids, although used for a short period, were effective in preventing a progression to renal failure in patients with membranous nephropathy.⁹⁾ With regard to mesangial proliferative glomerulonephritis, however, little

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information is available about therapeutical trials in comparison with its natural history.

Thus, we reviewed our experience in an attempt to delineate the natural history of mesangial proliferative glomerulonephritis, a major constituent of IgA nephritis. We also observed that Dextran sulfate, a mild anticoagulant, was promising in the treatment of this glomerular disease.

PATIENTS AND METHODS

Patients. In Kanazawa University Hospital and affiliated hospitals between February 1962 and August 1979, we evaluated, with percutaneous renal biopsies, those patients who showed persistent urinary abnormalities for more than one year and were clinically judged as having primary chronic glomerulonephritis. 246 cases were found to have mesangial proliferative glomerulonephritis of varying degrees. They consisted of 143 males and 103 females, and their ages ranged from 10 to 76 years, with the average being 35.4 years. Immunofluorescent studies

were performed on the renal tissues of 120 of the cases, and 101 (84.2%) of these were judged to belong to IgA nephritis according to the criteria described previously.¹⁰⁾ The remaining cases showed a negative, or equivocal staining. 56 patients who were examined in the latter part of the above study period were randomly selected for the treatment as shown below. The remaining, untreated 190 cases were conservatively followed with serial measurements of glomerular filtration rate (GFR). These 190 cases thus served as the basis of delineating the natural history of mesangial proliferative glomerulonephritis. 51 cases from the untreated group and 4 from the treated group underwent repeated renal biopsies at intervals of from one to 12.5 years (average, 3.3 years). There was no essential difference between the untreated and treated groups with regard to the patient's profile, mode of onset or other aspects of the clinical history.

Histologic grading. Glomerular alterations

Fig. 1. Representative glomerular changes. A: diffuse mild mesangial proliferation + segmental lesion (LGN+F). On the left, one can see a segmentally sclerotic focus with some reactive increase of epithelial cells, which adhered to Bowman's capsule. PAS, $\times 400$. B: diffuse moderate mesangial proliferative alteration (CGN). Note that there are more widened mesangial areas composed of both cell and matrix components, often compromising the capillary lumina. PAS, $\times 400$.

were graded on the basis of the following three items: (1) degree of mesangial proliferative change, (2) presence of focal and segmental lesions and (3) frequency of global sclerosis. All the renal specimens contained more than 10 glomeruli. Mesangial proliferation was divided into mild degree, and moderate or greater degree as shown in Figure 1. The presence of focal and segmental lesions (abbreviated as F) was defined as having segmental necrosis, sclerosis, and/or small crescents, in more than 20% of the total glomeruli obtained (Figure 1.A). If there was global sclerosis in more than 50% of the total glomeruli, usually along with widespread tubulointerstitial injuries, this was classified as advanced form. Thus, six forms of glomerular changes emerged: (1) mild mesangial proliferative glomerulonephritis (abbreviated as LGN), (2) LGN+F, (3) moderate or more mesangial proliferative glomerulonephritis (CGN), (4) CGN+F, (5) advanced mesangial proliferative glomerulonephritis (Adv.CGN) and (6) Adv.CGN+F.

Treatment. 56 patients received medication as shown in Table 1. All were given 1800 mg per day of Dextran sulfate. The drug was administered orally for 7 to 56 months (average, 25.4 months). In 13 subjects, one or more of the following drugs were added: 60,000 International Units of Urokinase were daily infused intravenously for 2 weeks, usually at the starting point of the treatment. 300 mg per day of Dipyridamole, administered orally, was prescribed for the same period as the Dextran sulfate. Warfarin doses were

adjusted to maintain Thrombotest (by Owen) in a range of 10% to 25%, and it was continued for the same period as Dextran sulfate. Prednisone was administered in a dose of 20 mg per day for the initial 2 to 3 months and then tapered over the following one to 3 months.

Coagulation studies. Apart from Thrombotest in the patients treated with Warfarin, the following parameters were regularly checked: bleeding time using Duke's method (normal: 2 to 6 minutes), platelet counts using Rees-Ecker's method (normal: 14 to $34 \times 10^4/\text{mm}^3$), fibrinogen level using the tyrosine method (normal: 170 to 410 mg/dl) and partial thromboplastin time (PTT) using a modified Quick's one-stage test (normal: 27 to 39 seconds).

Statistical analysis was performed using Student's *t*-test, and the life table analysis was done using the Mantel-Haenszel procedure,¹¹⁾ based on the concept of Cutler and Ederer.¹²⁾ A *p*-value less than 5% was regarded as significant.

