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Mesangial IgG Glomerulonephritis: A Distinct Type of Primary Glomerulonephritis

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Abstract. Fourteen cases of mesangial IgG glomerulonephritis characterized by exclusive or predominant mesangial IgG deposits are reported. The median age at onset was 19 yr (range, 13 to 47 yr). No patient exhibited evidence of systemic lupus erythematous or other systemic diseases. Proteinuria was present in all cases (median, 2.4 g/d; range, 1 to 13 g/d), microscopic hematuria in 12 cases, and macroscopic hematuria in two cases. Five patients were hypertensive at the time of referral. In all cases, renal biopsies revealed mesangial IgG deposits and varying degrees of mesangial matrix expansion, in the absence of significant mesangial cell proliferation. Complement component (mainly C3) deposits were present in virtually all cases. Subepithelial deposits were also noted in nine cases. IgG deposits were polyclonal and consisted mainly of IgG1 and IgG3 subclasses. In electron-microscopic analyses, deposits were electron dense and granular. Treatment was purely supportive. After a mean follow-up period of 11 yr, seven patients had experienced progression to chronic renal failure, including four who had reached end-stage renal failure. Three patients exhibited persistently normal renal function. For one patient, a symptomatic recurrence of mesangial IgG deposits in the renal graft was diagnosed 4 yr after renal transplantation. Such a recurrence highlights the specificity of this type of glomerulonephritis. Mesangial IgG glomerulonephritis is a distinct, albeit rare, type of glomerulonephritis that exhibits far from benign outcome and may recur in renal transplants.

Glomerular deposits are a major pathologic feature of a wide range of human glomerulonephritides and may be located in the mesangial, subepithelial, and subendothelial regions. Various patterns of mesangial glomerular deposits have been reported, including those containing Ig, complement components (1), amyloid proteins (2), fibronectin (3), and collagen type III (4). Glomerular Ig deposits are encountered in a large number of primary and secondary glomerulonephritides, such as lupus or cryoglobulinemic nephropathy.

Among primary glomerulonephritides, IgA nephropathy (IgAN), which was first described by Berger and Hinglais (5), is the most common condition associated with mesangial IgA deposits. Another type of primary glomerulonephritis with predominant mesangial Ig deposits has been identified under the eponym IgM nephropathy (6). This condition is characterized by mesangial IgM deposits, but its specificity remains controversial.

Rare cases of primary glomerulonephritis defined by exclusive or predominant mesangial IgG deposits were reported first by Sato *et al.* (7) and subsequently by Yoshikawa *et al.* (8). The clinical and biologic features of this mesangial "IgG nephropathy" remain poorly defined, and its existence as a distinct entity is still questionable. We describe 14 cases of mesangial IgG glomerulonephritis (MIG), with emphasis on long-term renal outcomes, and we report the first recurrence of MIG in a renal transplant.

Materials and Methods

We reviewed the pathologic findings for all renal biopsies examined in the Departments of Nephrology and Pathology at Hôpital Necker between 1972 and 2000. Biopsy specimens for light-microscopic analyses were fixed in Bouin's solution, embedded in paraffin, and sectioned at 2 μm. The sections were stained with Masson's trichrome, hematoxylin-eosin, periodic acid-Schiff, and silver methenamine stains. All pathologic features noted in light-microscopic analyses were graded by using a semiquantitative scale (−, absent; ±, very mild; +, mild; ++, moderate; +++, intense).

