PAPERS AND ORIGINALS

Isolated Glomerulonephritis with Mesangial IgA Deposits

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Summary

Mesangial deposits of IgA, occurring in the absence of systemic disease known to be associated with nephritis, were detected by immunofluorescence microscopy in renal biopsy specimens from 25 patients (4% of 630 specimens studied). Associated deposits of C3 were always present, usually with IgG, but IgM deposits were less common and C1q was never seen. On light microscopy most of the biopsy specimens showed mesangial or focal nuclear proliferation though some were normal.

Fifteen of the 25 patients presented with macroscopic haematuria, which was usually recurrent and preceded by a sore throat, whereas the remaining, and usually older, patients presented with persistent proteinuria and were more likely to have impaired renal function.

This incidence of "mesangial IgA disease" is less than that reported by French workers. There was a significantly high incidence of familial renal disease among these patients. No abnormalities of serum complement or IgA concentration were found.

Introduction

Immunofluorescent staining of renal biopsy specimens from patients with glomerulonephritis shows depostis of immunoglobulin and complement in most cases (except in patients with steroid-sensitive nephrotic syndrome). Usually the deposits are of IgG and C3, sometimes with IgM. Deposits of IgA are seen less commonly but are found within the capillary wall in the nephritis of systemic lupus erythematosus[1] and less frequently in other types of proliferative, and occasionally membranous, nephritis.[2]

Berger first drew attention to the association between IgA deposits in the mesangium (often with accompanying deposits of IgG and C3) and "idiopathic" focal proliferative nephritis and the clinical syndrome of recurrent macroscopic haematuria[1 3]; mesangial IgA deposits are also usually found in the nephritis of Henoch-Schönlein purpura.[1] Mesangial IgA deposits have since been reported as the commonest immunofluorescent finding accompanying "idiopathic" focal proliferative glomerulonephritis in two other large French series.[4 5] The terms "Berger's disease" and "mesangial IgA disease" are often applied to this condition, though it is not yet clear whether it is a single disease entity.[6]

Mesangial IgA deposits are less common in our experience than in the French series, occurring in only about 4% of renal biopsy specimens studied by immunofluorescence over four years. We describe here the characteristics of 25 patients with glomerular mesangial IgA deposits without systemic disease and discuss whether they suffer from a distinctive disease entity.

Patients

Immunofluorescence showed that 16 out of 400 specimens obtained for biopsy at Hammersmith Hospital in 1970-4 and nine out of 230 biopsy specimens obtained at Charing Cross Hospital in 1971-4 had IgA deposits, though the patients from whom the specimens were taken had no systemic disease (patients with Henoch-Schönlein purpura were excluded from this study). All except two of these patients were followed since renal biopsy. Clinical details of the 25 patients are shown in table I. Fifteen patients (cases 1-15) were mostly young men who presented with painless macroscopic haematuria, which was recurrent in all but three cases. The episodes of haematuria usually lasted one to three days, and were preceded in all but one patient (case 14) by sore throat and malaise for 24-48 hours; in three patients heavy exercise seemed to precipitate haematuria. One patient (case 14) had persistent macroscopic haematuria for one month and his renal function deteriorated rapidly over one year. Proteinuria was not heavy in these patients, and renal function remained normal

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except in three patients: in cases 8 and 14 terminal renal failure developed two years after presentation (the patient in case 8 received a cadaveric renal transplant), and in case 10 renal function was mildly impaired. Only these three patients and one other in this group were hypertensive.

The other 10 patients (cases 16-25) had no history of macroscopic haematuria and presented with persistent proteinuria of 1-5 g/24 hour and microscopic haematuria or, in one patient (case 23), nephrotic syndrome. These patients tended to be older at presentation and all but two (cases 11 and 24) were hypertensive. Renal function was mildly impaired in four and severely impaired in two of these 10 patients (table I).

