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IGA mesangial glomerulonephritis; Significance and pathogenesis of segmental-focal glomerular lesions

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Summary. A review of 430 renal biopsies from patients with various nephropathies processed by light microscopy, immunofluorescence and in part by electron microscopy revealed 82 cases with diffuse mesangial IgA deposition. Sixty-three cases appearing without signs of systemic disease were included in this study. The glomerular changes consisted of mesangial increase (31 cases mild, and 32 cases severe) and segmental-focal glomerular lesions (40 cases). Immunofluorescence revealed granular deposits of immunoglobulins and complement within the mesangium (IgG 9, IgM 25, IgA 63, C3 27, C1q 0) as well as segmentally in the wall of capillary loops (IgG 4/26, IgM 20/26, IgA 0/26, C3 16/26, C1q 7/26). Electron microscopic studies (40 cases) showed electron dense deposits in the mesangial region in all biopsies and deposits either electron dense (11 cases) or radiolucent (26 cases) at various sites along the basement membrane of capillary loops. Comparison between morphological findings and clinical data showed a significant correlation between segmental-focal glomerular lesion on the one hand, and proteinuria ($p < 0.01$), immune deposits along the capillary basement membrane ($p < 0.01$), and the increased mesangium ($p < 0.001$) on the other. Considering the macromolecular mesangial clearing function, the segmental-focal glomerular lesions may be due to newly arrived, infection related immune complexes which may not be cleared promptly by the mesangium, because its clearing function is impaired due to IgA deposition.

Key words: IgA mesangial glomerulonephritis – Segmental-focal glomerular lesions – Mesangial and capillary immune deposits – Mesangial function

Introduction

IgA mesangial glomerulonephritis (IgA GN) is defined by IgA deposits within the glomerular mesangium (Berger 1969) often combined with other

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immunoglobulins and complement. Therefore diagnosis depends exclusively on immunomorphology. The patients present a history of recurrent episodes of macroscopic or microscopic haematuria. The onset of haematuria coincidences with or soon follows an infection of the upper respiratory tract or less frequently other extrarenal infections. Proteinuria of more than 2 g/day is designated as a marker for an unfavourable outcome (Imbasciati et al. 1977; Van der Peet et al. 1977) and the disease tends to recur in grafted kidneys after transplantation (Berger et al. 1975).

Histologically, the patients exhibit a variable increase of mesangial matrix material, often associated with minimal or mild cellular proliferation. In addition, segmental-focal glomerular changes with or without crescent formation are most commonly noted (De Werra et al. 1973; McPhaul 1977). In reports from different countries, the frequency and therefore the evidence for IgA GN differs considerably. Mesangial IgA deposits have been reported as the commonest immunofluorescence finding in adult patients with idiopathic glomerular disease in France (18–25%; Berger 1969; Berger et al. 1980). A high incidence was noted (32%) in Japan (Kawamura 1978) and (33%) in Singapore (Sinniah 1980). Studies from other countries have shown a lower incidence (Zimmermann and Burkholder 1975).

The role of immunological reactions in the pathogenesis of glomerular IgA deposition is not well understood. It was suggested that either circulating IgA antigen-antibody complexes localize in the mesangium or that IgA antibodies are directed against an endogeneous or exogeneous antigen already present in the glomerular mesangium (Lowance et al. 1977).

The pathogenesis of segmental-focal glomerular changes in human IgA GN has not been seriously investigated although these lesions in particular are closely associated with the alterations of renal function. Considering the important role of macromolecular traffic through the glomerulus, increase of mesangial matric and deposition of IgA will considerably influence the mesangial clearing function, as shown experimentally (Keane and Raij 1980). Decreased mesangial transport function restricts the glomerular clearance of newly arrived macromolecules such as immune complexes, resulting in accumulation of such complexes along the glomerular basement membrane. This probably gives rise to segmental-focal glomerular lesions. The aim of this study, whilst not dealing with the pathogenesis of mesangial IgA deposition, is to show that the promotion factors for this disease are based on immune complex mediated inflammatory processes along the capillary loops and are not immediately associated with any IgA complexes circulating in the serum. In order to define the evidence and pathogenesis for segmental-focal glomerular changes and to clarify the possible role of deposits along the capillary walls seen by immunofluorescence (Syré 1980), we studied 63 patients with IgA GN. Clinical data and histological information were correlated with immunohistological findings.

