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Original Articles

IgA Nephropathy with Subendothelial Deposits

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Summary. IgA nephropathy with subendothelial deposits in the capillary walls of the glomeruli (IgA type 2) was compared histometrically and clinically with IgA nephropathy without subendothelial deposits (IgA type 1) and membranoproliferative glomerulonephritis with subendothelial deposits (MPGN). Study cases consisted of 32 biopsies from 26 patients of IgA type 1, 25 biopsies from 20 patients of IgA type 2 and 31 biopsies from 27 patients of MPGN. Histological changes of the glomeruli consisted of an increase in the mesangial matrix and hypercellularity in the mesangium in both types of IgA nephropathy, and the degree of the changes was a little higher in IgA type 2 than in IgA type 1 ($0.02 < P < 0.05$). Mesangial changes of MPGN were marked as compared with IgA type 1 and IgA type 2 ($P < 0.001$). Histometry of the mesangium on the cases followed up showed that the degree of mesangial thickening increased with lapse of time in IgA type 2 and MPGN, whereas it remained unchanged up to 13 years in IgA type 1. Proteinuria tended to be mild in IgA type 1, moderate in IgA type 2, and marked in MPGN. The impairment of renal function was observed in 21.9% of IgA type 1, in 36.0% of IgA type 2 and in 58.1% of MPGN. IgA type 2 has been shown to be pathologically and clinically intermediate between IgA type 1 and MPGN. These results suggest that there is a clinicopathological overlap between IgA nephropathy and MPGN with IgA deposition.

Key words: IgA nephropathy – Membranoproliferative glomerulonephritis – Subendothelial deposits.

Introduction

In IgA nephropathy, histological changes of the glomeruli consist of an increase in the mesangial matrix and hypercellularity in the mesangium with or without

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focal segmental accentuation. The pattern of IgA localization is predominantly mesangial and electron-dense deposits are, as a rule, exclusively in the mesangial regions (Berger, 1969; Maintz et al., 1972; McEnery et al., 1973; McCoy et al., 1974; Alexander et al., 1977). These facts seem to indicate that the site of glomerular injury is confined to the mesangium in IgA nephropathy. In some cases of IgA nephropathy, however, electron-dense deposits are observed not only in the mesangium but in the subendothelium of the peripheral capillary walls of the glomeruli (Davies et al., 1973; Levy et al., 1973; Lowance et al., 1973; Zimmerman et al., 1975; Clarkson et al., 1977; Zollinger and Mihatsch, 1978). Although these subendothelial deposits are not conspicuous because of their small size and small number, their presence in the peripheral capillary walls is thought to indicate that the site of glomerular injury is *not* confined to the mesangium. From this point of view, IgA nephropathy with subendothelial deposits in the capillary walls (IgA type 2) seems to be a little different from IgA nephropathy without deposits in the capillary walls (IgA type 1) and seems to be similar to membranoproliferative glomerulonephritis with subendothelial deposits (MPGN), in which dense deposits are present in both the mesangium and the capillary walls of the glomeruli (Habib et al., 1973; West, 1973; Anders and Thoenes, 1975; Zollinger and Mihatsch, 1978). The present study was undertaken to evaluate the pathological and clinical significance of subendothelial deposits in IgA nephropathy by comparing IgA type 2 with IgA type 1 and MPGN.

Patients and Methods

Out of 663 renal biopsies examined at the Department of Pathology, Toranomon Hospital between January 1, 1970 and May 31, 1979, 30 biopsy cases of IgA type 1, 23 of IgA type 2 and 31 of MPGN were selected for study. All the selected cases had at least 5 glomeruli suitable for histometry in a biopsy specimen and were in good condition for examination by immunofluorescence microscopy and electron microscopy. Repeat biopsies were examined in 6 patients of IgA type 1, in 5 patients of IgA type 2 and in 4 patients of MPGN. Four initial biopsies, which had been performed before January 1, 1970, were included in the study. Therefore, final study cases consisted of 32 biopsies from 26 patients of IgA type 1, 25 biopsies from 20 patients of IgA type 2 and 31 biopsies from 27 patients of MPGN.

In none of the cases studied was there any clinical or laboratory evidence to suggest an underlying systemic disease, such as systemic lupus erythematosus, rheumatic fever or Schönlein-Henoch purpura.

Light Microscopy. Kidney tissue for light microscopy was fixed in 6% neutral buffered formalin, embedded in paraffin, cut at 2 to 3 μ and stained with hematoxylin and eosin (HE), periodic acid-Schiff (PAS), Mallory Azan, Weigert's elastica-van Gieson stain, and periodic acid methenamine silver with HE counterstain (PAM).

Histometry. The area of the glomerular mesangium, which consists of mesangial matrix, mesangial deposits and mesangial cells, was measured by the point-counting method as described on a previous study (Hara, 1972) and the degree of mesangial thickening was shown by the ratio of the mesangial area to the glomerular area (Relative mesangial area). Point-counting was made on 2 to 3 μ sections stained with PAS at a magnification of × 500 by the use of a microscope (Axiomat Zeiss).

The number of mesangial cells was counted on the same sections used in the histometry of the mesangial area at a magnification of × 500, and the degree of hypercellularity in the mesangium was shown by the number of mesangial cells per 1,000 μ^2 glomerular area (Mesangial cell count).

Glomeruli with focal or segmental changes were not measured and only glomeruli with diffuse changes were measured by histometry.