TABLE I—*Clinical Details and Plasma Creatinine Levels at Time of Writing of 25 Patients with Mesangial IgA Deposits*

Case No.	Age at Presentation and Sex	Clinical Syndrome*	Plasma Creatinine (μmol/l)	Diastolic Blood Pressure > 90 mm Hg	Duration of Follow-up (Years)
1	8 M.	M.H., recurrent	97·2	–	2½
2	16 M.	M.H., recurrent	61·9	–	1
3	11 M.	M.H., recurrent	70·7	–	7
4	8 M.	M.H., recurrent	53·0	–	3
5	27 M.	M.H., recurrent	79·6	–	2
6	29 M.	M.H., recurrent	106·1	+	6
7	17 M.	M.H., single episode	106·1	–	—
8	27 M.	M.H., recurrent	Transplanted	+	3
9	13 M.	M.H., recurrent	79·6	–	4
10	13 M.	M.H., single episode	176·8	+	15
11	26 F.	M.H., recurrent	61·9	–	7
12	31 F.	M.H., recurrent	114·9	–	1
13	28 M.	M.H., recurrent	88·4	–	10
14	17 M.	M.H., persistent	On haemodialysis	+	1½
15	60 M.	M.H., recurrent	123·8	–	3
16	25 F.	Proteinuria	114·9	+	1
17	41 M.	Proteinuria	618·8	+	4
18	30 M.	Proteinuria	150·3	–	1
19	50 M.	Chronic renal failure	442·0	+	1
20	45 M.	Proteinuria	132·6	+	3
21	22 F.	Proteinuria	61·9	+	7
22	50 F.	Proteinuria	123·8	+	7
23	14 F.	Nephrotic syndrome	88·4	+	1
24	52 M.	Proteinuria	141·4	–	1
25	40 M.	Proteinuria	132·6	+	3

*M.H. = Macroscopic haematuria.

Conversion: SI to Traditional Units
Creatinine: 1 μmol/l ≈ 0·0113 mg/100 ml.

Of the 25 patients one (case 17) had ankylosing spondylitis and three (cases 9, 19, and 24) had psoriasis; one patient (case 10) had Australia antigenaemia and slightly abnormal liver function but no other patient had any coexistent illness. Five patients had a family history of renal disease. Two (cases 1 and 18) had a parent who had died of chronic renal failure, and the father of one (case 11) had hypertension and haematuria. The father of another patient (case 4) was under our care with chronic renal failure and this family had a striking history of haematuria and renal failure, without deafness, affecting males in the paternal line. The brother of one patient (case 6) was also under our care with impaired renal function and had macroscopic haematuria. None of these affected relatives had a renal biopsy. Apart from one patient (case 14) who was given a course of heparin, cyclophosphamide, and corcicosteroids, no patient received any treatment other than antihypertensive drugs.

Methods

Percutaneous needle biopsy specimens were prepared for light microscopy, immunofluorescence microscopy, and electronmicroscopy.

Light Microscopy.—Paraffin sections fixed in Dubosq-Brazil (Charing Cross cases) or formal mercury (Hammersmith cases) were routinely stained by haematoxylin and eosin, periodic acid-Schiff, Martius scarlet blue, Jones's silver impregnation for basement membranes, Congo red, Van Gieson and Moore's (Charing Cross cases) or Miller's (Hammersmith cases) elastic stains, and, in the Charing Cross cases, Wilder's reticulin and thioflavine-T.

Cryostat Sections.—Sections were incubated individually for 30 minutes with antisera monospecific for IgA, IgG, IgM, C3, fibrinogen, and C1q. All FITC-labelled antisera (Hoechst antisera in the Charing Cross cases and Wellcome in the Hammersmith cases) were tested for monospecificity by immunoelectrophoresis against normal human serum and, in addition in the Charing Cross cases, against specific myeloma sera (A, G, and M). Specific blocking with non-conjugated antisera always gave absent or grossly diminished fluorescence. Each investigation included an unstained section.

