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Histological Analysis of Serial Renal Biopsy Specimens from Children with Immunoglobulin A Nephropathy Not Treated with Immunosuppressants

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Background: Although pediatric immunoglobulin A nephropathy (IgAN) is considered to have a good prognosis, few studies have investigated histological changes over time in IgAN. Serial renal biopsies were performed during the course of the disease and histological changes were observed in patients who did not receive immunosuppressive treatment. To our knowledge, this is the first report of two or more histological evaluations of renal biopsies from patients with pediatric IgAN who did not receive immunosuppressive drugs.

Methods: Forty-two patients with biopsy-proven IgAN who did not receive immunosuppressive agents and underwent serial renal biopsies were followed in our hospital between 1990 and 2003. This retrospective study evaluated findings from renal biopsy specimens and medical records.

Results: Analysis of histological findings showed that 19 of 42 patients improved and 16 showed exacerbation of mesangial proliferation. Seven patients showed no obvious histological changes. Of the improved cases, 11 showed spreading of chronic lesions, and there was a significant difference between patients with and without segmental glomerular sclerosis or adhesion at the first biopsy. Of the exacerbated cases, only 5 of 16 patients showed strong active lesions at the first renal biopsy.

Conclusions: Histological changes were investigated in pediatric IgAN patients not receiving immunosuppressive treatment. The results suggest that, even if mesangial hypercellularity improves, chronic lesions may spread during the natural history of the disease. Predicting histological changes by using findings from renal biopsies performed early after onset is difficult; therefore, patients should be carefully followed. (J Nippon Med Sch 2023; 90: 253–261)

Key words: children, repeat biopsy, non-immunosuppressive treatment, acute and chronic lesions

Introduction

IgA nephropathy (IgAN) was first described in 1968 by Berger and Hinglais[1] and is now recognized as the most common primary glomerulopathy in the world. IgAN is associated with abnormalities of the immune system and is characterized by IgA deposition in glomeruli.

Several reports showed that the long-term prognosis of pediatric IgAN was better than that of adult IgAN[2–5], although the histopathological findings at the time of the initial renal biopsy, blood pressures, and severity of proteinuria varied among studies, and treatment ranged from no treatment to immunosuppressive drugs. During the last decade, an increasing numbers of studies have reported unfavorable outcomes for pediatric IgAN. Unfortunately, few studies have examined the results of findings from serial renal biopsies, and changes in renal tissue during the course of pediatric IgAN in patients not receiving immunosuppressive treatment are unclear.

Because of the school urinary screening system in Japan, most Japanese children with IgAN are identified at an early stage of the disease[6]. In other countries, the disease is often detected only after symptoms have developed. However, in Japan it has been possible to identify histological involvement of cases near the time of onset,

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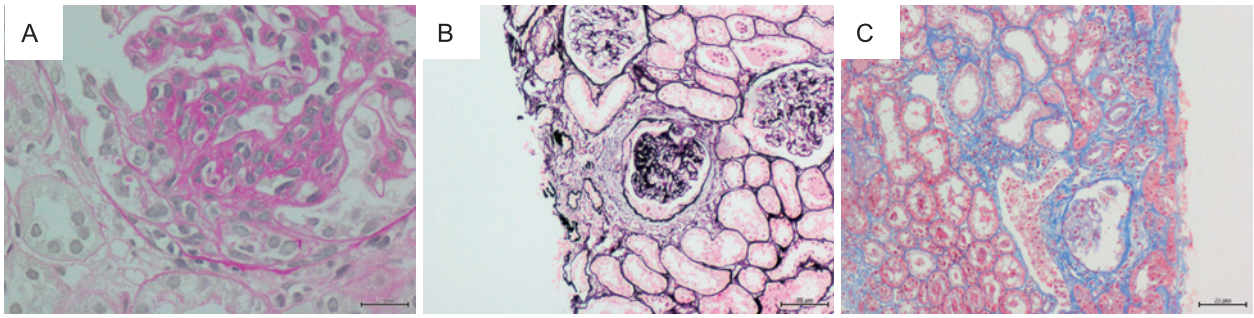

Fig. 1 Renal biopsy findings
A) Endocapillary hypercellularity consists of inflammatory cellular infiltration, segmental glomerulosclerotic lesions, and cellular crescent formation in the severely damaged glomerulus (PAS; × 400). (B) Collapsed glomeruli with pericapsular fibrosis are observed (silver stain, × 200). (C) Tubular atrophy and fibrosis of the interstitium are visible near severely damaged glomeruli (Masson trichrome stain, × 200)

when patients are asymptomatic. We examined how renal biopsy findings change in patients not using immunosuppressive drugs.

