Nephrology 1997; 3, S701–S707

Clinical Spectrum of IgA Nephropathy

A clinicopathological study of adult Japanese IgA nephropathy patients: Early stage cases and cases with exacerbation

HISAKI SHIMADA, NAOFUMI IMAI, YOSHIKAZU MIYAKAWA, TUKASA NAKAMARU, RYO KARASAWA, YUTAKA OSAWA, MITSUHIRO UENO, SHINICHI NISHI, YASUSHI SUZUKI AND MASAAKI ARAKAWA

Department of Medicine II, Niigata University School of Medicine, Niigata, Japan

Summary: Most cases of adult type IgA nephropathy (IgAN) have an insidious onset and asymptomatic course. However, some patients reveal recurrent macroscopic haematuria following episodes of respiratory or urinary tract infections. In order to clarify the correlation between clinical features and histological alterations or prognosis, 42 cases of early stage IgAN and 40 cases with acute exacerbation episodes were investigated and compared with a control group. Early stage cases were defined as having had a renal biopsy within 1 year after the first detection of urinary abnormalities, and had normal urinary findings within the 12 months before the first detection of urinary abnormalities. Acute exacerbation cases were defined as macroscopic haematuria or worsening of urinary abnormalities after acute infectious episodes and undergoing a renal biopsy within 120 days after the onset of these episodes. The early stage cases had better renal function and lower systolic and diastolic blood pressure than that of control group. They also showed milder changes in mesangial cell proliferation, mesangial matrix increase, totally sclerotic glomeruli, and tubulo-interstitial changes. However, it is important to note that glomerular and interstitial sclerotic changes were observed even in early stage cases. Endothelial detachment was noticed more frequently in the early stage cases. Acute exacerbation cases revealed lesions of endocapillary proliferation, mesangiolysis and endothelial detachment more frequently, although these changes were segmental in each glomerulus. There was no statistical difference in disease prognosis between cases with and without acute exacerbation. These data indicated that there are characteristic histological changes in early stage cases and acute exacerbation cases of IgAN.

Key words: early stage, IgA nephropathy, macroscopic haematuria.

INTRODUCTION

IgA nephropathy (IgAN) is characterized by IgA deposits predominantly in the glomerular mesangium,[1] and it is the most common type of primary glomerulonephritis in Japan. As acute onset type of this disease can be seen frequently in children, the histological evaluation of renal lesions at the initial and early stage has been studied mostly in paediatric cases.[2,3] In the early stage of IgAN in children, it is characteristic that mesangial hypercellularity is more prominent than an increase of matrix.[3] Cellular crescents and endocapillary proliferation are also observed at this stage.

The disease onset of IgA is not clear in most of adult patients. However, repeated episodes of macroscopic haematuria usually after mucosal infections are observed during the clinical course in some cases. We would like to clarify the clinical and histological characteristics of early stage IgAN and whether acute exacerbating episodes influence the renal histology and prognosis.

Correspondence: H Shimada, Department of Medicine (II), Niigata University School of Medicine, 1–757 Asahimachi-dori Niigata, Japan 951.

SUBJECTS AND METHODS

Subjects

Adult primary IgAN patients aged over 20 years were selected from the biopsy cases performed at the Niigata University Hospital and its affiliated hospitals from 1973 to 1996. Secondary IgAN cases with Henoch Schönlein purpura, collagen diseases, liver cirrhosis, diabetes mellitus and other renal diseases were excluded. Cases that were complicated with minimal change nephrotic syndrome and IgAN were also excluded from this study. Only the first biopsy was evaluated in each patient. From

1024 cases who matched these criteria, early stage cases, late stage cases, cases with recent acute exacerbation and cases without exacerbation were selected.

Early stage cases of IgAN were defined those who had received renal biopsy within 1 year after the first detection of urinary abnormalities. They were also confirmed to have normal urinary findings within 12 months before the first detection of urinary abnormalities. We divided early stage IgAN patients into two groups: (i) symptomatic onset; and (ii) asymptomatic onset groups. In symptomatic onset group infectious episodes affecting upper respiratory or urinary tracts followed by urinary abnormalities, including macroscopic haematuria, were observed as the onset symptoms. The cases that had urine abnormalities without clinical episodes were defined as the asymptomatic onset group. The cases who received a biopsy after 1 year or more from the first urinary abnormalities were selected as the late stage group.