Complement components were measured by single radial immunodiffusion using specific antisera. The patients' sera were tested for their capacity to activate the complement system in the cold by incubating with equal volumes of normal human sera at 4°C for six hours and subsequently detecting C3 conversion by crossed immunoelectrophoresis. Serum concentrations of immunoglobulins were measured by single radial immunodiffusion using commercial antisera.

Results

RENAL BIOPSIES

The details of biopsy findings are given in table II. Two specimens were normal on light microscopy, but most (18 out of 24) showed varying degrees of mesangial change, from mesangial matrix thickening to nuclear proliferation in the mesangial region; there was focal proliferation in only a few specimens. Glomerular scarring was seen in patients with more definite impairment of renal function. There was no obvious difference between biopsy specimens from patients with macroscopic haematuria and from those without, though the changes seen tended to be more advanced in the latter group.

Immunofluorescent studies showed strongly positive mesangial IgA and C3 deposits in all cases. In three specimens IgA was the only immunoglobulin detected but mesangial deposits of IgG were present in 17 out of 23 specimens. IgM was detected in 10 of 24 specimens, but the staining was usually weak and in five of the 10 present only in capillary loops. C1q was not detected in any of the 15 specimens studied. Fibrin was present in 19 out of 24 specimens but the staining was usually weak.

OTHER INVESTIGATIONS

All patients had normal antistreptolysin O titres and were negative for antinuclear antibodies. Serum concentrations of IgG, IgM, and IgA were normal in all cases in which they were measured (19) except for one case in which the serum IgA was 5·2 g/l (normal 1·25-5·0 g/l). Serum C3 concentrations were normal in all of 21 patients and serum total haemolytic complement was normal in all of 12 patients. Serum factor B, properdin, and C4 concentrations were normal in all but one of 19 patients tested: in case 1 there was a low C4. Fresh serum from 13 patients was examined for the generation of C3 converting activity at 4°C, but no such activity was detected. HL-A typing was carried out in 14 patients but no antigen occurred with higher than expected frequency.

Discussion

Several points of interest emerged from this study: firstly, the two types of presentation in patients with mesangial IgA deposits; secondly, our failure to find the high incidence of this abnormality reported by French nephrologists; thirdly, an unduly high incidence of familial renal disease; and, lastly, our failure to detect the abnormalities of serum complement or IgA concentrations reported by others.

Our patients with mesangial IgA deposits fell into two groups. There seems to be a group with a clinicopathological entity of macroscopic haematuria, usually recurrent and often preceded by sore throat, with mesangial or focal nuclear proliferation, increase in mesangial matrix, and mesangial IgA deposits (cases 1-15). Most have normal renal function though two patients developed terminal renal failure. The second group (cases 16-25) consists usually of older patients who present with proteinuria and are likely to have impaired renal function and high blood pressure.

The frequency of mesangial IgA deposits that we found accords more with that reported in series from the U.S.A.[2 7 8] than with the high frequency found in the French series [1 3-5 9].

TABLE II—*Details of Renal Biopsy Specimens in 25 Patients with Mesangial IgA Deposits*