Materials and Methods

Patients

This study included 42 patients (29 boys and 13 girls) with biopsy-proven IgAN who were followed at our hospital between 1990 and 2003. In our institute, IgAN patients who did not show nephrotic range proteinuria and were diagnosed with mild to moderate mesangial proliferation by renal biopsy were treated without steroids or other immunosuppressants until 2003. The reason for this was the absence of contemporaneous evidence supporting the use of steroids or immunosuppressive drugs in pediatric IgAN. Treatment was decided based on proteinuria severity. Patients with hematuria only were treated with antiplatelet agents, and patients with proteinuria and hematuria were treated with renin-angiotensin system inhibitors. The decision to start angiotensin II receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) therapy was left to the discretion of the attending physician. During the disease course, two or more renal biopsies were performed to re-evaluate renal damage. In 2003, there were only a few consensus-based treatments for IgAN, and the method of predicting the prognosis of IgAN was unclear. Therefore, renal biopsies were performed to determine the effectiveness of treatment. All patients provided written, informed consent before each renal biopsy. The results of clinical records and renal biopsies were studied retrospectively.

Histological Examination

Histological findings of the first and final renal biopsies were evaluated. Biopsy specimens were assessed using light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). Specimens for LM were stained using hematoxylin and eosin, periodic acid-Schiff, Masson trichrome, and periodic acid-methenamine silver stains. Specimens were evaluated visually, and no technique such as software analysis was used. The specimens were evaluated for percentage of mesangial hypercellularity, segmental glomerulosclerosis, cellular/fibrocellular or fibrous crescents, endocapillary hypercellularity, interstitial fibrosis and/or tubular atrophy, and necrotizing and obsolescent glomeruli. Since it was difficult to strictly distinguish between global glomerulosclerosis and obsolescent sclerosis, they were collectively referred to as obsolescent glomeruli. Disease improvement or worsening was determined histologically by the amount of mesangial hypercellularity, the degree of IgA deposition, and the presence of acute lesions (cellular or fibrocellular crescents, necrotizing lesions, and endocapillary hypercellularity), and/or expansion of chronic lesions (segmental glomerular sclerosis or adhesion, fibrous crescents, obsolescent glomeruli, and interstitial fibrosis and/or tubular atrophy) (**Fig. 1**). The number of glomeruli observed in each patient was 18 or more.

Statistical Analysis

After comparing two renal biopsies, we classified the patients into three groups on the basis of changes in mesangial cell hypercellularity, as follows: Group 1, improvement in mesangial hypercellularity; Group 2, no change in mesangial hypercellularity; and Group 3, worsening of mesangial hypercellularity. Clinical data (age, sex, cause of discovery, duration between renal biopsies, degree of proteinuria, and hematuria) from these three groups at the first and last biopsies are summarized in **Table 1**. In addition, histological changes between the in-

Table 1

	Total (N=42) Median ± SD (MIN - MAX)		Group 1 (N=19)	Group 2 (N=7)	Group 3 (N=16)	p-value*2 (1 vs 2)	p-value*3 (1 vs 3)	p-value*4 (2 vs 3)
Age (y)	11.5 ± 2.7 (6 - 16)		11	13	14	0.094	0.024	0.579
Sex		Male	13	6	10	0.534	0.781	0.413
		Female	6	1	6			
Cause of discovery						0.821	0.909	0.871
		SUS	15	6	13			
		macro	4	1	3			
Duration (months)	39.0 ± 25.1 (24 - 132)		37	36	41	0.364	0.461	0.341
Proteinuria (g/gCr) (first biopsy)	0.20 ± 0.72 (0.00 - 3.00)					0.910	1.000	0.720
		–	8	2	7			
		+	4	3	5			
		++	4	1	1			
		+++	3	1	3			
Hematuria (first biopsy)						0.778	0.756	1.000
		–	0	0	0			
		+	0	0	2			
		++	4	2	2			
		+++	15	5	12			
Proteinuria (g/gCr) (last biopsy)	0 ± 0.54 (0.00 - 2.60)					0.692	0.006	0.018
		–	15	6	6			
		+	1	0	3			
		++	2	1	3			
		+++	1	0	4			
Hematuria (last biopsy)						0.461	0.003	0.076
		–	12	3	2			
		+	4	2	3			
		++	0	1	4			
		+++	3	1	7			