RESULTS

Clinical features. Table 2 provides clinical features on the untreated and treated groups. Although the ages, periods from onset to the initial renal biopsy as well as the incidences of urinary findings and hypertension were variable, these factors were overall not essentially different between the two groups. In the present series, no patient with LGN, LGN+F or CGN disclosed nephrotic-range proteinuria or frank nephrotic syndrome.

Natural history. The follow-up periods and GFR levels at the starting and final points in both groups are shown in Table 3. In the untreated group, every form of glomerular change exhibited a significant decrease of GFR at the end of observation. Moreover, on the basis of time course of GFR during these periods and on the assumption that when a patient required dialysis therapy, kidney death occurred, the life-table curve of each glomerular change is depicted as seen in Figure 2. Although there was no statistical difference between LGN+F and CGN and between Adv.CGN and Adv.CGN+F, comparisons between LGN and others, LGN+F and CGN+F, CGN and CGN+F, and CGN+F and advanced forms had definite

Table 1. Contents of Therapeutic Regimens

Glomerular changes	DS alone	DS + UK	DS + DIP	DS + UK + DIP	DS + UK + PSL	DS + W + DIP + PSL	Total
LGN	11 (cases)	0	0	0	0	0	11
LGN+F	6	1	1	2	1	0	11
CGN	8	1	1	1	1	0	12
CGN+F	10	1	0	0	0	1	12
Adv. CGN	6	1	0	0	0	0	7
Adv. CGN+F	2	1	0	0	0	0	3
Total	43	5	2	3	2	1	56

Abbreviations:

DS; Dextran sulfate, UK; Urokinase, DIP; Dipyridamole, PSL; Prednisolone, W; Warfarin, LGN; mild mesangial proliferative glomerulonephritis, CGN; moderate or more mesangial proliferative glomerulonephritis, Adv. CGN; advanced mesangial proliferative glomerulonephritis, F; focal and segmental lesions.

Table 2. Clinical Features in Untreated and Treated Groups

Glomerular changes	Groups	No. of cases (males)	Age (years)	Periods from onset to the first biopsy (month)	Frequency (%) of		
					Hematuria (>5/HPF)	Proteinuria (>1 g/day)	Hypertension (>140/90 mmHg)
LGN	untreated	87(49)	24.5±1.2*	24.5±4.4	39.5	12.8	11.6
	treated	11(2)	30.1±3.3	27.6±11.0	70.0	20.2	27.3
LGN+F	untreated	20(10)	25.2±2.2	16.4±5.0	50.0	15.0	25.0
	treated	11(7)	33.5±5.4	39.5±12.0	72.7	36.7	9.1
CGN	untreated	34(20)	32.9±2.1	52.9±15.0	56.3	65.6	25.0
	treated	12(7)	33.8±5.0	83.8±39.5	72.7	27.3**	27.3
CGN+F	untreated	23(17)	29.2±2.3	49.5±15.6	63.6	68.2	43.5
	treated	12(5)	37.9±5.0	53.4±17.3	83.3	54.5	33.3
Adv. CGN	untreated	16(12)	32.3±3.6	58.9±18.1	31.3	75.0	81.2
	treated	7(6)	39.3±5.9	49.0±14.2	50.0	66.7	50.0
Adv. CGN+F	untreated	10(7)	30.8±2.9	29.4±10.2	50.0	90.0	80.0
	treated	3(1)	37.3±7.0	64.0±4.0	100.0	100.0	100.0

*Mean ± SE.
**Only this case was significant (p < 0.05), but no other cases were significantly different (untreated vs treated).

Table 3. Follow-up Periods and Renal Function in Untreated and Treated Groups

Glomerular changes	Groups	No. of cases	Follow-up periods (months)	GFR at starting point (ml/min)	GFR at final point (ml/min)
LGN	untreated	87	59.4±4.0*	115.8±2.8	101.6±2.7c***
	treated	11	29.1±3.0b**	86.6±6.6	114.1±8.5
LGN+F	untreated	20	57.7±6.6	108.0±5.6	82.5±8.2a
	treated	11	23.1±5.1b	77.7±7.1	92.8±6.7
CGN	untreated	34	56.2±5.5	84.3±4.8	60.8±6.2c
	treated	12	26.6±2.9b	70.1±7.8	86.7±8.8
CGN+F	untreated	23	48.4±4.9	66.7±6.0	33.3±8.7c
	treated	12	32.5±2.9a	71.7±9.3	84.0±13.7
Adv. CGN	untreated	16	24.9±7.1	32.3±3.6	3.2±2.2c
	treated	7	15.0±2.7	46.7±7.1	45.9±9.1
Adv. CGN+F	untreated	10	32.1±5.3	35.3±3.8	3.7±2.5c
	treated	3	20.3±4.5	29.0±6.2	22.3±8.9

*Mean ± SE.
**Comparison between untreated and treated groups.
***Comparison between GFR at starting and final points in the same group.
Abbreviations of statistical significance: a, p < 0.05, b, p < 0.01 and c, p < 0.001.

differences. All patients with LGN survived more than 10 years, but none with advanced forms did, and 10-year survival rates in LGN+F, CGN, CGN+F were 45%, 43.9% and 19.3%, respectively. It thus became evident that the severity of diffuse mesangial involvement and the presence of focal and segmental lesions in more than 20% were two critical determinants of the prognosis of mesangial proliferative glomerulonephritis.