Case No.	Light Microscopy		Immunofluorescence Microscopy						
	No. of Glomeruli	Comments	No. of Glomeruli	IgA	IgG	IgM	C3	C1q	Fibrin
1	—	Medulla only	5	++	++	−	++	−	−
2	8	Mesangial nuclear proliferation and matrix thickening	6	++	N.D.	−	+	−	±
3	12	Focal nuclear proliferation	4	++	+	N.D.	++	−	±
4	12	Mesangial nuclear proliferation in all	20	++	+	±	+	−	+
5	20	Normal	14	++	−	±	++	−	−
6	18	Mesangial nuclear proliferation	4	++	++	−	++	−	−
7	25	Mesangial matrix thickening; crescents in 2 glomeruli	4	++	−	−	+	−	+
8	10	5 Hyalinized; 5 focal proliferation; 1 crescent	9	++	+	−	++	−	±
9	2	Normal	2	++	−	+	++	−	−
10	10	Mesangial nuclear proliferation; some hyalinization	4	++	+	+	+	−	±
11	43	Slight focal and segmental nuclear proliferation; 7 glomeruli sclerosed	18	++	±	−	+	N.D.	±
12	9	Segmental increase in mesangial matrix in several glomeruli; focal and segmental nuclear proliferation in 1; 2 adhesions with associated fibroblastic capsular proliferation	23	++	+	−	+	N.D.	±
13	18	Focal and segmental increase in mesangial matrix; nuclear proliferation in region of 2 adhesions; 2 glomeruli sclerosed	2	++	−	−	++	N.D.	±
14	30	Diffuse mesangial matrix increase; total or segmental nuclear proliferation; adhesions and fibrous crescents	15	++	±	±	++	N.D.	+
15	37	Focal and segmental increase in mesangial matrix and nuclear proliferation	Not known	++	−	−	+	N.D.	±
16	15	Mesangial nuclear proliferation and matrix thickening	8	+	+	−	+	−	±
17	4	Focal proliferation and adhesions	2	++	N.D.	−	++	N.D.	N.D.
18	20	Mesangial nuclear proliferation and matrix thickening	7	++	++	−	++	−	±
19	10	6 sclerosed; 4 mesangial nuclear proliferation	Not known	++	−	±	+	−	+
20	25	Mesangial nuclear proliferation and matrix thickening	14	++	++	±	++	−	−
21	16	Mesangial nuclear proliferation with some focal scarring	7	++	+	±	±	−	+
22	14	Focal and segmental mesangial matrix increase; 1 adhesion; 6 glomeruli sclerosed	2	++	+	±	+	N.D.	±
23	32	No definite abnormality	14	++	±	−	++	N.D.	+
24	16	Focal and segmental increase in mesangial matrix; 2 adhesions present; 1 glomerulus sclerosed	6	++	+	±	±	N.D.	±
25	25	Focal and segmental mesangial matrix increase; 3 glomeruli sclerosed	6	++	+	−	++	N.D.	+

++ = Strongly positive. + = Positive. ± = Weakly positive. − = Negative. N.D. = Not done.

We found associated mesangial IgG deposits less often than the French workers, and IgM deposits were uncommon, in contrast to two other recent studies.[2 10] We have previously reported the presence of deposits of factor B and properdin with C3 in the mesangium in some of these patients,[11] which, with the absence of C1q deposits, suggests that any C3 present is being fixed via the alternative pathway of complement activation. This absence of C1q is in distinct contrast to a recent Dutch study, in which mesangial IgA deposits were invariably associated with C1q,[10] but it accords with the findings in a recent American series.[8] No other series has been reported from this country.

Five of our 25 patients had a family member with renal disease, which in three cases manifested with macroscopic haematuria and in one case affected several members of the same family. An unduly high-incidence of familial renal disease has been noted in patients with recurrent haematuria by other workers. Thus, seven out of 17 children,[12] three out of 31 patients,[13] and two out of 17 children[14] had a family member with overt renal disease, and in the last series 10 other relatives were found to have previously undetected microscopic haematuria. No immunofluorescence studies were performed in any of these series, which selected patients with recurrent haematuria rather than with mesangial IgA deposits. This suggests that a heritable factor contributes to this type of renal disease; HL-A typing of 14 of our 25 patients (including those with a family history), however did not show a disease-associated antigen, though the sample was small.

Serum concentrations of complement were normal, and cold activation of the complement system, as has been reported in one patient with mesangial IgA deposits and haematuria (the postulated activator being the patient's IgA),[15] was not detected in any of the patients studied. Unlike some French workers,[16] we saw no tendency towards abnormally high serum IgA concentrations in our patients.