Group 1: improved mesangial hypercellularity
Group 2: unchanged mesangial hypercellularity
Group 3: worsened mesangial hypercellularity
SUS: school urinary screening
macro: macrohematuria
Hematuria +-+++: result of test tape
Proteinuria +-+++: result of test tape

itial and final renal biopsies for each group are summarized in **Table 2**. Histological changes in the group without (Group 1a) and with (Group 1b) worsening of chronic findings in Group 1 were then compared (**Table 3**). To analyze risk factors for progression of chronic lesions, the Mann-Whitney U test was performed. The factors studied were age, sex, cause of discovery, duration between biopsies, degree of proteinuria, and hematuria. To evaluate renal histological findings, segmental glomerulosclerosis, cellular/fibrocellular or fibrous crescents, endocapillary hypercellularity, interstitial fibrosis and/or tubular atrophy, and necrotizing and obsolescent glomeruli present at the initial biopsy were studied.

The study protocol was approved by the Ethics Committees of Nippon Medical School Hospital (B-2020-284) and Nippon Medical School Tama Nagayama Hospital (No. 683) and was designed in accordance with the principles of the Declaration of Helsinki.

Results

Treatment and Clinical Course

Data from 42 patients were analyzed. Thirty-four cases were detected by the school urinary screening system and eight by gross hematuria. The median age at first renal biopsy was 11.5 ± 2.7 years (range, 6-16 years). Of the 42 patients, 24 underwent renal biopsy within 3 months,

Table 2

		Group 1 (N=19)		Group 2 (N=7)		Group 3 (N=16)		p-value (first vs last)
		First	Last	First	Last	First	Last	
	(%)	Mesangial hypercellularity						
	0-15	8	16	6	6	13	3	
	16-30	3	3	1	1	2	4	
	31-45	6	0	0	0	1	6	
	46-60	2	0	0	0	0	2	
	61-75	0	0	0	0	0	1	
Acute lesion	(%)	Cellular or fibrocellular crescents						
	0	15	19	7	7	11	14	
	1-10	2	0	0	0	5	1	
	11-20	2	0	0	0	0	1	
	(%)	Necrotizing lesions						
	0	18	19	7	7	13	15	
	1-5	1	0	0	0	2	1	
	6-10	0	0	0	0	1	0	
		Endocapillary hypercellularity						
	–	16	19	7	7	15	12	
	+	3	0	0	0	1	4	
Chronic lesion	(%)	Segmental glomerular sclerosis or adhesion						p<0.001
	0	4	4	5	2	10	0	
	1-10	10	12	1	4	4	6	
	11-20	4	2	1	1	2	3	
	21-30	1	1	0	0	0	3	
	31-40	0	0	0	0	0	2	
	41-50	0	0	0	0	0	1	
	51-60	0	0	0	0	0	0	
	61-70	0	0	0	0	0	1	
		Fibrous crescents						
	–	19	19	7	7	16	16	
	+	0	0	0	0	0	0	
	(%)	Obsolescent glomeruli						p=0.004
	0	16	9	6	4	10	4	
	1-10	2	7	0	2	6	5	
	11-20	0	3	1	1	0	4	
	21-30	1	0	0	0	0	1	
	31-40	0	0	0	0	0	1	
	41-50	0	0	0	0	0	1	
	(%)	Interstitial fibrosis/tubular atrophy						p<0.001
	0	12	9	5	5	13	1	
	1-5	7	6	2	2	3	10	
	6-10	0	4	0	0	0	5	

13 within 1 year, and five within 2-4 years after the first abnormal urinalysis report. A follow-up renal biopsy was performed at a median of 39.0 ± 25.1 months (24-132 months) after the first biopsy. No patient had symptoms or signs other than microscopic or macroscopic hematuria and/or proteinuria. None of the patients had hypertension or nephrotic range proteinuria (> 3.5 g/day). All patients received dipyridamole, and some with worsening proteinuria received ARB or ACE-I therapy. Chinese herbal treatments were not used.