Immunofluorescence Microscopy. Kidney tissue for immunofluorescence microscopy was snapfrozen in dry ice and acetone mixture, and cut at 3 to 4 μ. After fixation in 95% alcohol, the sections were incubated with FITC-labeled antisera to human IgG, IgA, IgM, β_1C-globulin and fibrin/fibrinogen (Fuji Zoki, Japan; Hoechst, Germany) at 37° C for 50 min. Monospecificity of the antisera was checked by immunoelectrophoresis.

Four specimens, which had not been frozen at the time of renal biopsy, were immunohistologically examined on tissue embedded in paraffin. Formalin-fixed and paraffin-embedded tissue was cut at 2 to 3 μ. After deparaffination, the sections were incubated with 0.1% protease (Sigma Chemical, USA, type VII) in 0.5 M Tris/HCl buffer for 30 min. Following incubation of the sections with antisera to human IgG, IgA, IgM and β_1C-globulin (Fuji Zoki, Japan; Hoechst, Germany) at room temperature for 20 min, they were washed in PBS (pH 7.2) for 5 min and then incubated with FITC-labeled goat anti-rabbit antiserum at room temperature for 20 min. Details of the indirect immunofluorescence technics employed have been described (Huang, 1975; Endo et al., 1977).

Electron Microscopy. Kidney tissue for electron microscopy was fixed in 2.5% glutaraldehyde, buffered with 0.1 M phosphate (pH 7.2) and postfixed in 1% osmium tetroxide. After embedding in epoxy resin, sections were cut on a Porter-Blum ultramicrotome, stained with uranyl acetate and lead citrate, and viewed in a Hitachi HU-12 electron microscope.

Four specimens, which had not been fixed in glutaraldehyde at the time of renal biopsy, were examined on tissues embedded in paraffin. After deparaffination, small fragments of the tissue were immersed in 0.1 M phosphate buffer (pH 7.2) for 24 h, and fixed in 1% osmium tetroxide. After embedding in epoxy resin, sections were cut on a Porter-Blum ultramicrotome, and stained with uranyl acetate and lead citrate.

Almost the whole area of the largest cut-surface of one or two glomeruli was ultrastructurally examined in every case.

Clinical Observations. Age, sex, time of onset, urinary findings, blood pressure and renal function tests were examined. Hypertension was defined as systolic blood pressure above 150 mm Hg or diastolic blood pressure above 90 mm Hg. The impairment of renal function was defined as creatinine clearance of less than 80 ml per minute per 1.48 sq.m. of body surface area. A nephrotic syndrome was defined by the association of urinary protein more than 3.5 g per 24 h and hypoproteinemia under 6.0 g per dl.

Results

Light Microscopy

Histological changes of the glomeruli consisted of an increase in the mesangial matrix and hypercellularity in the mesangium, and the capillary walls of the glomeruli seemed to be normal in IgA type 1 and also in most cases of IgA type 2 (Figs. 1a, 3, 4). Consequently, it was difficult to distinguish histologically between IgA type 1 and IgA type 2. In some cases of IgA type 2, however, a slight double contour of the capillary wall was observed locally in a small number of glomeruli in a biopsy specimen (Figs. 1a, 1b). The degree of the mesangial changes varied considerably from case to case in both IgA type 1 and IgA type 2. Nodular hyaline substance in the mesangium, which indicates a large deposit, was sometimes observed sparsely in both types of IgA nephropathy, but it was rare in MPGN. Glomeruli with focal or segmental accentuation