Material and methods

A review of 430 renal biopsies from patients with various glomerular and non glomerular diseases processed between 1977 and 1980 by light microscopy and immunofluorescence showed

82 cases with diffuse mesangial IgA depositions. Nineteen cases were excluded from this study because the biopsy specimens contained less than ten glomeruli (15 cases) or symptoms of systemic diseases were evident (4 cases). Ten of the remaining 63 patients underwent open surgical biopsy; other biopsies were obtained by percutaneous technique. For light microscopy, all specimens were fixed in 8% phosphate buffered formalin (pH 7.4), embedded in Paraplast plus (Sherwood Medicals, St. Louis, MO, USA) and cut into 3 µm thick sections. These sections were stained with haematoxylin-eosin, periodic-acid Schiff (PAS), silver methenamine and acid fuchsin orange G (AFOG; Zollinger and Mihatsch 1978). For all specimens several serial sections were examined and at least ten glomeruli were studied in each case. Increase of mesangial matrix was graded semiquantitatively on a scale of 1+ to 4+ (1+ and 2+, mild; 3+ and 4+, severe), and segmental-focal glomerular lesions were noted.

Immunofluorescence studies were performed on paraffin embedded material according to the method described by Huang (1975). From all biopsy specimens unstained 3 µm thick parallel sections from the same block as used for light microscopy were dewaxed in xylene and rehydrated prior to incubation with 0.1% pronase (Pronase Type VII, Sigma Chem. Comp., St. Louis, MO, USA) in 0.5 M tris/HCL buffer, pH 7.5 for 15 min at 37° C. Sections were transfered into ice cold tris/HCL buffer for 1 hr to stop protease action and then subjected to indirect immunofluorescence according to the method described elsewhere (Denk et al. 1976). In each case the following unlabeled antibodies were used as the first layer: antihuman IgG, IgM, IgA, C3 and C1q, all raised in rabbits (Behring Werke AG., Marburg, FRG). All these sera appeared to be monospecific giving a single strong line against normal human serum or human plasma on immunoelectrophoresis. Fluorescein conjugated antisera against rabbit IgG, raised in goats (Behring Werke AG, Marburg, FRG) were used as second layer after a buffer wash. Thereafter the slides were washed in buffered saline and mounted in buffered glycerol. For examination a Leitz Dialux microscope equipped with Ploem Opak epiillumination with a filter combination 3/3 was used. The intensity of fluorescence was graded from − to 3+ (− negative, 3+ maximal intensity).

Material for electron microscopic studies was available in 40 cases. A small portion of fresh material was fixed immediately in 2.5% cacodylate buffered glutaraldehyde (pH 7.4) postfixed in osmium ferrocyanide solution and embedded in Epon 812. Ultrathin sections were cut on a LKB ultramicrotome, double stained with methanolic uranyl acetate and basic lead citrate and examined on a Zeiss EM 9S electron microscope. Two glomeruli were studied in each biopsy.

The following *clinical findings* with age and sex were included in our evaluation; mode of presentation indicative for biopsy, duration of disease (period between the first renal symptom and renal biopsy), blood pressure (hypertension was defined by a diastolic blood pressure above 95 mm Hg), proteinuria (above 0.5 g/die) (Relman and Levinsky 1971), serum creatinine (mg %). Haematuria was considered to be absent when there were less than 3 red blood cells per high power field, and was graded into microscopic and macroscopic haematuria.

The correlation between the immunofluorescence findings, glomerular changes and the clinical data was tested by chi square test and the exact Fisher test.

Results

Clinical features

Thirteen of the patients were women and 50 were men. The ages ranged from 8–59 years for the men (mean 35.1 ± 12.9 years) and from 16 to 53 years for the women (mean 34.2 ± 11.3 years). Before the renal biopsy was performed, the renal symptoms had been observed for periods of 2 to 1,560 weeks ($\bar{x} = 25$ weeks). Renal function was impaired (serum creatinine more than 1.2 mg%) in 31 patients (49%) and serum creatinine levels above 2.0 mg% occurred in ten male patients (15.8%), nine older than 35 years.

In this group elevated diastolic blood pressure or proteinuria did not occur more often than in the other patients.

Of the 63 patients, 18 suffered from a respiratory tract infection, 7 from non-specific fever, 2 from pneumonia, 2 from periostitis of the jaws, 3 from urinary bladder infections, and one from non-specific colitis in the last three months before renal symptoms occurred or renal biopsy was performed. One patient had liver cirrhosis, and in another case gross haematuria was preceded by CO intoxication.

Morphological features

Light microscopy. The glomerular changes consisted of increased mesangial matrix, segmental-focal lesions and glomerular obsolescence. Minimal to mild diffuse increase of mesangial matrix was observed in 31 cases (Fig. 1a). Mesangial cell proliferation was usually mild or absent. Moderate to severe increase of mesangial matrix (Fig. 1b) was observed in 32 cases mostly in combination with slight to moderate increase of mesangial cells. By silver impregnation marked increase of mesangial matrix exhibited a wire-mesh appearance (Fig. 2e). Closely related to the mesangial basement membrane AFOG positive deposits were frequently encountered (Fig. 1c).

