IgA localisation in glomerular diseases

W. LAWLER, GEORGE WILLIAMS, P. TARPEY, E. JOAN ACHESON, AND N. P. MALLICK

From the Departments of Pathology and Renal Medicine, Manchester Royal Infirmary and Medical School, University of Manchester

SUMMARY The structural changes found on light and electron microscopy study of 25 renal biopsy specimens that showed significant glomerular IgA deposition on immunofluorescence were correlated with relevant clinical data. The morphology of a wide range of glomerulopathies seen included mesangial proliferative (60%), membranous (12%), rapidly progressive proliferative (8%), mesangio-capillary (8%), and no light microscope change (8%). Four of the 15 cases (60%) of mesangial proliferative glomerulonephritis were associated with focal segmental sclerosis and 10 with focal segmental and focal global sclerosis. In addition, 7 of the 15 cases showed capsular crescents. The clinicopathological correlations indicated that the prognosis in this group is unfavourable when focal global sclerosis and capsular crescents are present, particularly when both occur in the same biopsy specimen.

Only in the last 10 years has it been realised that IgA may be localised, along with other immunoglobulins, within diseased glomeruli in a wide range of glomerulopathies. Occasionally it may be the only immunoglobulin present (Berger, 1969; Hyman *et al.*, 1973; Lowance *et al.*, 1973; Roy *et al.*, 1973; McCoy *et al.*, 1974; Morel-Maroger and Verroust, 1975; Woodroffe *et al.*, 1975; Zimmerman and Burkholder, 1975). We therefore reviewed our renal biopsy material and studied further those cases in which there were significant glomerular IgA deposits. We then correlated our pathological findings with the clinical data

Material and methods

A total of 193 percutaneous renal biopsy specimens were reviewed. On immunofluorescence 8 were strongly and 17 moderately positive for IgA. These 25 cases with significant glomerular IgA (13% of the total) formed the basis of the study. Lesser amounts of IgA were found in a further 24 cases. Our techniques for immunofluorescence, light microscopy, and electron microscopy have been described previously (Lawler *et al.*, 1976).

Results

IMMUNOFLUORESCENCE

These results are summarised in Table 1. IgA, together with the third fraction of complement, was

the sole localising immunoglobulin in three cases; in 12 it was present with IgM; in nine with both IgM and IgG, and in one case with IgG. In 13 cases IgA was the predominant localising immunoglobulin; in six there was no predominant immunoglobulin; and in three, IgG predominated.

MORPHOLOGY

The light and electron microscopy findings in the 25 cases were reviewed. The morphological diagnoses included a wide range of glomerulopathies (Table 1). Patients with membranous, rapidly progressive proliferative, and mesangiocapillary glomerulopathies presented characteristic features. No glomeruli were available for light microscopy in case 19, and this was therefore unclassifiable. Two patients with no light microscope change showed occasional sub-epithelial complexes electronoptically.

On light microscopy 15 (60%) of the 25 cases showing undue accentuation of mesangial cells and matrix were designated mesangial proliferative glomerulonephritis. In some cases these changes were of a mild order (Fig. 1) while in others they were much more marked (Fig. 2). In only one of these 15 cases was there mesangial proliferation alone. In four it was associated with focal segmental sclerosis (Fig. 3) and in the remaining 10 with focal segmental and focal global (total) sclerosis. Seven of these 15 cases also featured capsular crescents. These findings are shown in Table 2. In this group immunofluorescence was confined mainly to mesangial regions (Fig. 4), although peripheral capillary loops

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Table 1 Immunofluorescence findings and morphological diagnosis on renal biopsy in 25 cases of glomerulopathy