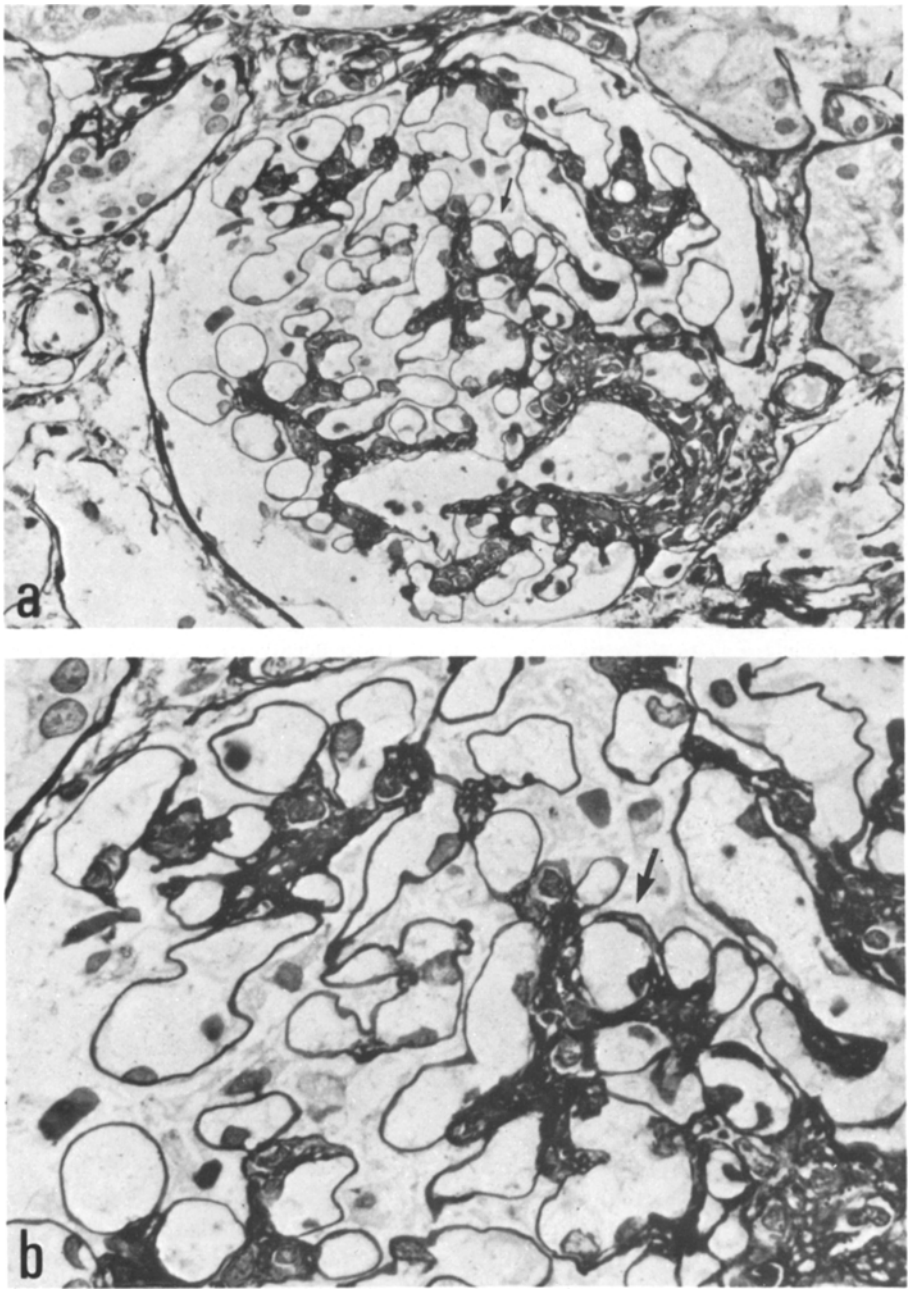


Fig. 1a and b. Biopsy from patient N. K., IgA type 2. **a** A glomerulus showing mesangial thickening. Capillary walls are apparently normal except for a slight double contour *(arrow)*. (PAM, × 250). **b** Detail of a slight double contour of the capillary wall in Fig. 1a. (PAM, × 500)

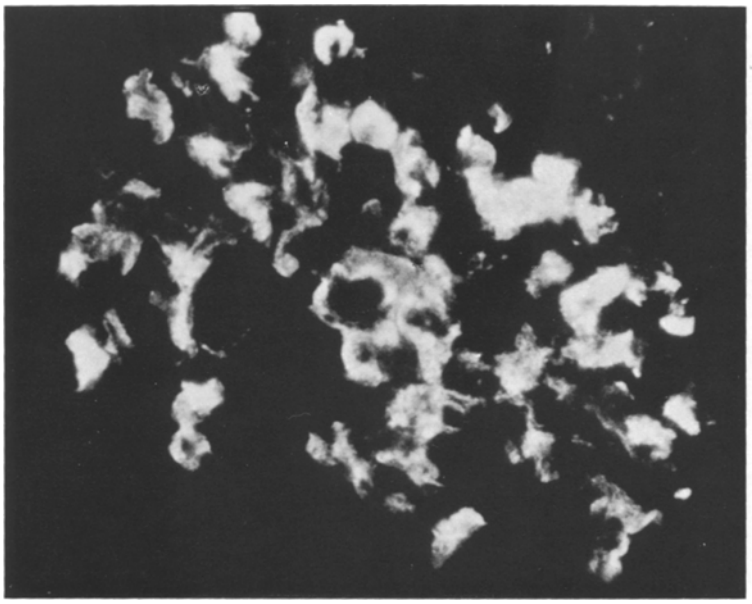


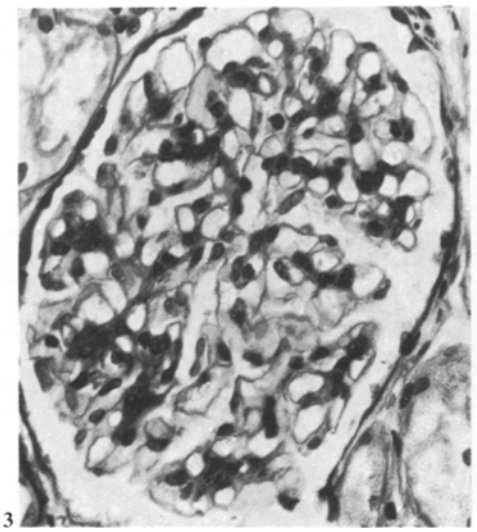
Fig. 2. The same case as in Fig. 1. A glomerulus showing massive deposition of IgA in the mesangium with a slight deposition of IgA along a part of capillary walls. (×240)

of the mesangial changes were observed in 34.4% (11/32) of IgA type 1 and in 20.0% (5/25) of IgA type 2, but the number of such glomeruli is usually small in a biopsy specimen, and most glomeruli showed diffuse changes of the mesangium. In MPGN, on the other hand, glomeruli showing focal or segmental changes were observed in 38.7% (12/31) of the biopsies.

The degree of mesangial thickening increased a little in repeat biopsies of IgA type 2 (Figs. 3, 4). The increase was mild and not so distinct as seen in the histometric comparison. The glomeruli of IgA type 1, on the other hand, showed no significant difference between an initial biopsy and a repeat biopsy. In the 4 cases of MPGN followed up, mesangial thickening became more prominent in their repeat biopsies.