We subsequently assessed the influence of acute exacerbation episodes on renal histological changes and prognosis. IgA nephropathy with acute exacerbation was defined those with macroscopic haematuria or a worsening of urine abnormalities after acute infectious episodes. The cases who were biopsied within 120 days after these episodes were selected in order to clarify acute histological changes. The cases that did not show any clinical exacerbation were selected as the control group.

Histological examination

Renal biopsy specimens were divided into three fragments for light, electron and immunofluorescent microscopy and were prepared for observation as previously described.[4] Glomerular changes on light microscopy were evaluated and scored for each glomerulus. The average of each score was calculated. The scores of cellular proliferation, and the matrix increase in the mesangium were graded into 6 grades ranging from from 0 (minimal change) to 5 (diffuse global marked). Other glomerular changes, such as global or segmental sclerosis, endocapillary proliferation, leucocyte exudation, duplication of glomerular basement membrane (GBM), crescent formation, and tufts adhesion to the Bowman's capsule as well as tubulo-interstitial lesions were scored into 5 grades according to the incidence of each lesion. Grade 0 represents incidence from 0 to 4%, grade 1 for 5–24%, grade 2 for 25–49%, grade 3 for 50–74% and grade 4 for 75–100%. Light microscopic evaluation was studied by single pathologist (MU). In electron microscopic lesions, the presence or absence of endocapillary proliferation, epithelial detachment, mesangiolysis, endothelial detachment and GBM injury were evaluated.

Table 1 Comparison of clinical data at the time of biopsy between early and late stage IgAN groups

	Early stage	Late stage
Case number	42	153
Male:female	17:25	91:62*
Age	36.1±13.2	36.0±10.9
Proteinuria (g/day)	0.9±1.4	1.1±1.0
s-Cr (mg/dL)	0.8±0.2	1.1±0.5†
Ccr (mL/min per 1.48 m^2)	103±30	86±33†
Hypertension (over 150/90 mmHg)	12%	23%
Systolic BP (mmHg)	121±16	129±17†
Diastolic BP (mmHg)	74±10	79±13*
Duration from first urine abnormalities to biopsy (M)	4.9±3.5	77.3±67.3†

*$P<0.05$; †$P<0.01$, Ccr, creatinine clearance.

Statistical analysis

The Student *t*-test or Chi-squared method were used to analyse differences in clinical data on biopsy and parameters of electron microscopic findings. The Wilcoxon unpaired test was used to analyse differences in light microscopic findings. Kaplan Meier method was used to analyse differences in renal prognosis.

RESULT

Early and late stage IgAN

Because of the strict criteria of patient selection described previously, only 42 cases (4% of initial IgAN cases) were confirmed to be early stage IgAN. The late stage IgAN group consisted of 153 cases.

Clinical data at the time of biopsy in the early and late stage groups are shown in Table 1. The mean duration from the first urine abnormalities to renal biopsy was 4.9 months in the early stage group and 77.3 months in late stage group ($P<0.01$). Female predominance, better renal function and lower systolic and diastolic blood pressure were observed in early stage group ($P<0.05$).

Concerning light microscopic findings in the early and late stage groups, mesangial cell proliferation and matrix increase were milder in early stage (Fig. 1). The incidence of globally sclerotic glomeruli was also lower in the early stage group, although the incidence of segmental sclerosis in glomeruli were not different between two groups. Endocapillary proliferation, mostly segmental, was observed in 25% of the early stage group and 17% of the late stage group, in whom it was noticed only in 5–24% of glomeruli available for observation. There was no significant difference in leucocyte exudation, GBM duplication and crescent formation. However, both capsular adhesion and tubulo-interstitial