Pathological Findings

At the first biopsy, 41 patients were diagnosed with

Table 3

		Group 1a (N=8)		Group 1b (N=11)		p-value
		First	Last	First	Last	
	(%)	Mesangial hypercellularity				
	0-15	4	8	4	8	
	16-30	2	0	1	3	
	31-45	1	0	5	0	
	46-60	1	0	1	0	
Acute lesion	(%)	Cellular or fibrocellular crescents				p=0.524
	0	7	8	8	11	
	1-10	0	0	2	0	
	11-20	1	0	1	0	
	(%)	Necrotizing lesions				p=0.394
	0	8	8	10	11	
	1-5	0	0	1	0	
		Endocapillary hypercellularity				p=0.361
	–	6	8	10	11	
	+	2	0	1	0	
Chronic lesion	(%)	Segmental glomerular sclerosis or adhesion				p=0.041
	0	1	3	3	1	
	1-10	6	5	4	7	
	11-20	1	0	3	2	
	21-30	0	0	1	1	
		Fibrous crescents				
	–	8	8	11	11	
	+	0	0	0	0	
	(%)	Obsolescent glomeruli				p=0.649
	0	7	8	9	1	
	1-10	1	0	1	7	
	11-20	0	0	0	3	
	21-30	0	0	1	0	
	(%)	Interstitial fibrosis/tubular atrophy				p=0.961
	0	5	7	7	2	
	1-5	3	1	4	5	
	6-10	0	0	0	4	

mesangial proliferative glomerulonephritis, and one patient was diagnosed with minor glomerular abnormality (MGA). Thirty patients showed focal (less than 50%) mesangial cell proliferation, and 11 showed diffuse proliferation. All patients, except for the patient with MGA, showed segmental proliferation.

Comparison of kidney tissue from the first and last biopsies showed that 19 patients showed histological improvement of mesangial hypercellularity (Group 1), 7 patients showed no obvious histological changes (Group 2), and 16 patients showed exacerbation of mesangial hypercellularity (Group 3). In the 19 patients in Group 1 with improved mesangial hypercellularity, 11 showed spread of chronic lesions (Group 1b); however, the other eight patients showed no worsening of chronic lesions (Group 1a) at the last biopsy.

Of the 16 patients with exacerbation, only five had an active lesion at the first renal biopsy. The other 11 patients showed MGA or focal segmental glomerulonephritis with mild mesangial cell proliferation. Two patients with no active lesions at the first biopsy had severe active lesions (cellular or fibrocellular crescents) in the last biopsy.

Results of Statistical Analysis

The clinical profiles of groups 1 to 3 are summarized in **Table 1**, making a total of 42 cases. The median age