Immunofluorescence Microscopy

IgA deposition was predominant in all cases of IgA type 1 and IgA type 2, and was accompanied by IgG and IgM deposition with various combinations as shown in Table 1. The pattern of immunoglobulin localization was predominantly mesangial in IgA type 1 and also in IgA type 2, but a slight deposition of immunoglobulin along a part of the peripheral capillary walls was also often observed in the latter (Fig. 2). On the other hand, IgA was also predominant in 16 of 31 biopsies (51.6%) of MPGN. IgA deposition in MPGN was as a rule mesangially as well as peripherally located, but it was predominantly mesangial in 7 cases of MPGN. The pattern of β_1C-globulin localization was



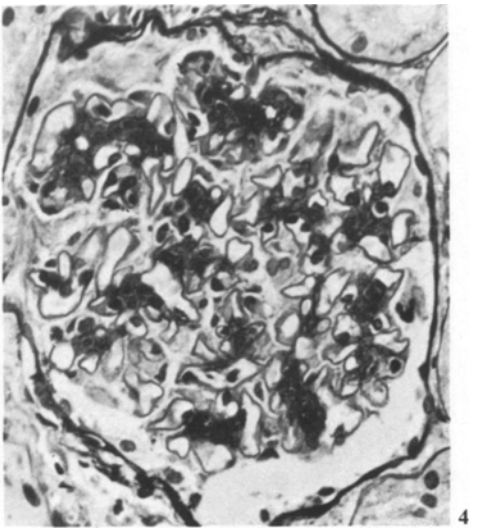


Fig. 3. Initial biopsy from patient M.K., IgA type 2. A glomerulus showing mild mesangial thickening and normal capillary walls. (PAS, × 200)

Fig. 4. Second biopsy, obtained 42 months after initial biopsy presented in Fig. 3. Mesangial thickening is more prominent in Fig. 4 than in Fig. 3. (PAS, × 200)

Table 1. Combinations of immunoglobulin deposition

Type of immunoglobulin	IgA type 1	IgA type 2	MPGN
A	13	7	4
A+G	9	10	10
A+M	7	2	4
A+G+M	3	6	9
G	0	0	2
G+M	0	0	2
M	0	0	0

mesangial in IgA type 1 and IgA type 2, but it was peripheral or, mesangial as well as peripheral in MPGN.

Electron Microscopy

Mesangial deposits were present in all cases of IgA type 1 and IgA type 2, and they were sometimes very large in both types of IgA nephropathy (Fig. 5a). Subendothelial electron-dense deposits, which differentiate IgA type 2 from IgA type 1, were observed sparsely scattered in the capillary walls distant from the mesangium and their size was small (Figs. 5a, 5b, 6, 7). The number of subendothelial deposits in the capillary walls was small as compared with that of mesangial deposits, and their localization was usually restricted to a small