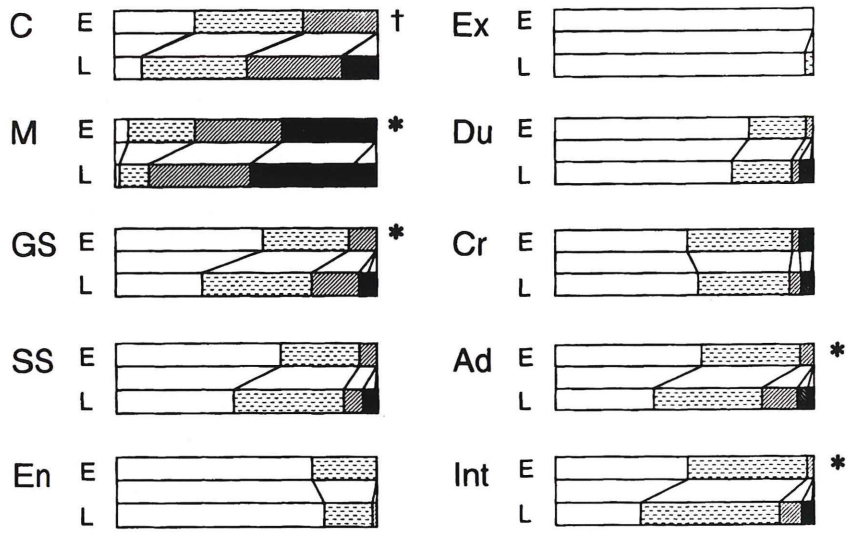

Fig. 1 Comparison of light microscopic findings between early (E) and late (L) stage IgAN groups. Each histological change was graded according to its intensity. * $P<0.05$, † $P<0.01$. C, proliferation of masangial cells; M, increase of mesangial matrix; GS, global sclerosis; SS, segmental sclerosis; En, endocapillary proliferation; Ex, exudation of PMN; Du, duplication of GBM; Cr, crescent formation; Ad, adhesion; Int, tubulo-interstitial changes. □,0; ▨,1; ▨,2; ▧,3; ■,4.

changes were significantly milder in the early stage group.

Histological comparison was also performed on electron microscopic findings (Fig. 2). The presence of endocapillary proliferation, epithelial detachment, mesangiolysis, and GBM injury were not significantly different between the two groups. Endothelial detachment was observed in 59% of the early stage and 16% of the late stage cases, which was significantly different.

Symptomatic and asymptomatic onset cases in early stage IgAN

Forty-two cases of early stage IgAN were divided into symptomatic onset and asymptomatic onset groups. Among 14 cases with symptomatic onset, the presenting symptom at onset was macroscopic haematuria in eight cases, and acute infection episode in six cases. Among the 28 asymptomatic onset cases, 21 were found their urinary abnormalities on annual examination, and the seven other cases were detected on other examinations.

Clinical data at the time of renal biopsy for both of these groups are shown in Table 2. The symptomatic onset cases were significantly younger in age. No significant difference was found in proteinuria, renal function and blood pressure between both groups. The duration from first urinary abnormality to biopsy was shorter in symptomatic onset group, but not significantly different between two groups.

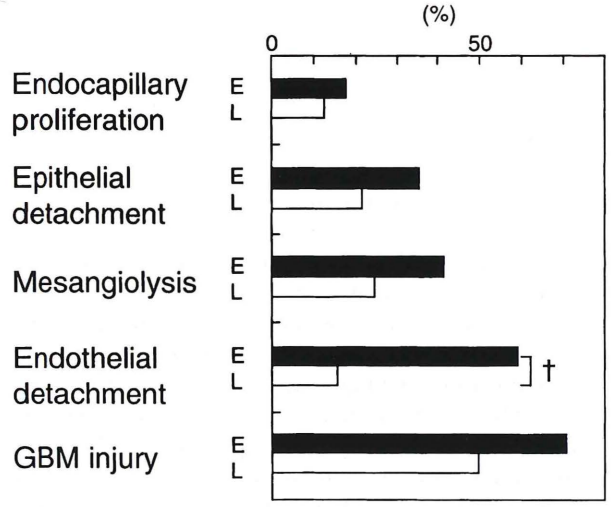

Fig. 2 Comparison of electron microscopic findings between early (E) and late (L) stage IgAN groups. Percentage of cases with each histological change are demonstrated. † $P<0.01$.

Table 2 Comparison of clinical data at the time of biopsy between symptomatic and asymptomatic onset in early stage IgAN groups

	Symptomatic onset	Asymptomatic onset
Case number	14	28
Male:female	4:10	13:15
Age	29.9±9.3	39.2±13.9*
Duration from symptom to biopsy (day)	88±57	
Proteinuria (g/day)	0.6±0.7	1.1±1.6
s-Cr (mg/dL)	0.7±0.2	0.8±0.2
Ccr (mL/min per 1.48m^2)	113±28	97±31
Hypertension (over 150/90 mmHg)	23%	7%
Systolic BP (mmHg)	124±22	120±13
Diastolic BP (mmHg)	74±10	74±9
Duration from first urine abnormalities to biopsy (M)	3.7±2.2	6.2±4.6

*$P<0.05$; Ccr, creatinine clearance.