Segmental focal changes in capillary loops consisted of loop sclerosis (28 cases; Fig. 2d), segmental cellular increase (14 cases; Fig. 2a) and adhesions of tuft to the Bowman's capsule (36 cases; Fig. 2c), the latter often associated with either cellular (Fig. 2b) or fibrotic crescents. In four specimens cellular as well as fibrotic crescents occurred in the same biopsy specimen, but in different glomeruli. Sometimes AFOG positive droplets were stainable along the capillary walls. They were quite distinct from resorption droplets in epithelial cells.

Glomerular obsolescence was frequently observed (in 33 cases more than 10% of glomeruli were sclerosed), being both of the collapse type as well as the glomerulonephritic type (Zollinger and Mihatsch 1978). Thickening of small arteries was seen only in 18 cases without significant correlation to glomerular obsolescence or segmental focal lesions. Interstitial changes were observed in 21 specimens. Fibrosis and small infiltrates of mononuclear cells were found adjacent to changes in Bowman's capsule which resulted from tuft adhesions or crescents. Fibrosis was also noted in areas of tubular atrophy with or without mononuclear cell infiltration, the latter occurring sometimes periveneously.

Immunofluorescence

All cases showed a granular mesangial deposition of IgA. IgA distribution was diffuse and all glomeruli in all cases were involved in the same manner (Fig. 3a, b) except for collapsed glomeruli. The intensity of fluorescence was estimated at 2+ to 3+ in the majority of cases. Deposition of IgA was more often combined with IgM than IgG, and the third complement component was present in 27 specimens (Table 1). C1q was never observed

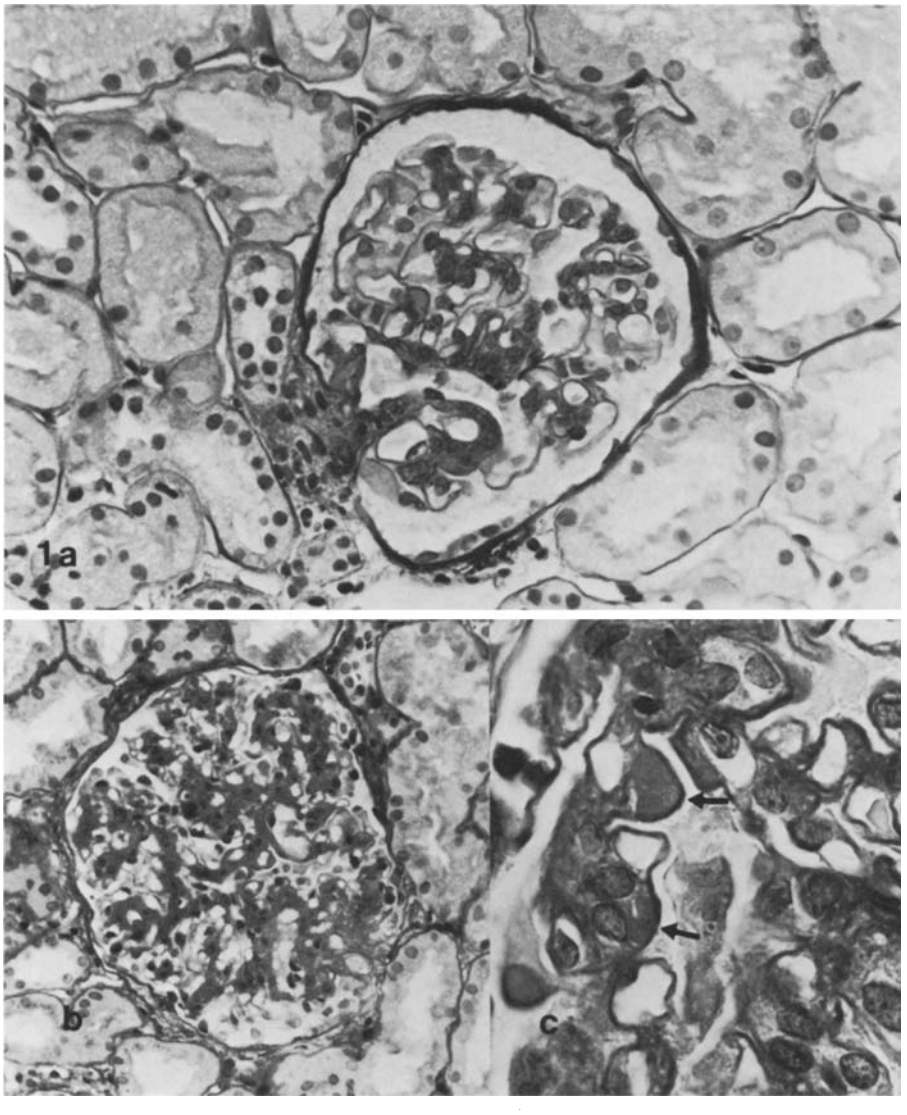

Fig. 1a–c. Glomerular mesangial lesions in IgA GN. **a** Mild increased mesangium (PAS ×40). **b** Severe increased mesangium with moderate cell proliferation (AFOG ×25). **c** AFOG positive deposits within the mesangium (↗) (AFOG ×100)