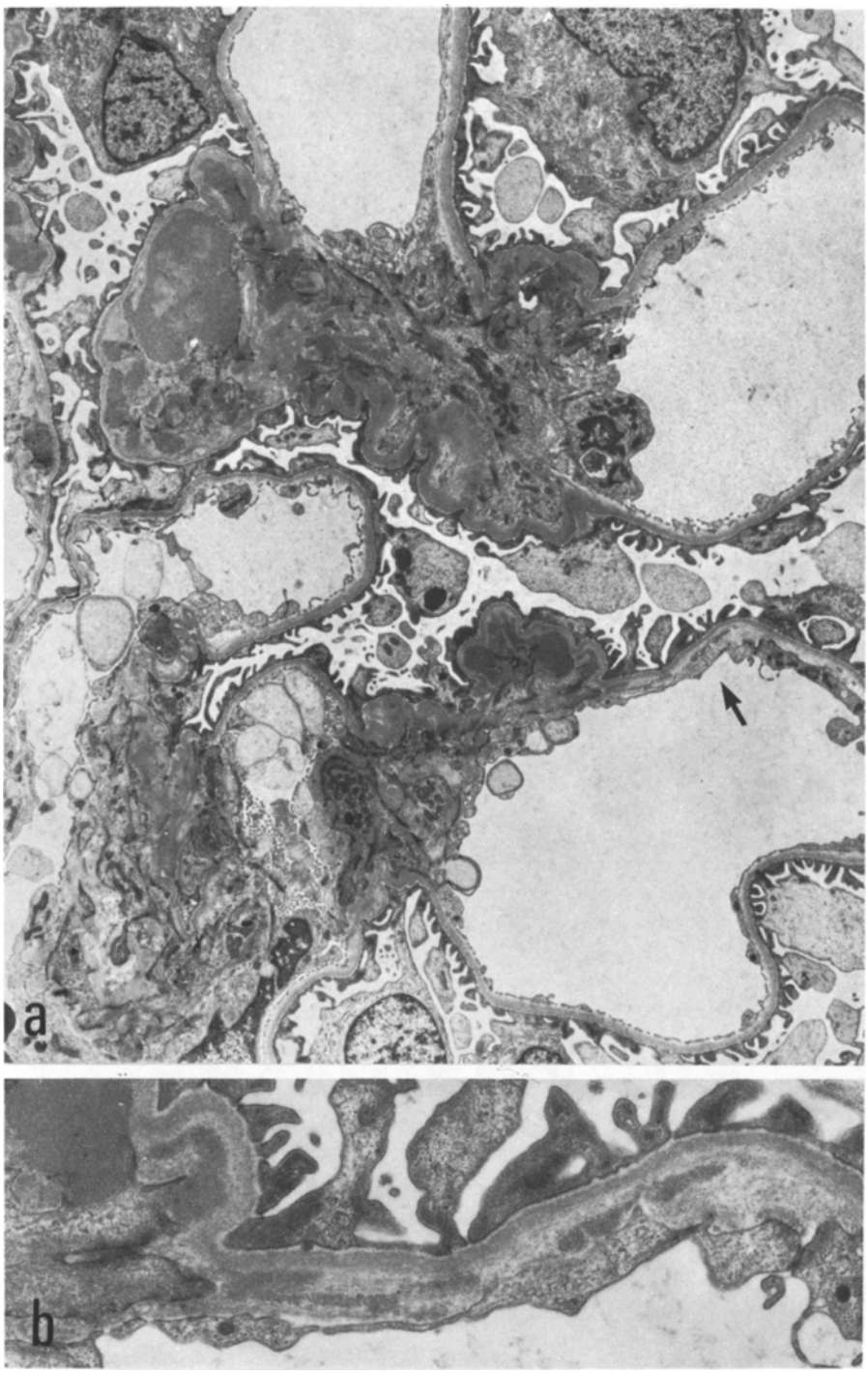
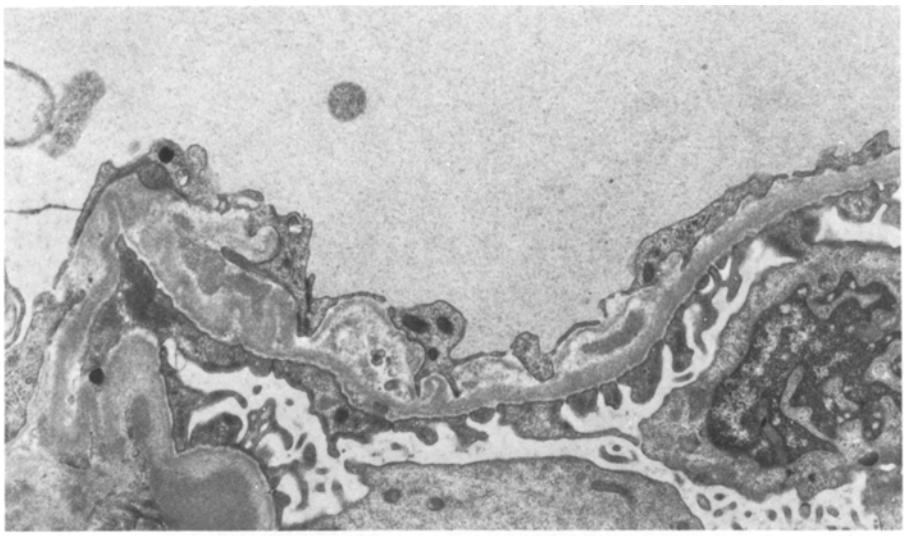


Fig. 5a and b. The same case as in Fig. 1. **a** Subendothelial deposits are present in a part of capillary walls *(arrow)*, and they are much smaller than mesangial deposits. (×3,840). **b** Detail of subendothelial deposits in Fig. 5a. (×14,400)



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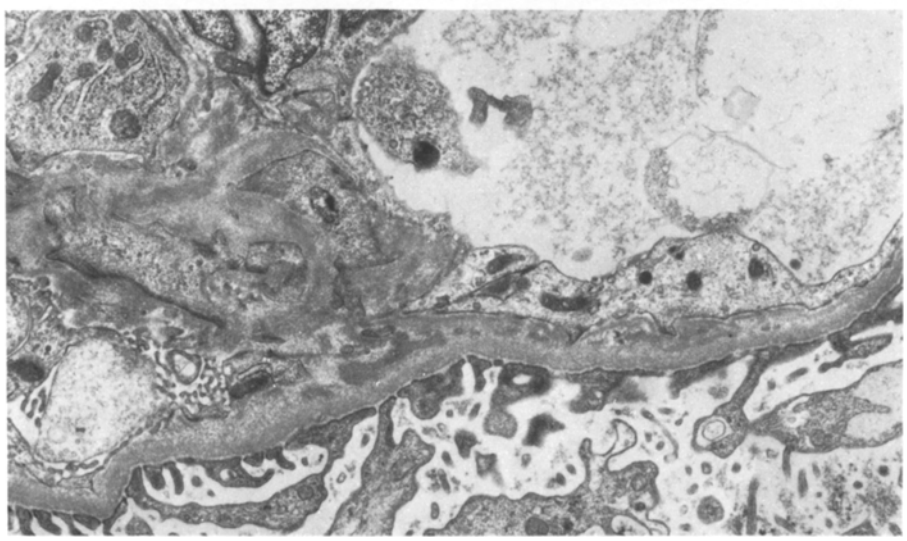

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Fig. 6. The same case as in Fig. 1. Mild thickening of the lamina rara interna adjacent to a subendothelial deposit. (×8,640)

Fig. 7. Biopsy from patient N.Y., IgA type 2. Interrupted linear arrangement of small subendothelial deposits in the capillary wall near the mesangium. (×8,640)

number of capillary loops of the glomeruli (Fig. 5a). Subendothelial deposits sometimes lay in a interrupted linear arrangement in the capillary walls near the mesangium (Fig. 7). Subendothelial deposits were similar to mesangial deposits in granularity and in electron density, and had no structure suggestive of fibrin. The basement membrane of the capillary walls, where subendothelial deposits were located, showed no change or mild thickening of the lamina