Case no.	IgA	IgG	IgM	Fibrinogen	C ₃	Morphological diagnosis
1	+++	Neg	+	Neg	++	Mesangial proliferative
2	++	Neg	+	Neg	+	" "
3	++	Neg	Neg	Neg	++	" "
4	+++	+	+	Neg	+	Rapidly progressive proliferative
5	++	Neg	+	Neg	+	Mesangial proliferative
6	++	Neg	+	Neg	+	" "
7	++	Neg	++	Neg	++	" "
8	++	++	++	Neg	++	Mesangiocapillary
9	+++	Neg	+	Neg	++	No light microscope change with immune complex disease
10	++	Neg	Neg	Neg	+	Mesangial proliferative
11	++	Neg	++	Neg	++	" "
12	++	+	+	Neg	+	" "
13	+++	+	+	Neg	+++	" "
14	++	Neg	+	+++	+++	Mesangiocapillary
15	++	+++	+	Neg	++	Membranous
16	+++	Neg	++	Neg	++	Mesangial proliferative
17	+++	Neg	+	Neg	++	" "
18	++	+	++	Neg	Neg	No light microscope change with immune complex disease
19	+++	Neg	+++	Neg	++	No glomeruli for light microscopy
20	++	+++	+	+	++	Membranous
21	++	Neg	Neg	No gloms	No gloms	Mesangial proliferative
22	+++	Neg	+	Neg	+++	" "
23	++	+++	Neg	Neg	Neg	Membranous
24	++	+	+	++	+	Mesangial proliferative
25	++	++	+	Neg	+	Rapidly progressive proliferative

Fig. 1 Glomerulus showing mild mesangial proliferation. (PAS × 400)

occasionally reacted (Fig. 5). Electron microscopy confirmed the mesangial proliferative changes and also revealed numerous discrete immune complexes in mesangial regions. In many glomeruli immune complexes were confined to the mesangia, the peripheral capillary loops appearing normal apart from

a mild degree of flattening and fusion of the epithelial foot processes (Fig. 6). In a few glomerular loops subendothelial immune complexes extended into paramesangial areas (Fig. 7) and in rare instances involved entire peripheral capillary loops (Fig. 8). Comparison of the morphological diagnoses with

Fig. 2 Glomerulus showing more marked mesangial proliferation. (PAS $\times$ 400)

Fig. 3 Glomeruli showing focal segmental sclerosis. (PAS $\times$ 350)

Table 2 Analysis of morphology of 15 cases of mesangial proliferative glomerulonephritis

Case no.	Total no. of glomeruli	Total sclerosis	Segmental sclerosis	Capsular crescents
1	19	3	5	—
2	22	1	6	—
3	39	1	3	1
5	55	5	8	8
6	25	—	2	—
7	15	3	1	2
10	7	6	1	—
11	26	5	3	7
12	7	—	2	1
13	8	3	1	—
16	29	3	5	3
17	6	2	1	—
21	8	—	2	2
22	21	5	5	—
24	26	—	—	—

immunoglobulin distribution in the 25 cases (Table 1) shows that the three cases with IgA alone and most of the cases with predominant IgA localisation had a mesangial proliferative glomerulonephritis. In

the three patients with membranous glomerulopathy glomerular IgG predominated.

CLINICAL DATA

The relevant data from the clinical notes and follow-up records of the 25 patients are summarised in Table 3. Renal function, as represented by serum creatinine levels, was assessed at presentation in all cases and disclosed functional impairment in four (cases 4, 11, 14, and 25). Serum complement (as CH_{50}), measured at presentation in 19 cases, was slightly depressed in three (cases 2, 13, and 15). Serum IgA levels were estimated as normal on admission in three cases (cases 4, 6, and 10). Further immunochemical studies on all the 25 cases are in progress. Two patients (cases 5 and 24) had successful radiotherapy and chemotherapy for Hodgkin's disease before presentation.

The patient in case 6, presenting with non-thrombocytopenic purpura and a nephrotic syndrome, had a poorly differentiated squamous

Fig. 4 Fluorescent IgA in immune complex deposits confined to the mesangial regions. (IF $\times$ 300)

Fig. 5 Fluorescent IgA in immune complex deposits mainly in mesangial regions but also in occasional peripheral capillary loops. (IF $\times$ 300)

Fig. 6 Electron micrograph showing an increase in mesangial cells and matrix (Mes), immune complexes confined to the mesangial region (solid arrows), and some flattening and fusion of the epithelial cell (Ep) foot processes (open arrows). Also shown are the capillary lumina (CL) and the urinary space (US). (TEM $\times 3035$)

carcinoma of his bronchus. Resection of the tumour produced remission of the purpura and nephrotic syndrome. After 18 months, despite metastatic disease, he showed no recurrence of purpura or proteinuria but died from carcinomatosis. No patient presented with systemic lupus erythematosus. In one, however (case 7), who developed symptoms suggestive of SLE three years after presentation, renal function gradually deteriorated and he died from a subarachnoid haemorrhage. The patient in case 23, who had seropositive rheumatoid arthritis of many years' duration, presented with the nephrotic syndrome soon after starting gold therapy. His symptoms remitted completely after stopping treatment.