in mesangial areas. In addition to these mesangial deposits, granular fluorescence occurred at some capillary loops mostly at the epithelial side of the basement membrane in 26 cases (Fig. 3c, d). These peripheral deposits consisted of IgG, IgM, C3 and C1q whereas IgA was never demonstrable at this site. The distribution was segmental and focal and a variable number of glomeruli was involved.

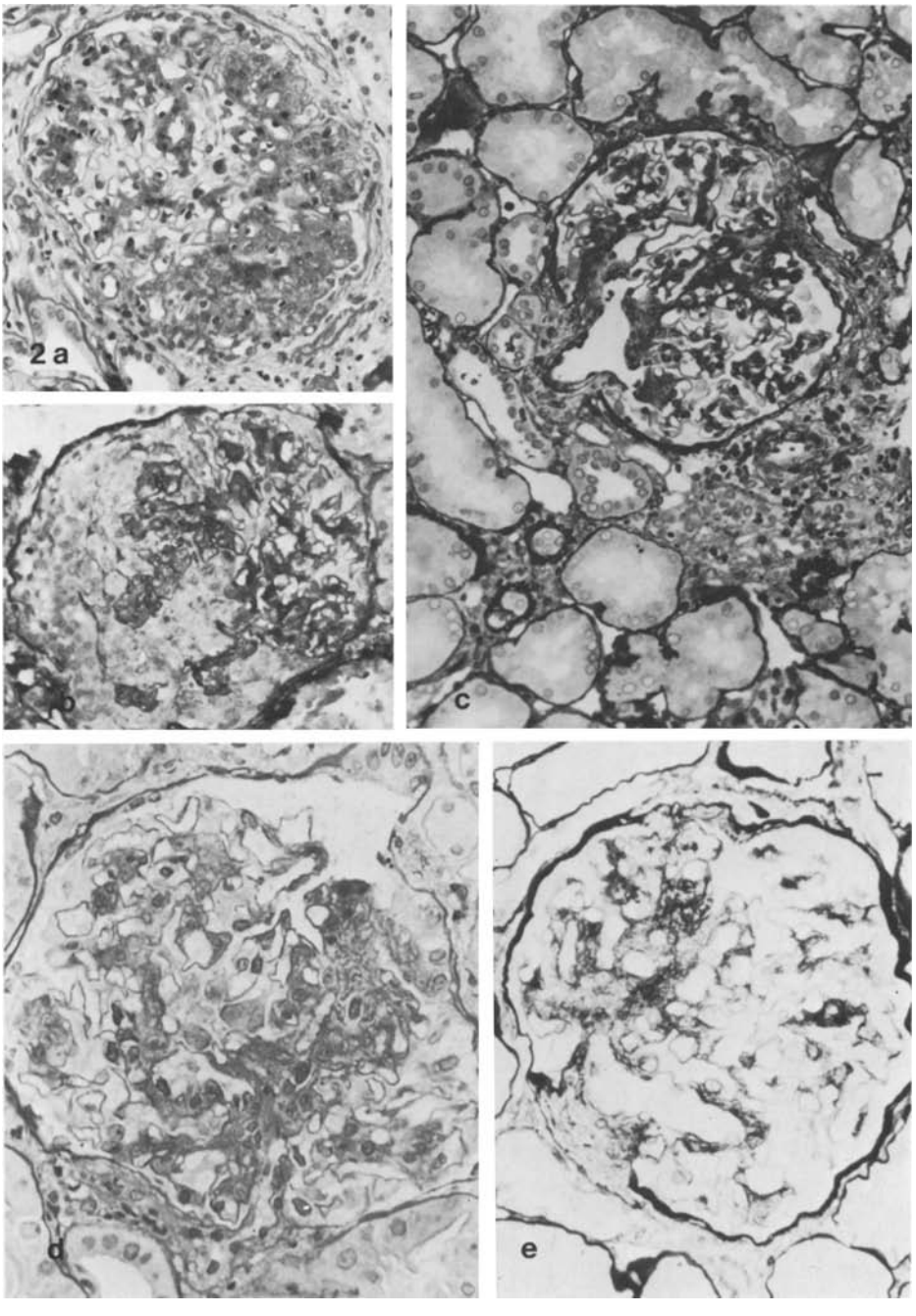

Fig. 2a–e. Segmental glomerular lesions in IgA GN. **a** Marked segmental cellular proliferation. (PAS ×25). **b** Cellular crescent and collaps of some capillary loops. (AFOG ×25). **c** Adhesions between capillary loops and Bowman's capsule. (Silver methenamine ×25). **d** Loop sclerosis with a partial crescent. (PAS ×40). **e** Wire-mesh appearance of mesangial matrix. (Silver methenamine ×40)