Table 2. Values for the relative mesangial area and the mesangial cell count

	IgA type 1	IgA type 2	MPGN
Number of biopsies	32	25	31
Relative mesangial area (%) (Mean ± S.D.)	14.22 ± 2.54	15.87 ± 2.70	20.50 ± 5.25
Mesangial cell count per 1,000 μ^2 glomerular area (Mean ± S.D.)	1.90 ± 0.25	2.06 ± 0.25	2.24 ± 0.35

rara interna (Figs. 5b, 6). Tiny intramembranous dense deposits were observed in 3 cases of IgA type 2 and in a case of IgA type 1. Subepithelial deposits in the capillary walls were minimally present in a case of IgA type 2 and in none of IgA type 1. Subendothelial deposits in MPGN tended to be larger than those in IgA type 2 in size as well as in number, and were often accompanied by subendothelial formation of basement membrane-like material. In the cases followed up, neither transition between IgA type 1 and IgA type 2 nor transition between IgA type 2 and MPGN was observed.

Histometry

The degree of mesangial thickening varied considerably from case to case as shown in Fig. 8, but the difference in degree among IgA type 1, IgA type 2 and MPGN was statistically significant (Table 2). That is to say, the relative mesangial area was larger in IgA type 2 than in IgA type 1 ($0.02 < P < 0.05$), and was the largest in MPGN ($P < 0.001$). As for the degree of hypercellularity in the mesangium, there was also a similar tendency among the three groups (Fig. 9, Table 2); the number of mesangial cells was larger in IgA type 2 than in IgA type 1, and was the largest in MPGN ($0.02 < P < 0.05$, respectively).

Histometry of the mesangial area on repeat biopsies demonstrated a contrast between IgA type 1 and IgA type 2 as shown in Fig. 10. Thus, the degree of mesangial thickening increased with lapse of time in IgA type 2, whereas it remained unchanged up to 13 years in IgA type 1. The degree of mesangial thickening in MPGN increased with lapse of time, as shown in Fig. 11.

The degree of hypercellularity in the mesangium showed no definite tendency in the repeat biopsies of the three groups.

Clinical Observations

The 26 patients of IgA type 1 consisted of 14 males and 12 females from the age of 13 to 54 years at the time of their initial biopsy, while 20 patients of IgA type 2 consisted of 12 males and 8 females aged from 16 to 44 years. In MPGN, 27 patients consisted of 13 males and 14 females from the age of 16 to 49 years at the time of their initial biopsy. None of the cases studied