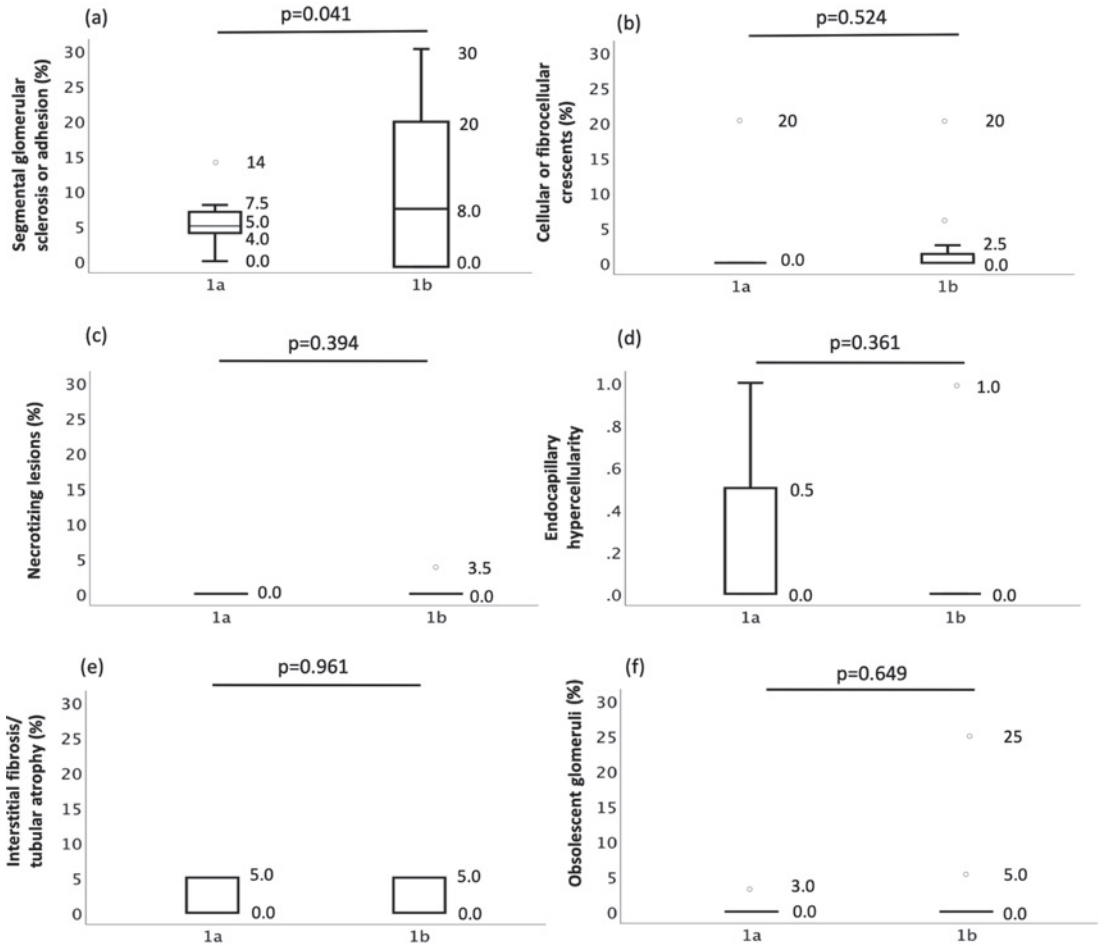

Fig. 2 Histological features of the first kidney biopsy in Groups 1a and 1b.
There is a significant difference only in the degree of segmental glomerular sclerosis or adhesion (p=0.041). No significant differences are found in other histological findings (cellular/fibrocellular crescents, p = 0.524; necrotizing lesions, p = 0.394; endocapillary hypercellularity, p = 0.361; interstitial fibrosis and/or tubular atrophy, p = 0.961; and obsolescent glomeruli, p = 0.649).

was 11.5 ± 2.7 (6-16) years, the median interval between biopsies was 39.0 ± 25.1 (24-132) months, and the median level of proteinuria at the first visit was 0.20 ± 0.72 (0.0-3.00) g/gCr. When comparing the clinical profiles of Group 1 to 3, there were no significant differences in sex, cause of discovery, or interval between biopsies. In a comparison of groups by age, Group 3 was significantly older than Group 1. In a comparison of groups by proteinuria severity, there were no significant differences at the time of the first renal biopsy, but at the time of the final renal biopsy, proteinuria was significantly worse in Group 3 than in the other groups. Similarly, there were no significant differences in hematuria at the time of the first renal biopsy. At the time of the final renal biopsy, there was no significant difference between Group 2 and Group 3, but Group 3 had a high level of hematuria.

Histological changes at the time of the initial and final renal biopsy of each group are shown in **Table 2**. In Group 3, histological analysis showed a significant increase in segmental glomerular sclerosis or adhesion ($p < 0.001$), obsolescent glomeruli ($p = 0.004$), and interstitial fibrosis/tubular atrophy ($p < 0.001$). Other histological findings did not significantly differ (data not shown). Because chronic findings worsened in some patients in Group 1, cases without (Group 1a) and with (Group 1b) worsening of chronic findings were compared (**Table 3**). There was a significant difference between the two groups in the degree of segmental glomerular sclerosis or adhesion at the first renal biopsy ($p = 0.041$), but no significant difference in other findings (cellular/fibrocellular crescents, $p = 0.524$; necrotizing lesions, $p = 0.394$; endocapillary hypercellularity, $p = 0.361$; interstitial fibrosis and/or tubular atrophy, $p = 0.961$; and obsolescent glomeruli, $p = 0.649$) (**Fig. 2**).