Table 1. Immunofluorescence findings in IgA mesangial GN ($n=63$)

Mesangial deposits	n	Capillary deposits								
		IgM	IgM + C3	IgM + C3 + C1q	C3	IgG + IgM + C3	C3 + C1q	IgG	IgG + IgM	IgM + C1q
IgA	25	2	3	/	3	1	1	/	/	/
IgA + IgM + C3	13	2	/	1	/	/	/	/	/	1
IgA + C3	8	2	1	1	/	/	/	/	1	/
IgA + IgM	8	1	/	1	/	/	1	1	/	/
IgA + IgM + IgG + C3	4	/	/	/	/	/	/	/	/	/
IgA + IgG	3	1	/	/	/	1	/	/	/	/
IgA + IgG + C3	2	/	/	1	/	/	/	/	/	/
Total	63	8	4	4	3	2	2	1	1	1

Electron microscopy

Electron microscopic studies showed an increased mesangial matrix and electron dense deposits usually beneath the basement membrane and less frequently within the mesangial matrix. These deposits varied in size from tiny granules to large deposits protruding the mesangial basement membrane into the urinary space (Fig. 4f). Electron dense deposits were also encountered at various positions along the basement membrane of capillary loops far from the mesangial area. These were located in 9 out of 40 cases in the lamina rara externa (Fig. 4b, c) and one time within the lamina densa and the lamina rara interna respectively. Mostly these deposits were small, but sometimes large hump-like deposits were observed (Fig. 4a), however only a few capillary loops of a glomerulus were affected. Furthermore, 26 out of 40 specimens showed a variable thickening of the basement membrane with radiolucent areas containing minute electron dense granules and thread-like structures (Fig. 4d, e). These changes resemble dissolved deposits as seen in other immune complex mediated glomerulonephritis (Zollinger and Mihatsch 1978).

Clinicopathologic correlations

Correlation of clinical data and morphological findings are shown in Table 2. Mesangial and capillary deposition of immunoglobulins and complement was present in 26 patients. The capillary immunoglobulin and complement deposition correlate with the segmental glomerular abnormalities ($p<0.01$), the proteinuria ($p<0.001$) and interstitial fibrosis ($p<0.05$). Interstitial fibrosis occurred more often in the group of patients older than 35 years in combination with elevated diastolic blood pressure ($p<0.01$), reduced renal function ($p<0.05$), proteinuria ($p<0.05$) and segmental glomerular changes. Segmental-focal glomerular lesions were found in 40 patients mainly in the group younger than 35 years ($p<0.05$). A further significant