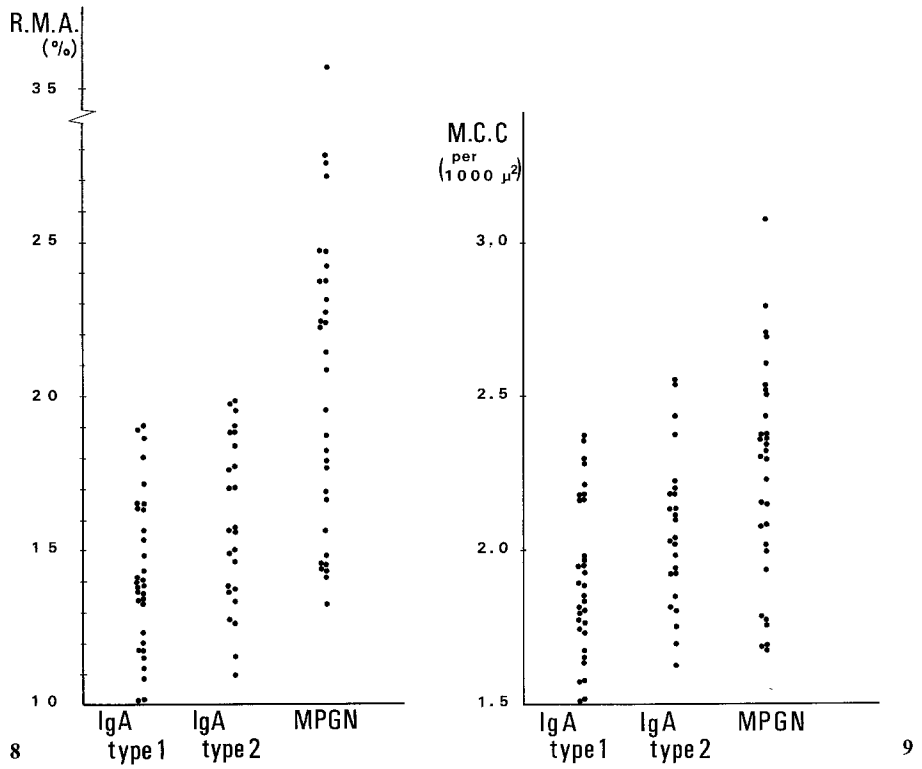

Fig. 8. The relative mesangial area (R.M.A.) in IgA type 1, IgA type 2 and MPGN

Fig. 9. The mesangial cell count (M.C.C.) in IgA type 1, IgA type 2 and MPGN

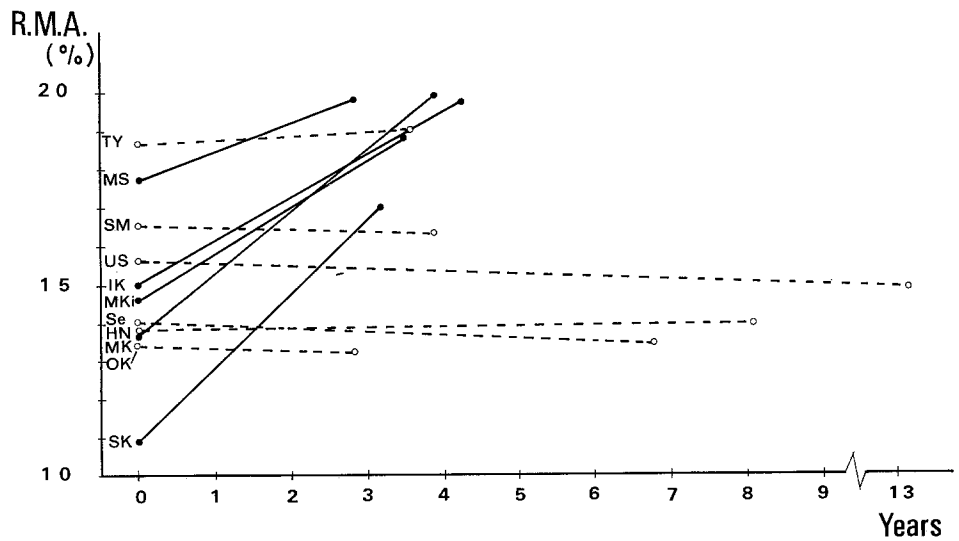

Fig. 10. The relative mesangial area (R.M.A.) of initial and repeat biopsies in IgA type 1 and IgA type 2. IgA type 1: o----o, IgA type 2: ●——●

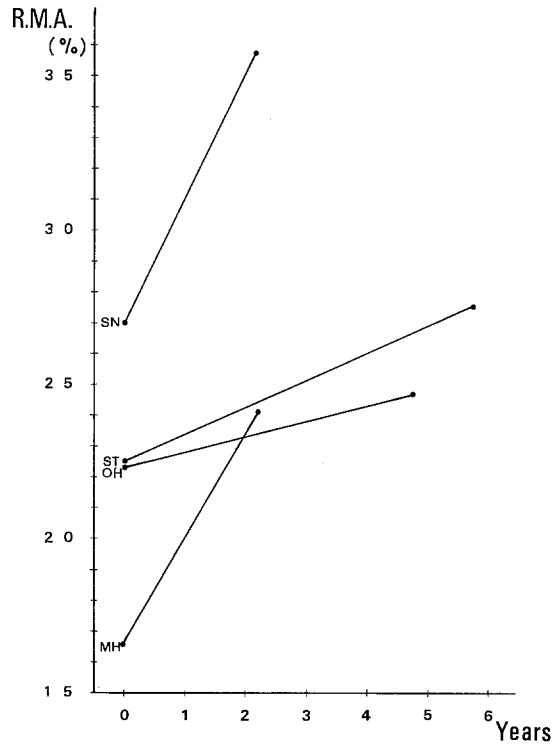

Fig. 11. The relative mesangial area (R.M.A.) of initial and repeat biopsies in MPGN

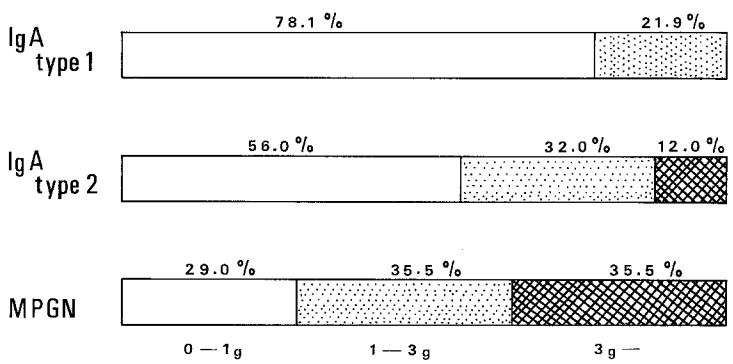

Fig. 12. Urine protein per 24 h in IgA type 1, IgA type 2 and MPGN

had an antecedent episode suggestive of poststreptococcal acute glomerulonephritis.

The impairment of renal function was present in 21.9% (7/32) of IgA type 1, in 36.0% (9/25) of IgA type 2 and in 58.1% (18/31) of MPGN. The incidence of hypertension did not differ between IgA type 1 (15.6%:5/32) and IgA type 2 (16.0%: 4/25) and was very high in MPGN (35.5%: 11/31). The incidence of mild proteinuria below 1.0 g. of protein per 24 h was 78.1% (25/32) in

IgA type 1, 56.0% (14/25) in IgA type 2 and 29.0% (9/31) in MPGN. Marked proteinuria above 3.0 g. of protein per 24 h was present in none of IgA type 1, in 12.0% (3/25) of IgA type 2 and in 35.5% (11/31) of MPGN (Fig. 12). A nephrotic syndrome was present neither in IgA type 1 nor in IgA type 2, but it was present in 3 patients of MPGN. As for the degree of haematuria, there was no significant difference between IgA type 1 and IgA type 2, and most cases of both types of IgA nephropathy showed mild or moderate microscopic haematuria.

There was no difference in clinical manifestations between IgA predominant MPGN and the other MPGN.