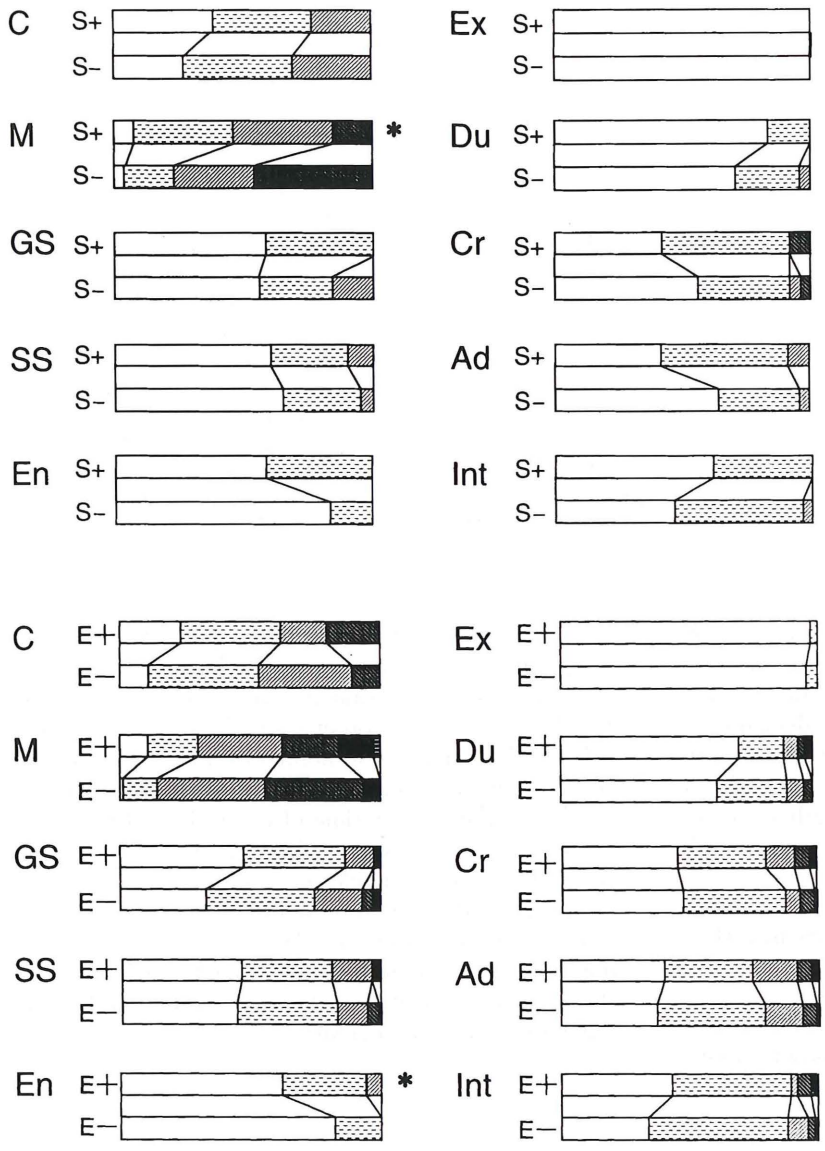

Fig. 3 Comparison of light microscopic findings between symptomatic (S+) and asymptomatic (S−) onset in early stage IgAN groups. Each histological change was graded according to its intensity. * $P<0.05$. C, proliferation of mesangial cells; M, increase of mesangial matrix; GS, global sclerosis; SS, segmental sclerosis; En, endocapillary proliferation; Ex, exudation of PMN; Du, duplication of GBM; Cr, crescent formation; Ad, adhesion; Int, tubulo-interstitial changes. □,0; ▦, 1; ▨,2; ▧,3; ■,4.