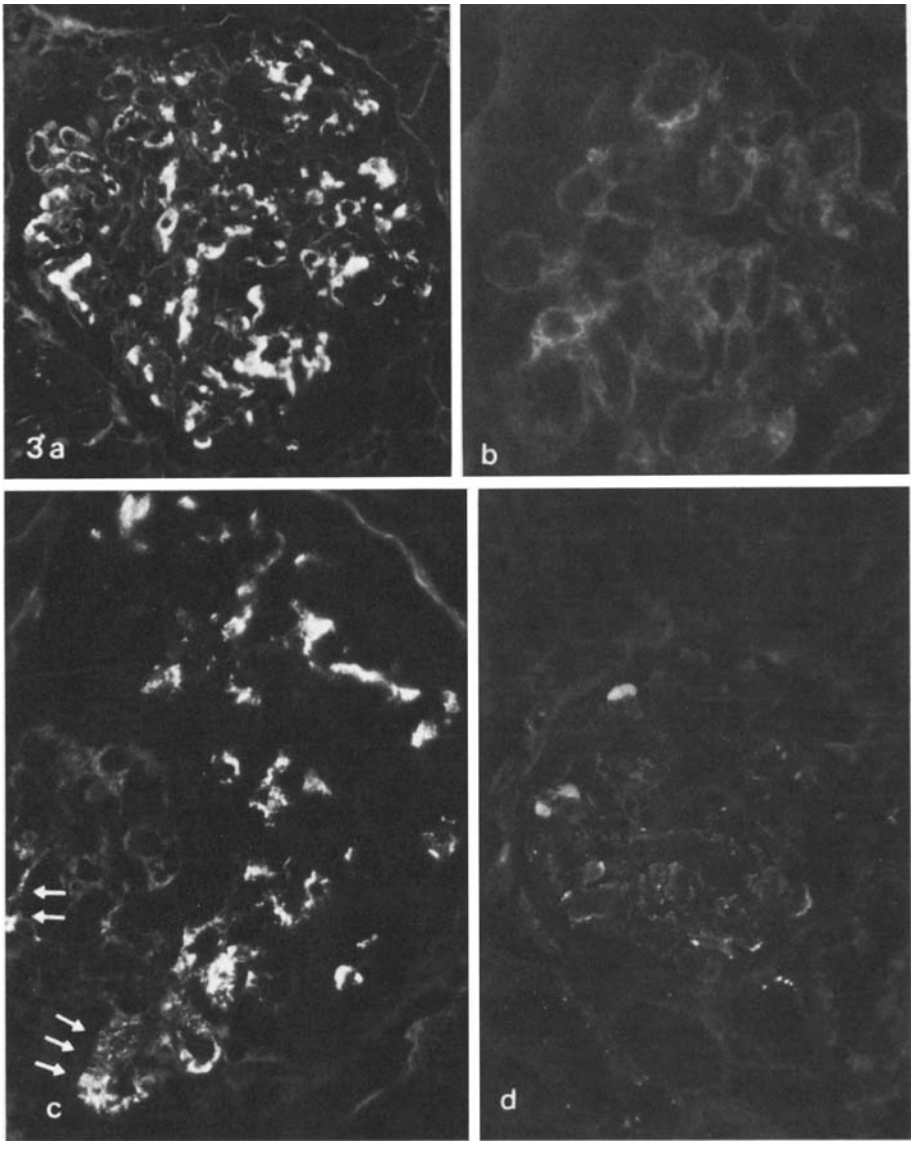

Fig. 3a–d. Immunofluorescence patterns in IgA GN. **a** Heavy mesangial deposits (Anti-IgA ×25). **b** Tiny mesangial deposits (Anti-IgA ×63). **c** Mesangial and capillary (↗) deposits (Anti-IgM ×50). **d** Capillary deposits (Anti-C1q ×25)

correlation was found between segmental-focal lesions and proteinuria ($p < 0.01$) and the degree of mesangial increase ($p < 0.001$). The amount of protein in the urine was significantly higher in patients with glomerular and interstitial changes than in those with minor glomerular abnormalities. Elevated serum creatinine levels were found in patients older than 35 years ($p < 0.01$)