PROGRESS

All patients have been followed up for at least one year. Renal function in one patient (case 4) has

significantly improved; one patient (case 25) was admitted in renal failure and died two months later; and another patient (case 14), who presented with malignant hypertension, proteinuria, and renal failure, has been lost to follow up. Out of seven patients (cases 5, 7, 8, 11, 17, 20, and 21) who have shown some deterioration in renal function since biopsy three (cases 8, 11, and 17) have progressed to renal failure and four (cases 5, 7, 20, and 21) have shown mild progressive functional impairment. Two patients (cases 6 and 7) have died from other causes (see above).

REPEAT BIOPSIES

Two patients had repeat biopsies and two others had had previous biopsies. The clinical features in three (cases 1, 7, and 22) did not change between biopsies, and in sequential biopsies in all three the morphology was similar. In the fourth patient (case 4)

Fig. 7 Immune complexes extend from mesangial region (Mes) into subendothelial areas of two capillary loops (arrows). Capillary lumina (CL), endothelial (En), and epithelial (Ep) cells are identified. (TEM $\times 3035$)

the first biopsy showed a rapidly progressive proliferative glomerulonephritis. Renal function much improved after the biopsy and 18 months later repeat biopsy showed only mesangial proliferation.

Clinicopathological correlations

Although patients with mesangial proliferative glomerulonephritis had a range of clinical presentations macroscopic haematuria and non-thrombocytopenic purpura accounted for more than half (Table 4). Five patients have developed renal failure and four have shown mild deterioration in renal function (see above). These findings are compared with the morphological diagnoses in these cases (Table 4).

Patients with mesangial proliferative glomerulonephritis and renal failure or deterioration were further analysed for associated focal segmental sclerosis,

global sclerosis, and epithelial capsular crescents (Table 5). Despite the limited number of patients in each group, seemingly the prognosis is less favourable when focal global sclerosis or capsular crescents apply and particularly when both are present in the same biopsy specimen.

Discussion

Significant glomerular IgA deposition was the criterion for selecting cases for this study. Two cases showed no significant abnormality by light microscopy although both had discrete subepithelial immune complexes on electron microscopy. In the three with membranous glomerulonephritis IgG dominated as the localising immunoglobulin. These findings agree with those of Berger *et al.* (1971), Burkholder (1974), Heptinstall (1974), and Morel-Maroger and Verroust (1975), who found that IgG

Fig. 8 Immune complexes occur subendothelially (arrows) and involve the entire peripheral capillary loops. (TEM $\times 6810$)

invariably and IgA rarely contribute to glomerular immunoglobulin deposition in membranous glomerulonephritis.

One of our patients (case 23) had long-standing seropositive rheumatoid arthritis. His glomerulopathy, thought to be due to gold therapy, completely remitted after gold was withdrawn. Zimmerman and Burkholder (1975), reviewing 18 patients with IgA nephropathy, included one patient 'who had a long history of rheumatoid arthritis', but they did not state whether the patient was given gold therapy. Two patients had a rapidly progressive proliferative glomerulonephritis. This has previously been found in association with IgA deposition by Hyman *et al.* (1973) and Morel-Maroger *et al.* (1973). Two patients had mesangiocapillary glomerulonephritis. Although IgG and IgM are the most common immunoglobulins in this disease IgA may also be found (Hyman *et al.*, 1973; Anders and Thoenes, 1975; Morel-Maroger and Verroust, 1975; Tighe, 1975; Davis and Cavallo, 1976).

Fifteen (60%) of our patients had mesangial proliferative glomerulonephritis with or without focal segmental or global sclerosis or crescents. Studies of patients with significant glomerular IgA localisation, with or without macroscopic haematuria, have shown that an increase in mesangial cells and matrix is the abnormality most often seen on light microscopy (Davies *et al.*, 1973; McEnery *et al.*, 1973; van de Putte *et al.*, 1974; Vernier *et al.*, 1975; Kupor *et al.*, 1975).