These functional features were consistent with the serial histological studies as shown in Figure 3. A majority of patients with mild, or moderate or

greater degree of mesangial proliferation alone remained relatively stable. Particularly, a few cases with LGN displayed the same change even after more than 10 years. In contrast, the glomerular forms with the focal and segmental lesions showed frequent transitions to more severe forms with rare exceptions.

Effects of treatment. Although with shorter follow-up periods, the treated group (as seen in Table 3) showed no significant deterioration of the renal function. GFR in the first 4 glomerular forms tended rather to increase after the treat-

Fig. 2. The life-table curves of the untreated group depicted by Mantel-Haenszel's procedure.

5-year (and 10-year) survival rate in LGN, LGN+F, CGN, CGN+F, Adv.CGN and Adv.CGN+F were 100% (100), 90.0 (45.0), 87.7 (43.9), 50.2 (19.3), 12.5 (0) and 0 (0), respectively.

Statistical difference of the life-table curve of each glomerular form was as follows (Mantel-Haenszel chi-square test).

	LGN	LGN+F	CGN	CGN+F	Adv. CGN	Adv. CGN+F
LGN		P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
LGN+F			NS	P<0.001	P<0.001	P<0.001
CGN				P<0.001	P<0.001	P<0.001
CGN+F					P<0.01	P<0.01
Adv. CGN						NS

ment. Correspondingly, the serial renal biopsies in 4 cases showed a histological improvement, although one case with CGN+F subsequently returned to the previous level (Figure 3). Figure 4 gives the life-table curves of the treated group. The statistical difference which was observed between LGN and other glomerular forms in the untreated group disappeared in the treated group, implying a prognostic amelioration. However, except for the Adv.CGN form, a paired comparison of the curves of the untreated and treated groups did

Fig. 3. Results of serial renal biopsies. In the untreated group, glomerular changes without or with focal and segmental lesions in less than 20% (LGN, CGN) remained relatively stable, while those forms with F component frequently progressed with transitions to the more severe ranks. In the treated group, one case with LGN+F was transformed into LGN as were 3 cases with CGN+F into CGN, although one of the latter subsequently returned to the previous rank.

not reach any significant level, probably due to a shorter observation period in the latter.

Coagulation parameters. As seen in Figure 5, a gradual decrease of platelet counts, fibrinogen levels, and a mild prolongation of PTT developed with the continuation of treatment for the more than one year. These findings were judged to be consistent with the actions of Dextran sulfate. However, it should be noted that all these changes occurred within the range of normal values. Bleeding time also remained within normal limits, and none of the patients were complicated by hemorrhaging problems. There was no adverse reaction attributable to Dextran sulfate or other medications throughout the whole course of the treatment.

DISCUSSION

Mesangial proliferative or mesangioproliferative glomerulonephritis so far reported is strikingly heterogeneous. 44 subjects studied by Brown et al¹³⁾ showed mild, pure mesangial proliferative lesions with a favorable clinical outcome. Bhasin et al¹⁴⁾ have described 11 patients, of mesangial proliferative glomerulonephritis characterized by

Fig. 4. The life-table curves of the treated group. 5-year survival rates in LGN, LGN+F, CGN, CGN+F, Adv.CGN and Adv.CGN+F were 100%, 100, 100, 75.0, 75.0 and 66.0, respectively. Statistical difference of the life-table curve of each glomerular form was as follows (Mantel-Haenszel chi-square test).

LGN	LGN+F	CGN	CGN+F	Adv. CGN	Adv. CGN+F
LGN	NS	NS	NS	+	+
	LGN+F	NS	NS	NS	NS
		CGN	NS	+	+
			CGN+F	NS	P<0.05
				Adv. CGN	NS

+: tendency ($P < 0.10$), NS: not significant. Comparison between untreated and treated groups disclosed a significant difference in Adv.CGN ($P < 0.05$), but none of other forms reached any significant level.

glomerular IgM deposition, of whom 9 presented with nephrotic syndrome. According to the review article by Rosen et al,¹⁵⁾ these cases belong rather to a condition surrounding minimal change nephrotic syndrome and focal glomerular sclerosis. On the other hand, 211 patients of primary mesangioproliferative glomerulonephritis with urinary abnormalities lasting more than one year, reviewed by Migone et al,¹⁶⁾ are similar to our cases, although they have not mentioned the natural history. The present series was selected on clinicopathological basis, i.e., clinical diagnosis of primary chronic glomerulonephritis and the light-microscopic findings of mesangial proliferative

Fig. 5. Time course of coagulation parameters. Platelet counts and fibrinogen levels gradually decreased, while PTT prolonged in the same manner, but these changes were never beyond the normal range.

erative glomerulonephritis. Nephrotic syndrome was observed only in those cases with more severe or advanced forms as a common complication of advanced chronic glomerulonephritis. When immunofluorescent studies were performed on about one half of the patients, a majority met the criteria of IgA nephritis.