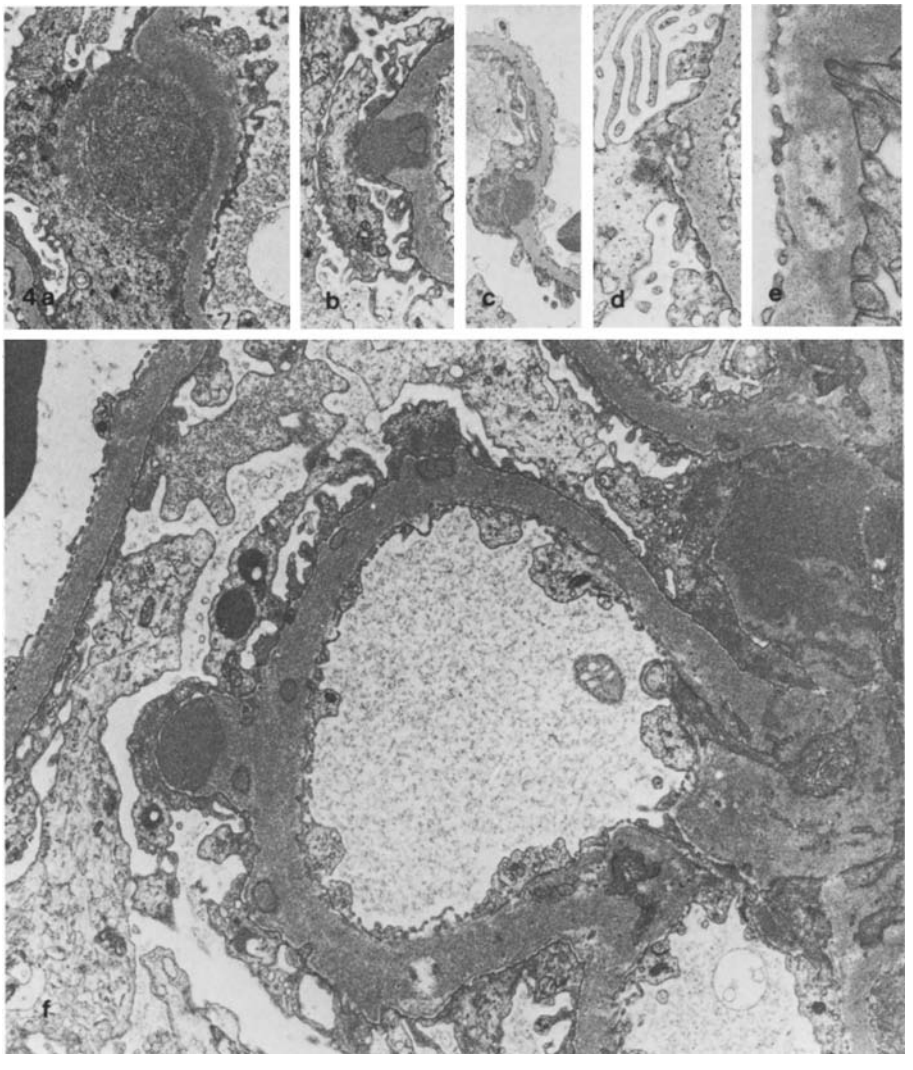

Fig. 4a–f. Electron micrographs from IgA GN. **a** Hump-like deposit (×8,400). **b** Epimembraneous deposit (×8,100). **c** Epimembraneous deposit with spike formation (×7,500). **d** Thread-like structures at the subepithelial side of basement membrane (×8,100). **e** Intramembraneous radiolucent area (×27,000). **f** Mesangial deposits protruding into the urinary space and various deposits along the capillary basement membrane (×8,400)

and in combination with raised diastolic blood pressure ($p<0.01$). In 21 specimens more than 30% of all glomeruli exhibited segmental focal lesions and 15 patients of this group presented impaired renal function ($p<0.05$). No relationship was detected between sex and duration of symptoms prior to biopsy on the one hand, between either of these and serum creatinine levels, proteinuria, haematuria, elevated diastolic blood pressure or morphological changes on the other hand.

Table 2

	No. of Patients	Age 35 years	Duration of disease prior to biopsy $\bar{x}$ [a]
Mesangial and capillary deposits	26	12	11
Interstitial fibrosis	21	15*	10
Segmental-focal glomerular lesions	40	15*	20
Proteinuria >0.5 g/die	19	9	8
Serum creatinine >1.2 mg%	31	21**	17
Total	63	31	31

* $p<0.05$
** $p<0.01$
*** $p<0.001$

[a] $\bar{x}$ = median observation period = 25 weeks

Discussion

According to other reports (McCoy et al. 1974; Clarkson et al. 1977), IgA and IgM represented the most common immunoglobulins within the mesangium. This is in contrast to others (Berger 1969; Katz et al. 1976) which state a more frequent combination of IgA and IgG. As noted by others, the complement component C3 could be demonstrated exclusively in the mesangium and never the earlier complement components, which would seem to indicate activation of complement via the alternate pathway (Zimmermann and Burkholder 1975; Hood et al. 1981). However, in some reports (Mc Coy et al. 1974; Zimmermann and Burkholder 1975) the combination of IgA and C3 within the mesangium was found more frequently. We cannot exclude that during paraffin embedding procedures a part of the complement component C3 was destroyed.

A short time after the initial report of IgA GN by Berger (1969) it was observed that some of the patients developed decreased renal function (De Werra et al. 1973; Berger et al. 1980) and that prognosis of this disease becomes more unfavorable with severity of proteinuria (Van der Peet et al. 1977; Hood et al. 1981). Along with others (Imbasciati et al. 1977; Michalk et al. 1980), we were able to show a close correlation between segmental-focal glomerular lesions and proteinuria. Reduced renal function appeared much more often in cases where more than one third of all glomeruli were affected by segmental-focal lesions. However, the impaired renal function is independent of duration of renal symptoms leading to biopsy and is not sex specific in our series, although there is a strong predominance of male patients.

Segmental-focal glomerular lesions consisting of cell proliferation, collapse and sclerosis of individual capillary loops and of adhesions of the glomerular tuft with the Bowman's capsule (Fig. 2) have been frequently described in detail (McPhaul 1977; De Werra et al. 1973), but without consideration of their pathogenesis. For several reasons, IgA in aggregated

Diastolic blood pressure > 95 mm Hg	Serum-creatinine >1.2 mg%	Hematuria	Protein-uria >0.5 g/die	Increase of mesangium	Segmental-focal glomerular lesions	Inter-stitial fibrosis
8	15	20	14***	19**	23**	13*
12**	15*	15	10*	16**	17*	–
14	21	33	17**	27***	–	17*
7	10	14	–	14*	17**	10*
16**	–	24	10	19	21	15*
22	31	52	19	32	40	21

form or as immune complex does not appear to be directly involved in the development of capillary lesions. Firstly, immunofluorescence investigations show IgA exclusively within the mesangial region (Table 1) only occasionally extending to the subendothelial space adjacent to the mesangium. In addition in contrast to other types of immune complex mediated glomerulonephritis IgA can not be demonstrated along the capillary basement membrane. Secondly, IgA fails to activate complement by the classical pathway, and indications for pathway activation of complement are absent within the capillary loops as opposed to the mesangium.