In the cases of IgA type 1 followed up, all the 6 patients had been in normal renal function at the time of their initial biopsy, but 3 of the 6 (SM, US and HN in Fig. 10) showed a mild impairment of renal function at the time of the second. In the cases of IgA type 2 followed up, all the 5 patients had been in normal renal function at the time of their initial biopsy, but 4 of the 5 were in impaired renal function at the time of the second biopsy. Although the other one (SK in Fig. 10) remained within normal renal function, his urine protein per 24 h had been markedly increased at the time of the second biopsy. In MPGN, on the other hand, 2 of the 4 patients (SN and OH in Fig. 11) had already shown the impairment of renal function at the time of their initial biopsy. All of the 4 had fallen into impaired renal function before the time of their second biopsy, and the renal function of the patients SN and OH were more severely deteriorated at the time of the second biopsy.

Discussion

On the basis of electron microscopic findings, IgA nephropathy has been subdivided into two groups according to the absence (IgA type 1) or presence (IgA type 2) of subendothelial deposits in the peripheral capillary walls of the glomeruli. Subepithelial or intramembranous deposits in the peripheral capillary walls of the glomeruli are also observed in some cases of IgA nephropathy, but they are rare as compared with subendothelial deposits (Davies et al., 1973; Levy et al., 1973; Lowance et al., 1973; Clarkson et al., 1977; Zollinger and Mihatsch, 1978). In addition, 4 of the 5 cases, which had either subepithelial or intramembranous deposits in the present study, had subendothelial deposits in the peripheral capillary walls, and the 4 cases were included in the group of IgA type 2.

It is usually difficult to distinguish histologically between IgA type 1 and IgA type 2, because the histological changes are confined to the mesangium in both types of IgA nephropathy. In some cases of IgA type 2, however, a slight double contour of the capillary wall is locally observed in a small number of glomeruli in a biopsy specimen. Immunofluorescence microscopy is also not effective enough to distinguish between the two, because the pattern of immunoglobulin localization is predominantly mesangial in both types of IgA nephropathy.

On the other hand, the histological borderline between IgA type 2 and a mild form or an early stage of MPGN is not clear, because the double contour of the capillary wall is often restricted to a small number of capillary loops of the glomeruli in the latter (Zollinger and Mihatsch, 1978). Indeed, distinction between IgA type 2 and two cases of MPGN in the present study could be made only by electron microscopy. The number and the size of subendothelial deposits tend to be much smaller in IgA type 2 than in MPGN, and mesangial interposition is not, as a rule, observed in IgA type 2.

IgA deposition was predominant in 51.6% of MPGN biopsies in the present study. This result is in accord with the report that IgA deposition is not specific for IgA nephropathy and IgA deposition is observed in a wide variety of glomerular lesions (Hyman et al., 1973).

The degree of change, consisting of increased matrix and hypercellularity in the mesangium, was histometrically a little higher in IgA type 2 than in IgA type 1, and was, highest in MPGN. Proteinuria tended to be mild in IgA type 1, moderate in IgA type 2 and marked in MPGN. The incidence of the impairment of renal function was higher in IgA type 2 than in IgA type 1, and was the highest in MPGN. The incidence of hypertension was not different between IgA type 1 and IgA type 2, and hypertension was the most frequent in MPGN. In the histometry of the mesangium on the cases followed up, the degree of mesangial thickening increased with lapse of time in IgA type 2 and MPGN, whereas it remained unchanged up to 13 years in IgA type 1. These results indicate that IgA type 1 is in better accord, than IgA type 2, with the clinicopathological entity of IgA nephropathy described originally by Berger (Berger, 1969). IgA type 2 seems to be pathologically and clinically intermediate between IgA type 1 and MPGN.

Several studies on MPGN report that there is often little change or even an improvement of glomerular morphology in repeat biopsies of MPGN (Cameron et al., 1970; Habib et al., 1973; Kincaid-Smith, 1973; West, 1973; Bohle et al., 1974). The results of the present study, however, showed that the glomerular mesangium in MPGN tends to enlarge with lapse of time, as long as the clinical manifestations are getting worse. Renal function decreased in all the 4 patients of MPGN and in 4 of the 5 patients of IgA types 2 in the present study. It may also be worthy of note that mild impairment of renal function appeared gradually in 3 of the 6 patients of IgA type 1 in spite of no progression of the glomerular changes. All the 3 patients were hypertensive. Vascular factors may play the leading role in the impairment of renal function in IgA type 1.

Neither transition between IgA type 1 and IgA type 2 nor transition between IgA type 2 and MPGN was observed in the cases followed up, but it should be further examined in a larger number of cases. It may be quite possible that IgA type 2 is closely related to a mild from or an early stage of MPGN with IgA deposition, judging from the fact that IgA type 2 is similar to MPGN in the presence of subendothelial deposits, in the tendency of the mesangium to enlarge with lapse of time, and in the high incidence of the impairment of renal function with moderate to marked proteinuria. The pathological and

clinical features of IgA type 2 seem to suggest that there is an overlap clinicopathologically between IgA nephropathy and MPGN with IgA deposition.

The mildness of the clinical manifestations of IgA type 1 is thought to be attributable to the morphological features of IgA type 1 that glomerular changes are restricted to the mesangial regions, and that the mesangial changes are mild. We conclude that it is important to subdivide IgA nephropathy into two types according to the presence or absence of subendothelial deposits in the peripheral capillary walls of the glomeruli, because clinical manifestations and prognosis of the two types of IgA nephropathy have been shown to differ considerably.

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