Most authors have commented on the presence of focal segmental sclerosis, focal global sclerosis, and epithelial crescent formation but few have tried to correlate the histological appearances with prognosis. Roy *et al.* (1973) suggest that the combination of segmental glomerular sclerosis and proteinuria is synonymous with a more serious prognosis. Levy *et al.* (1973) ascribe the worst prognosis to the group with diffuse glomerulonephritis and focal crescents. Sissons *et al.* (1975) state that glomerular scarring was a feature in patients with impairment of renal

Table 3 Clinical data in 25 cases of glomerular disease with glomerular IgA deposits

Case no.	Age at onset (years)	Sex	Presenting complaint	At presentation				Onset to biopsy (months)	Duration of disease (years)	Progress
				Blood pressure (mm Hg)	Serum creatinine	Proteinuria (g/24 h)	Haematuria			
1	35	F	PrU	140/105	0.8	3	Micro	28	6½	No change
2	17	F	NTP and NS	130/65	0.7	1.5	"	31	6½	No further purpura. Mild PrU
3	24	M	Haematuria	130/90	0.8	0.3-0.5	Macro	26	3	No change. IMH
4	18	M	NTP and NS	140/90	1.8	14-16	Micro	1	3½	Renal function improved
5	20	F	Haematuria and NS	N	1.0	10-18	Macro	2	4	HD. Slow deterioration of renal function
6	71	M	NTP & NS	130/70	0.9	1.3	Micro	1	2	Carcinoma bronchus (See text)
7	37	F	NS	150/90	0.9	4	"	72	7	? SLE (See text)
8	19	F	NS	130/80	1.0	11-15	"	8	1½	Died in renal failure
9	26	M	PrU	130/80	0.9	2-3	"	5	3	No change
10	53	M	Haematuria	150/100	1.5	1-2	Macro	84	10	No change. No further haematuria
11	51	M	NS	180/130	1.8	5	Micro	1	1	Died in renal failure
12	4	F	NTP & NS	ND	N	ND	ND	156	15	Asymptomatic 12 years then recurrence of NTP and PrU. PrU continues
13	22	F	PrU	140/80	1.1	2-5	Micro	1	3	No change
14	27	M	PrU	Raised	2.6	6	Nil	9	—	Malignant H/T. Renal failure. Lost to follow-up
15	32	M	NS	130/80	1.1	20	"	3	1½	No change
16	20	M	PrU	140/90	0.8	4-11	Micro	8	2	No change
17	17	M	PrU	N	0.9	6-15	ND	72	6½	Malignant H/T. Renal failure
18	7	M	NS	N	1.0	ND	Nil	216	19	Intermittent NS. No change
19	25	F	Haematuria	N	0.9	Mild	Macro	36	4	No change. IMH
20	40	M	NS	150/90	1.4	10-14	Micro	14	2½	Mild deterioration in function
21	34	M	Haematuria	140/90	1.4	Heavy	Macro	18	3	Mild deterioration and mild H/T
22	39	M	Haematuria	130/80	1.0	5-6	"	66	6½	No change
23	52	M	NS	140/90	0.9	10-21	Nil	12	1½	Rheumatoid arthritis (See text)
24	44	M	NS	N	0.9	12	"	7	1	HD. No change
25	55	M	PrU	130/80	26	ND	ND	1	2 months	Admitted in renal failure. Dead after 2 months

PrU = proteinuria. NTP = non-thrombocytopenic purpura. NS = nephrotic syndrome. H/T = hypertension. HD = Hodgkin's disease. N = normal. ND = not done. Micro = microscopic. Macro = macroscopic. SLE = systemic lupus erythematosus. IMH = intermittent macroscopic haematuria.

Conversion: Traditional units to SI—Creatinine: 1 mg/100 ml = 88.4 µmol/l. Pressure: 1 mm Hg = 0.133 kPa.

function. Imbasciati *et al.* (1975) comment that 'functional impairment was related to the diffusion of the glomerular sclerosis'. Our findings suggest that focal global sclerosis, capsular crescents, and particularly both together, adversely influence prognosis.

Glomerular IgA is common in systemic lupus erythematosus (Svec *et al.*, 1967; Koffler *et al.*, 1969; McCluskey, 1970; Rothfield *et al.*, 1972). It is therefore surprising that none of our patients with IgA glomerular localisation presented with SLE, although one subsequently developed symptoms suggestive of this disease.