However, immunoglobulin and complement deposition in the wall of individual capillary loops can be demonstrated (Fig. 3). The composition of such capillary deposits show marked differences to the mesangial immunofluorescence pattern. In addition to IgG, IgM and C3, C1q is also present here, whereas IgA deposits are absent. The composition of capillary deposits is similar to that of immune complexes of other types of glomerulonephritis.

Further evidence for the immune complex nature of these capillary deposits is given by electron microscopy. The electron dense deposits along and within the capillary basement membrane (Fig. 4) lack a direct junction with the mesangium. Some appear humplike, some resemble deposits characteristic for epimembraneous glomerulonephritis, and these lie within the lamina rare externa of the basement membrane partially or completely surrounded by basement membrane material. Furthermore, all stages of dissolution of deposits can be seen such as in deposits of other immune complex mediated glomerulonephritis (Zollinger and Mihatsch 1978).

If we assume that these capillary deposits represent immune complexes the importance of circulating immune complexes that play an essential pathogenetic role in the development of several types of human glomerulonephritis becomes evident, especially considering the common occurrence of complexes in infections. As pointed out by others (McCoy et al. 1974) and shown in our study, infections, especially of the respiratory tract occur frequently in patients with IgA GN. These infections are often associated with simultaneous or subsequent haematuria (Zimmermann and Burkholder 1975; De Werra et al. 1973). However, other diseases than infections can give rise to circulating immune complexes as recently demonstrated in pa-

tients with alcoholic liver disease (Penner et al. 1978) and in patients with hepatic cirrhosis (Woodrooffe et al. 1980).

Our immunofluorescence and ultrastructural studies seem to indicate an immune complex origin for the development of segmental-focal lesions, but no evidence of a direct IgA involvement. In contrast, there is some evidence for an indirect relationship between mesangial IgA deposits and segmental-focal lesions, namely the significant correlation between segmental-focal lesions and the enlarged mesangium.

Recently much attention has been given to a mesangial role for the transport of high molecular weight substances. It seems that high molecular weight substances which cannot permeate the capillary basement membrane pass via the subendothelial space into the mesangial region where they may be either phagocytosed or transported to the renal interstitium. Therefore is seems possible that alterations of mesangial structures e.g. through deposition of other high molecular weight substances disturb the mesangial transport mechanism, as shown recently by Keane (1980).

IgA accumulation within the mesangium can be attributed a similar effect upon the mesangial clearing function, and it is reasonable to hypothesize that in IgA GN two different closely related mechanisms take place. The first consists of mesangial deposition of IgA very probably resulting in a decreased mesangial clearance. The cause of this deposition has not yet been clarified. The second mechanism depends on the reduced macromolecular mesangial clearing function. Small amounts of newly arrived, infection related immune complexes cannot be promptly transported to the mesangial region and accumulate along the glomerular basement membrane. They are now able to display their destructive capacity by activating complement. The presence of C1q in capillary walls implies complement activation via the classical way.

Since fresh and old loop lesions are sometimes present in the same biopsy specimen, the accumulation of immune complexes proceeds in batches as also noted in the haematuria following infection. The spread of inflammatory process from the capillary to the interstitium with simultaneous destruction of Bowman's capsule may explain the described significant correlation between segmental-focal glomerular lesions and interstitial changes. Both have a close relation with reduced renal function and therefore must be seen as associated with an unfavourable outcome of this disease.

Nevertheless there are some cases of IgA GN which last for many years without morphological or functional changes, but with recurring haematuria and infections. The cause of this phenomenon can be seen either in the absence of infection related immune complexes or in the amount of deposited IgA within the mesangial region. Smaller amounts of IgA decrease the mesangial clearing function insufficiently to allow immune complexes to accumulate in greater amounts at the glomerular capillary walls. However, it should be mentioned that isolated deposition of IgM within the mesangium can produce similar effects, as recently demonstrated (Bhasin et al. 1978).

If infection related circulating immune complexes have a significant role in the development of segmental-focal glomerular lesions in IgA GN it becomes evident that infections in patients with this nephropathy must be combated at an early stage to prevent or stop decreasement of renal function, as corroborated by Beaufils et al. (1977), and Lagrue et al. (1981).

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