Chronic glomerulonephritis is currently regarded as a syndrome,⁶⁾ from which various morphological entities such as membranous nephropathy and membranoproliferative glomerulonephritis have been separated, leaving mesangial proliferative glomerulonephritis as a major constituent. Moreover, application of the immunofluorescent technique has isolated IgA nephritis, mainly from the last condition. It is this clinicopathological entity that the present study is aimed.

Mesangial proliferative glomerulonephritis as defined above was further divided according to the following three considerations: the severity of mesangial proliferative lesions, the presence of focal and segmental lesions in more than 20%, and the frequency of global sclerosis. It emerged from this subdivision that there were two critical determinants of the prognosis: the degree of mesangial proliferation, and the presence of focal and segmental lesions. The observation that

diffuse mesangial lesions of a moderate or greater degree have a progressive nature has amply been shown in several series of IgA nephritis cases.¹⁷⁻²⁰⁾ It is also acceptable that the presence of global sclerosis at a frequency of more than 50% accompanies an ominous implication.

Of note is the fact that mild mesangial proliferation with focal and segmental lesions in more than 20% (LGN+F) revealed a progressive course. This glomerular form had been classified as focal glomerulonephritis before the introduction of the immunofluorescent procedure. Since, by this technique, the pathological processes were found to be diffuse-global rather than focal-segmental, we have adopted the above term instead of focal glomerulonephritis. In any case, the prognosis of focal glomerulonephritis has been controversial. Previous reports²¹⁻²³⁾ have stated that focal glomerulonephritis follows a benign clinical course, whereas recent works have noted a progressive nature.^{24, 25)} In the present series, the LGN form which showed a benign outcome included occasional cases with focal and segmental lesions in less than 20%. Therefore, a milder form of focal glomerulonephritis may be much less progressive. On the contrary, in their series of proliferative focal glomerulonephritis, Zollinger and Mihatsch²⁵⁾ have observed that the overall survival rate during 10 years was 58% in cases without crescents, while it was 36% in those with crescents of less than 50%. The latter data is comparable to our results. Kincaid-Smith and Yeung²⁴⁾ have also described 10-year death or renal failure rate at 44% in males and 11% in females, with focal and segmental proliferative glomerulonephritis. The sex difference was not verified in our series. Moreover, Syre²⁶⁾ has emphasized the significance of segmental-focal glomerular lesions in IgA nephritis, since there was a positive correlation with the amount of proteinuria and the degree of mesangial increase.

The pathogenesis of focal-segmental lesions remains to be solved. But, Gabbiani et al²⁷⁾ have been able to induce experimentally focal glomerular lesions in rabbits by the infusion of very large, poorly soluble or insoluble immune complexes into the renal arteries. Whether this is

applicable to human cases awaits further investigation. Apart from the participation of immune complexes, Shigematsu et al^{28, 29)} have demonstrated by ultrastructural techniques that focal and segmental lesions frequently observed in IgA nephritis are characterized by the activation of the focal coagulatory process and an influx of fibrin-like materials into the Bowman's space, which eventually lead to focal and segmental disorganization.

In the present series, the administration of Dextran sulfate and other medications appeared to be promising in maintaining renal functions and, in some, improving glomerular lesions. Dextran sulfate (MDS-KOWA, molecular weight 7,000, sulfate content 18.2%), called heparinoid, is well absorbed from the alimentary canal. It has been used clinically as an antihyperlipidemic and antiarteriosclerotic agent in Japan. Its main actions are known to be, (1) acceleration of lipidemia-clearing activity, (2) enhancement of blood fibrinolytic activity, (3) inhibition of blood coagulation and (4) inhibition of platelet aggregation.³⁰⁾ It is, therefore, possible to have a combined use with Urokinase,³¹⁾ or with an antithrombotic or Dipyridamole. Although other medications were also used in some cases, we believe that the effects in the treated group were mainly derived from Dextran sulfate. Since, as above, the focal and segmental lesions are associated with intravascular coagulation, this drug would be a candidate which can be prescribed safely for longer periods without causing adverse reactions. It is noteworthy that the survival rate of patients with global sclerosis in more than 50% was improved by the treatment beyond the natural history. Thus, the present preliminary results should deserve further study and confirmation.

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