Discussion

The present study confirmed that, when segmental glomerulosclerosis is present from an early stage, chronic lesions develop even after mesangial hypercellularity has resolved in pediatric IgAN. Of the 42 patients, mesangial cell proliferation worsened in 16 and improved in 19, but chronic findings worsened in 11 of these patients. The reason for choosing mesangial hypercellularity as a criterion is that mesangial proliferation is considered to be the initial change in IgAN. In terms of increased mesangial area, the pathogenesis of IgAN differs for children and adults. In adults, increased mesangial area in IgAN is mainly due to expansion of the mesangial matrix, whereas in children, IgAN is mainly due to hypercellularity of mesangial cells[7]. Some reports have noted an association between mesangial hypercellularity and proteinuria in pediatric IgAN, and Yoshikawa et al.[8] stated that, "in childhood IgAN, the greater the initial degree of mesangial proliferation, the worse the renal prognosis at diagnosis." Thus, the present cases were grouped according to changes in mesangial hypercellularity. The present histological findings suggest that the histological prognosis is worse than previously reported. Histological analysis of the last renal biopsy showed a significant difference in the progression of chronic lesions, which was related to the presence of segmental glomerulosclerosis or adhesion in the first biopsy. To our knowledge, this is the first study of pediatric IgAN to use two or more histological evaluations of patients not using immunosuppressive drugs.

Evidence from the increasing number of studies of outcomes for pediatric IgAN[3,9–12] indicates that during a follow-up period of up to 20 years the renal survival rate is better for children than for adults. However, these reports included patients with IgAN of varying severity who were treated with a variety of methods; we are not aware of a study that followed histological changes in the same patients. In Japan, where school urinary screening has been performed since 1974, early detection of IgAN in children is common. Thus, we were able to collect data on histological involvement at or soon after disease onset, when the patient is asymptomatic. According to the Japanese Society of Nephrology clinical practice guidebook for the diagnosis and treatment of chronic kidney disease[13], renal biopsy is recommended for cases of prolonged hematuria with mild proteinuria (≥0.20 g/gCr) for 6-12 months, moderate proteinuria (≥0.50 g/gCr) for 3-6 months, and severe proteinuria (≥1.0 g/gCr) for 1-3 months. Some evidence suggests that assessment of IgAN using only proteinuria severity may lead to underestimation and that a repeat biopsy follow-up may help identify patients who actually need treatment[14]. There are very few reports of serial renal biopsies during the natural course of the disease, and there is no report of a comparative study of two or more renal biopsies in children who were treated at the early stage of the disease and did not receive immunosuppressive agents during follow-up. Thus, we studied 42 patients with early stage IgAN who underwent kidney biopsies at least twice and compared the histological findings.

Several pathological factors have been identified as risk factors for IgAN[15–17]. Although there is consensus regarding the Oxford classification because of its high predictive power, its validity for children is limited because it was based on an analysis of patients with severe proteinuria (>1.0 g/day) who varied widely in age[18]. Therefore, information on long-term outcomes of IgAN presenting with minor presentations is rare. Gutierrez et al.[4] studied 141 white adults presenting with minor proteinuria (<0.5 g/day/1.73 m^2) who were not receiving corticosteroids or immunosuppressants. After a median follow-up of 108 months, five (3.5%) experienced a serum creatinine increase of >50%, and 1 (0.7%) showed a >100% increase. They reported that the only significant histological difference was segmental glomerulosclerosis. Higa et al.[5] analyzed 106 pediatric IgAN patients with mild proteinuria (<0.5 g/day/1.73 m^2); 67% of the patients received no medication or only ACE-I therapy. Although none of the patients progressed to stage 3 chronic kidney disease (eGFR <60 mL/min/1.73 m^2) within 15 years, four required immunosuppressive therapy. They reported no significant differences in pathological factors between these four patients and the other patients who did not receive immunosuppressants. These and the present findings suggest that it is difficult to predict future histological renal damage from renal biopsy results performed early in the disease course or in patients with mild proteinuria.