Fig. 4 Comparison of light microscopic findings between IgAN groups with exacerbation (E+) and without exacerbation (E−). Each histological change was graded according to its intensity. * $P<0.05$. C, proliferation of mesangial cells; M, increase of mesangial matrix; GS, global sclerosis; SS, segmental sclerosis; En, endocapillary proliferation; Ex, exudation of PMN; Du, duplication of GBM; Cr, crescent formation; Ad, adhesion; Int, tubulo-interstitial changes. □,0; ▦, 1; ▨,2; ▧,3; ■,4; ▤,5.

On light microscopy (Fig. 3), an increase of mesangial matrix was milder in the symptomatic onset group. The grade of mesangial cell proliferation, and global or segmental sclerosis of glomeruli, were not different between symptomatic and asymptomatic onset groups. Scattered endocapillary proliferation was observed in 44% of the symptomatic onset group and 17% of the asymptomatic onset group, respectively, although the difference was not statistically significant. The incidence of leucocyte exudation was less than 4% of all cases in both groups. There was also no difference in crescent formation, capsular adhesion and tubulo-interstitial changes between both groups. It is important to note that 58% of the symptomatic onset and 36% of the asymptomatic onset cases revealed crescent formation in 5–74% of glomeruli. An electron microscopy study were performed on six and 11 cases of symptomatic and asymptomatic onset groups, respectively. There was no significant differencein the five parameters.

IgAN with or without acute exacerbation

The clinical and histological data of the cases with or without acute exacerbation were compared (Table 3). Forty cases were selected as acute exacerbation cases, in whom 26 showed macroscopic haematuria. The clinical data at the time of biopsy were not different in both groups. The duration from exacerbation to biopsy in acute exacerbation group was approximately 60 days. There was no significant difference in scores of mesangial cell proliferation, an increase of mesangial matrix, and global and segmental sclerosis between groups with and without exacerbation (Fig. 4). The incidence of endocapillary proliferation was significantly higher in

Table 3 Comparison of clinical data at the time of biopsy between IgAN groups with and without exacerbation

	With exacerbation	Without exacerbation
Case number	40	178
Male:female	15:25	96:82
Age	33.2±12.4	37.1±11.8
Duration from exacerbation to biopsy (day)	60±41	
Proteinuria (g/day)	1.3±1.4	1.2±1.0
s-Cr (mg/dL)	0.9±0.4	1.1±0.5
Ccr (mL/min per 1.48m^2)	91±32	86±32
Hypertension (over 150/90 mmHg)	15%	19%
Systolic BP (mmHg)	126±19	128±18
Diastolic BP (mmHg)	75±14	78±13
Duration from first urine abnormalities to biopsy (M)	13.9±28.3	53.0±61.1†

†$P<0.01$.

cases with acute exacerbation. These lesions were observed in 40% of cases with acute exacerbation, although it was segmental and mild in each glomerulus. No difference was noticed in the grade of crescent formation, adhesion and tubulo-interstitial changes between the two groups.

Electron microscopy revealed a higher incidence of mesangiolysis and endothelial detachment in acute exacerbation cases (Fig. 5). Mesangiolysis was observed in 47 and 16% in cases with and without acute exacerbation, respectively. No difference was seen in the incidence of endocapillary proliferation, epithelial detachment and GBM injury.

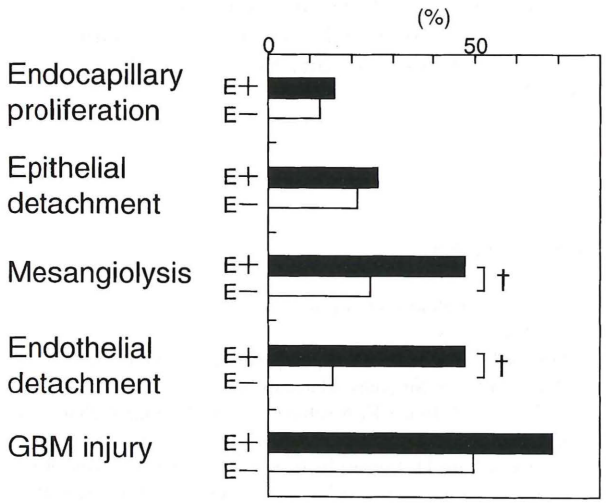

Fig. 5 Comparison of electron microscopic findings between groups of IgAN with exacerbation (E+) and without exacerbation (E−). Percentage of cases with each histological change are demonstrated. †$P<0.01$.