The mechanism of mesangial IgA deposition in these patients is not clear. Assuming that the IgA is of pathogenetic significance it is usually suggested that either circulating IgA antibody-antigen complexes localize in the mesangium or IgA antibody is directed against an endogenous or exogenous (possibly viral in view of the preceding pharyngitis) antigen already in the mesangium. It may be relevant to the former possibility that mice with chronic lymphocytic choriomeningitis virus infection show heavy IgA deposits.[17] Nevertheless, there is some experimental evidence to support the latter concept: Mauer *et al.*[18] have produced a model in which nephritis results from interaction of circulating antibody with exogenous antigen localized in the mesangium.

The antecedent pharyngitis also suggests that the IgA may be of mucosal origin, but despite one positive preliminary report[2] several investigators have failed to show IgA secretory piece in

the mesangium in these cases.[7 8 19] Aggregated IgA can fix complement by the alternative pathway,[20] and it is possible that IgA immune complexes are responsible for the complement fixation in these patients, particularly as IgA is sometimes the only immunoglobulin present, as in three of our cases. Mesangial IgA deposits may recur in patients who have received renal transplants,[21] which further suggests some humoral mechanism (we did not perform a biopsy on our single transplanted kidney).

In making comparisons with other series one must not only consider the French and American studies, in which, as in our study, patients were selected for having mesangial IgA deposits, but also the numerous reports[6 22] over the past 50 years[23] that have discussed children and adults with the syndrome of recurrent macroscopic haematuria[10 12 13 24-30]. These emphasize the usually associated focal nephritis and generally good prognosis, but only the more recent reports give details of immunofluorescent studies.[10 30]

It is apparent from the literature and from our own experience that there is no consistent relation between recurrent haematuria, mesangial or focal proliferative nephritis, and mesangial IgA deposits. Recurrent haematuria is the presenting feature of other histological types of nephritis, may also occur in patients with entirely normal renal biopsy specimens, and is not always associated with mesangial IgA deposits. Moreover, in about half the cases in which mesangial IgA deposits are found they are not associated with recurrent haematuria. Finally, in our experience, mesangial IgA deposits are not the commonest finding in "idiopathic" focal or mesangial proliferative nephritis, focally distributed IgG, IgM, and C3 deposits being commoner. We and others have also found IgA deposits outside the mesangium in occasional cases of proliferative and membranous nephritis.[2]

Thus, though a subgroup of patients with mesangial IgA deposits are distinguished by having recurrent macroscopic haematuria, when considered as a whole patients with mesangial IgA deposits do not seem to present a completely uniform picture. Until more is known about the mechanisms resulting in IgA deposition in the glomerulus and the precise pathogenetic role of IgA in these patients it seems debatable whether the use of terms such as "mesangial IgA disease" and "IgA nephropathy" is warranted.

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Treatment of Superficial Thrombophlebitis: A Randomized, Double-blind Trial of Heparinoid Cream*

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Summary

In a prospective, double-blind, randomized trial the efficacy of a heparinoid in ointment form was assessed in treating superficial thrombophlebitis developing after continuous intravenous infusion. One hundred surgical patients were studied, and clinical examination and the iodine-125-labelled fibrinogen test used to assess the results. The mean time required for the relief of local symptoms and signs and the rate of local decline in radioactivity differed significantly between patients receiving the heparinoid cream and those receiving the placebo.

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Introduction

Superficial thrombophlebitis remains a common complication of continuous intravenous infusion,[1 2] despite the use of plastic infusion sets and various types of pre-sterilized plastic cannulae. Though the condition is rarely responsible for serious illness,[3] it often causes considerable pain and discomfort at the site of the infusion. Commonly used treatments may limit extension of the process and relieve pain but they do not remove the thrombus; this occurs by spontaneous fibrinolysis. Heparinoid cream