Treatment protocols remain unclear for IgAN patients with a benign clinical presentation. A randomized controlled trial of 78 children that compared treatment with combination therapy consisting of prednisolone, azathioprine, heparin-warfarin, and dipyridamole with control therapy consisting of heparin-warfarin and dipyridamole found a significant difference in segmental glomerular sclerosis after 2 years of treatment, with a significantly higher rate of glomerular sclerosis in the control group[19]. Ieiri et al.[20,21] reported the efficacy of early detection and

therapy for IgAN patients presenting with glomerular hematuria and mild proteinuria, who are reported to be at an early stage of IgAN. In their report, steroid pulse therapy combined with tonsillectomy significantly increased the probability of clinical remission in IgAN patients with glomerular hematuria and minor proteinuria, and it was more effective in those with less severe histological findings. They also compared an early-treatment group, in which patients were treated within 3 years of onset of urinary abnormalities, and a late-treatment group in which patients were treated later than 3 years after onset. The clinical remission rate was higher in the former group, regardless of whether patients had mild or severe glomerular lesions. Szeto et al. concluded that IgAN presenting with hematuria and minor proteinuria is usually progressive[22]. The present results indicate that chronic lesions, such as glomerulosclerosis, are exacerbated despite histologically reduced mesangial hypercellularity and clinically reduced proteinuria. These and past results suggest it may be better to treat IgAN patients with immunosuppressants. However, Shima et al.[23] reported the possibility of spontaneous remission without medical treatment in pediatric IgAN patients with minor glomerular abnormalities or mesangial proliferation and implied that refraining from aggressive treatment in mild IgAN patients was important. Temporary clinical remission of IgAN has often been reported[23], but the incidence and duration of such episodes are unknown. In one study, the only factor that prevented temporary remission was sclerosis. The authors noted that acute lesions can be altered by appropriate treatment and are therefore no longer considered to be prognostic factors. In contrast, chronic lesions are difficult to treat and may be prognostic. In the present study, only segmental glomerular sclerosis or adhesion on the first biopsy affected progression of chronic findings. Although interstitial lesions such as fibrosis may affect prognosis, the early timing of biopsies in the present study may have prevented us from observing a significant difference in relation to such lesions.

In the current study without immunosuppressive treatment, even though the first renal biopsy showed only mild mesangial proliferation without active lesions, serial renal biopsies showed progression of mesangial hypercellularity and worsening of chronic lesions in five Group 3 patients. Although one of these patients showed no evidence of an active lesion at the second biopsy, two patients showed endocapillary hypercellularity, and the other two patients showed cellular crescent formation and ultimately required dialysis. In contrast, 10 of the 15 patients with chronic lesions on the first renal biopsy did not experience disease progression. Thus, even when the initial findings of renal biopsy were minor, it was difficult to predict disease course from a single biopsy soon after onset. In contrast, a comparative serial study of renal tissue found that 11 of 19 patients who showed improved mesangial hypercellularity developed chronic renal damage. There was a significant difference in the progression of chronic disease in relation to whether segmental glomerulosclerosis or adhesion was present at the first renal biopsy. The present results suggest that segmental glomerular sclerosis or adhesion may be an important finding in determining whether temporary clinical remission occurs, especially in patients with mild urinary findings.

Finally, although early intervention in the treatment of pediatric IgAN is controversial in Japan, where, unlike other countries, IgAN is usually detected at an early stage, continuous follow-up is important for all patients.

Conclusion

We evaluated serial renal biopsy findings of 42 pediatric IgAN patients who were followed in our institute and not treated with steroids or immunosuppressants. The present results suggest that, even if mesangial hypercellularity improves, chronic lesions may spread during the course of IgAN. In cases of improvement in mesangial hypercellularity, there were differences in subsequent progression of chronic findings, which depended on the severity of segmental glomerulosclerosis or adhesion at the first biopsy. Predicting histological changes from histological findings at an initial renal biopsy is not easy, especially because the first renal biopsy is often performed relatively early. Therefore, patients must be followed carefully.

Author Contributions: E.Y and T.Y designed the study. E.Y performed the measurements and analysed the data. E.Y and T.Y designed the figures, interpreted the results and contributed to the manuscript. Y.I supervised the project.

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