Four patients with non-thrombocytopenic purpura (Henoch-Schönlein anaphylactoid purpura) at

presentation had glomerular deposition of IgA—an association which is well documented (Urizar *et al.*, 1968; Evans *et al.*, 1973; Heptinstall, 1974; Crumb, 1976; Travis *et al.*, 1976).

None of our patients had clinical or biochemical evidence of liver disease. Although gammaglobulins were recognised in the glomeruli of patients with liver disease over 10 years ago (Sakaguchi *et al.*, 1965; Salomon *et al.*, 1965), only recently has it been realised that IgA is principally involved and associated with mesangial proliferation (Callard *et al.*, 1975; André and André, 1976).

No patients in our series had a family history of macroscopic haematuria or other renal disease. This contrasts with the findings of Sissons *et al.* (1975)

Table 4 Correlations between morphological diagnosis, presenting features, and renal function deterioration

Morphological diagnosis	Presenting feature				Renal function deterioration		Total cases
	Nephrotic syndrome	Proteinuria	Macroscopic haematuria	Non-thrombocytopenic purpura and nephrotic syndrome	Renal failure	Mild deterioration	
No light microscope change	1	1	—	—	—	—	2
Membranous	3	—	—	—	—	1	3
Rapidly progressive proliferative	—	1	—	1	1	—	2
Mesangiocapillary	1	1	—	—	2	—	2
No glomeruli for LM	—	—	1	—	—	—	1
Mesangial proliferative	3	4	5	3	2	3	15
Total	8	7	6	4	5	4	

Table 5 Comparison of the different morphological features in the group of patients with mesangial proliferative glomerulonephritis and renal function deterioration

Morphology	No. of cases	Renal failure	Mild deterioration
MP alone without crescents	1	—	—
MP alone with crescents	—	—	—
MP + focal segmental sclerosis without crescents	1	—	—
MP + focal segmental sclerosis with crescents	2	—	1
MP + focal segmental and global sclerosis without crescents	6	1	—
MP + focal segmental and global sclerosis with crescents	5	1	2
Total	15	2	3

MP = mesangial proliferation

and Zimmerman and Burkholder (1975), in which 5 out of 25 and 2 out of 18 patients respectively with mesangial IgA deposits had such a family history. Sissons *et al.* (1975) also point out that in several studies of patients selected on account of recurrent haematuria rather than glomerular IgA deposition there is also a high incidence of familial renal disease. Seventeen of our 25 patients with glomerular localisation of IgA were men, 8 were women. Male predominance is a feature in most series of cases in which IgA has been a significant localising immunoglobulin.

The role of IgA as a glomerular immunoglobulin is unknown (Whitworth *et al.*, 1976). As a sole localising immunoglobulin it is rare other than in cases of mesangial proliferative glomerulonephritis in which the immune complexes, as identified by immunofluorescence and electron microscopy, are mainly of mesangial location. Germuth and Rodriguez (1973, 1975) believe this site of deposition is characteristic of relatively insoluble and larger complexes formed in slight antibody or antigen excess, depending on the size of the reactants and antibody avidity.

Several authors, in discussing mesangial IgA localisation, comment that the onset or exacerbations, or both, of clinical symptoms were often preceded by upper respiratory infections (Berger, 1969; McCoy *et al.*, 1974; Dobrin *et al.*, 1975; Sissons *et al.*, 1975; Zimmerman and Burkholder, 1975) and

suggest that the IgA may be of mucosal origin. However the absence of secretory component with glomerular IgA (Lowance *et al.*, 1973; Dobrin *et al.*, 1975; Whitworth *et al.*, 1976) led Dobrin *et al.* to suggest that either the glomerular IgA is not secretory IgA or it is not derived from the secretory immune system.

The observation that IgA may be the only localising immunoglobulin in a few patients with mesangial proliferative glomerulonephritis suggests that it has an effector rather than a mere secondary, passive role in this immunopathological process (Lowance *et al.*, 1973). However, we also found significant amounts of IgA in cases with membranous, rapidly progressive proliferative and mesangiocapillary glomerulopathies, and it is difficult to implicate IgA as a single or major cause of the glomerular lesions in these cases.

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