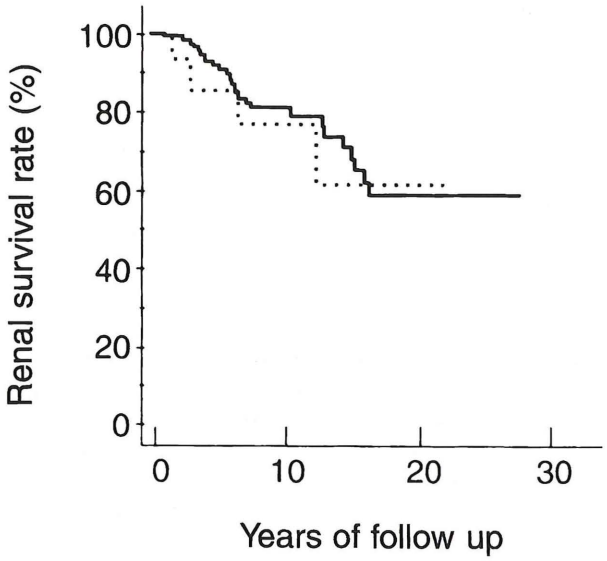

Fig. 6 Comparison of renal survival rate between IgAN groups with and without acute exacerbation episodes. Renal survival rate was estimated using Kaplan Meier method. Doted line expresses survival curve of cases with exacerbation, solid line, cases without exacerbation.

Renal survival was compared between the two groups using Kaplan Meier method (Fig. 6). The renal survival rate after 20 years from biopsy was 61% in cases with exacerbation and 59% in cases without exacerbation.

DISCUSSION

Early stage and late stage IgAN

It is difficult to select early stage cases accurately because the disease onset of IgAN is often insidious and the exact time of onset is obscure particularly in adults. In order to assess the onset time precisely, urine examination before the first detection of urinary abnormality is indispensable. Our criteria were intended to select only definite cases of early stage IgAN. As far as we know, this is the first report focusing on exact onset time of IgAN.

There are some differences between histological changes in IgAN in adults and children. In paediatric cases of early stage IgAN, Yoshikawa *et al.*[3] indicated that mesangial hypercellularity was observed before mesangial matrix proliferation had become apparent. However, Zimmerman *et al.*[5] reported that an increase of mesangial cells was seldom very striking in adult patients, although sometimes present. In this study, which dealt early stage adult IgAN, mesangial cell proliferation was significantly milder compared with that of late stage cases. Mesangial cell proliferation occurs on the later phase of the disease in adults, accompanying the increase of mesangial matrix.

Chronic changes, such as mesangial matrix proliferation, global sclerosis of glomeruli, glomerular adhesive lesion and interstitial changes were mild in the early stage cases compared with those of late stage cases. Clarkson *et al.*[6] reported that with disease duration, the mesangium became increasingly occupied by excessive matrix and that tubular atrophy with interstitial scarring progressed in most biopsies. Our findings also indicated that these histological alterations showed progression in correlation with the duration of the disease.

It should be noted that these sclerotic changes were also observed in certain incidences, even in early stage cases. Glomerular and interstitial sclerotic change seemed to occur at the very early stage of the disease. It is speculated that histological alteration, including sclerotic changes, precedes clinical onset of urinary abnormality in adult IgAN cases because disease progression in these patients appears to be slow. However, further examination will be needed to clarify this problem.

On electron microscopy, the early stage cases had significantly more lesions of endothelial detachment. This might be the first characteristic change observed in early stage IgAN at onset, though the mechanism and course of the lesion remains unclear.

Symptomatic and asymptomatic onset cases in early stage IgAN

Macroscopic haematuria is the most common symptom at onset. It is more frequent in children than in adults. There is also a distinct geographical difference in the incidence of macroscopic haematuria in adult patients. In European countries the reported incidence of macroscopic haematuria exceeded 50%,[7,8] whereas in Japan, the incidence range was from 15 to 31%.[9–12] In the present study, macroscopic haematuria was observed in 19% (8/42) of early stage IgAN patients. This geographical difference is considered to occur, partially because of the different criteria of renal biopsy, but mainly due to difference in disease features.[7]

In the symptomatic onset group, cases were generally younger, which might influence the difference in grade of mesangial matrix increase. The difference of endocapillary proliferation on light microscopy between symptomatic and asymptomatic group did not reach to statistical significance. Further collection of cases who had renal biopsy immediately after symptomatic onset, may bring statistical difference in that point.

IgAN with or without acute exacerbation

Few reports have focused on the endocapillary proliferative changes in IgAN. In the present study, light microscopy showed that endocapillary proliferation was more frequent in cases with recent acute exacerbation episodes, although no significant difference in endocapillary proliferation was on electron microscopy. A complication of post streptococcal acute glomerulonephritis could be ruled out by detailed clinical and histological examinations.

In cases with and without acute exacerbation, mesangial cell proliferation did not differ between two groups. Mesangial cell proliferation is not a feature of acute exacerbation, as seen in paediatric IgAN.

On electron microscopy, cases with acute exacerbation revealed lesions of mesangiolysis, and endothelial detachment more frequently. Mesangiolytic lesion were constantly connected to widened subendothelial space, which was evaluated as endothelial detachment. Mesangiolysis has been known to be an early and important change in various type of glomerulonephritis,[10] and was thought to progress to cellular proliferation as well as matrix production.

The prognostic significance of macroscopic haematuria was controversial. Clarkson *et al.*[6] demonstrated that renal function and lesions were significantly better in patients with macroscopic haematuria than those without it. However, Bennet and Kincaid-Smith[13] reported that renal function became significantly worse in those with macroscopic haematuria, and emphasized the high incidence of crescent formation in these cases. We evaluated the influence of acute exacerbation including macroscopic haematuria and/or acute infectious episodes on renal prognosis and revealed that there was no significant differences between two groups with and without exacerbation. There were no differences in the incidence of crescent formation in these two groups.

Despite the limited number of cases in this study, we were able to demonstrate some histological features that are likely to occur at the clinical onset or acute exacerbation of IgAN. However, as various histological alterations were observed even in asymptomatic cases, it is often difficult to predict histological changes from clinical information.

REFERENCES

1. Berger J. IgA glomerular deposits in renal disease. *Transplant. Proc.* 1969; **1**: 939–44.
2. Hogg RJ, Silva FG. IgA nephropathy in children. In: Clarkson AR (ed.) *IgA nephropathy*. Martinus Nijhoff, Boston 1987; 16–38.
3. Yoshikawa N, Iijima K, Maehara K *et al.* Mesangial changes in IgA nephropathy in children. *Kidney Int.* 1987; **32**: 585–9.
4. Suzuki S, Sato H, Kobayashi H *et al.* Comparative study of IgA nephropathy with acute and insidious onset. *Am. J. Nephrol.* 1992; **12**: 22–8.
5. Zimmerman SW, Burkholder PM. Immunoglobulin A nephropathy. *Arch. Intern. Med.* 1975; **135**: 1217–23.
6. Clarkson AR, Seymour AE, Thompson AJ, Haynes WDG, Chan Y-L, Jackson B. IgA nephropathy: A syndrome of uniform

morphology, diverse clinical features and uncertain prognosis. *Clin. Nephrol.* 1977; **8**: 459–71.
7. D'Amico G, Imbasciati E, Barbiano G *et al.* Idiopathic IgA mesangial nephropathy: clinical and histological study of 374 patients. *Medicine* 1985; **64**: 49–60.
8. Rodicio JL. Idiopathic IgA nephropathy. *Kidney Int.* 1984; **25**: 717–29.
9. Sakai O. IgA nephropathy in adults: Clinical features. In: Arakawa M, Gejyo F (eds) *Recent studies of IgA nephropathy in Japan*. Nishimura, Niigata, 1989; 89–104.
10. Shigematsu H, Kobayashi Y, Tateno S, Hiki Y, Kuwao S. Ultrastructual glomerular loop abnormalities in IgA nephritis. *Nephron* 1982; **30**: 1–7.
11. Shirai T, Tomino Y, Yoshiki T, Itoh T. IgA nephropathy: clinicopathology and immunopathology. *Contr. Nephrol.* 1978; **9**: 88–100.
12. Yokoska H, Nagase M, Maeda T, Koide K. Mesangial IgA glomerulonephritis: Clinicopathological study of 85 cases. *Contr. Nephrol.* 1978; **9**: 101–110.
13. Bennett WM, Kincaid-Smith P. Macroscopic hematuria in mesangial IgA nephropathy: Correlation with glomerular crescents and renal dysfunction. *Kidney Int.* 1983; **23**: 393–400.