Tissues for immunofluorescence (IF) analyses were stained with FITC-conjugated, monospecific, anti-human μ, γ, α, κ, or λ chain or C3, C1q, or C4 antibodies (Dako, Glostrup, Denmark). The specificity of these antibodies was documented by the absence of staining of normal kidneys and the blockade of staining by exposure of the tissues to anti-human IgG antibodies. Additional staining with monoclonal antibodies against IgG subtypes (a gift of Dr. Pierre Aucouturier, INSERM Unit 25, Hôpital Necker, Paris, France) was performed with six biopsy specimens. Direct and indirect IF methods were used, and the intensity of fluorescence was graded (−, absent; ±, very mild; +, mild; ++, moderate; +++, intense). For electron-microscopic anal-

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yses, renal tissues were fixed in glutaraldehyde and osmium tetroxide, dehydrated, and embedded in Epon 812 resin (GBEM Services, Quebec City, Canada). Ultrathin sections stained with uranyl acetate and lead citrate were examined by using a Philips EM300 electron microscope (Philips Medical Systems, Best, The Netherlands).

Inclusion criteria were based on IF findings. We selected all cases of primary glomerulonephritis with exclusive or predominant mesangial IgG deposits. The diagnosis of primary glomerulonephritis was made when ongoing infections and systemic diseases, mainly systemic lupus erythematous (SLE), were excluded. Infections were ruled out on the basis of clinical examination results and the findings of repeatedly normal erythrocyte sedimentation rates and C-reactive protein levels. American College of Rheumatology revised criteria were used for the exclusion of SLE (9). Antinuclear antibodies were detected by indirect IF on Hep2 cells, and anti-DNA antibodies were detected by radioimmunoprecipitation (Farr test). Nephrotic syndrome was defined by heavy proteinuria (>3 g/d), low serum protein concentrations (<60 g/L), and hypoalbuminemia (<30 g/L). Microscopic hematuria was defined by a urinary erythrocyte count of >10,000 erythrocytes/ml in uncentrifuged urine. The GFR was estimated by using the Cockcroft-Gault formula. Renal failure was defined by a calculated creatinine clearance of <75 ml/min. High BP was defined as a systolic pressure of ≥140 mmHg and/or a diastolic pressure of ≥90 mmHg. All data are presented as median (range).

Results

Clinical and Laboratory Findings

We reviewed 2693 cases of primary glomerulonephritis diagnosed in our institution between 1972 and 2000. Exclusive or predominant mesangial IgG deposits, in the absence of any evidence of SLE, infections, or other systemic diseases, were noted in 14 cases (Table 1). Six cases of MIG were diagnosed between 1972 and 1980, five cases between 1981 and 1990, and three cases between 1990 and 2000. There were four female and 10 male patients. The age at onset was 19 yr (range, 13 to 47 yr). The duration of illness at the time of referral was 3 yr (0 to 17 yr). Six patients were hypertensive at the time of referral.

At the time of referral, all patients exhibited proteinuria (2.5 g/d; range, 1 to 13 g/d) but only one patient (patient 11) manifested signs of nephrotic syndrome. Microscopic hematuria was observed for 11 patients, whereas bouts of gross hematuria were observed for two patients (patients 4 and 5). In one case (patient 4), gross hematuria coincided with upper respiratory tract infections. Ten patients exhibited normal renal function at referral. The serum creatinine concentration was 89 μM (range, 53 to 230 μM), and the creatinine clearance was 89 ml/min (range, 40 to 138 ml/min). For all non-nephrotic patients, serum IgG, IgA, and IgM levels were normal. For all patients, CH50, C3, and C4 levels were normal and antinuclear antibody and/or anti-DNA antibody assays remained negative during the follow-up period. Repeated serum and urine immunoelectrophoresis demonstrated no monoclonal Ig component for any of the patients. Assays for cryoglobulinemia yielded negative results for 12 tested patients. Hepatitis B virus antigen (HBs) antigen assays yielded negative results for 12 tested patients and positive results for one (patient 8). Anti-hepatitis

Table 1. Clinical characteristics of 14 patients with IgG nephropathy at renal biopsy[a]

Patient No.	Gender	Age at First Symptom (yr)	Duration of Illness (yr)	BP (mmHg)	Cr (μM)	CrCl (ml/min)	P (g/d)	H
1	F	19	10	135/100[b]	62	78	2.5	+
			27	145/100	89	55	1.9	−
2	M	45	6	140/80	99	60	3.1	+
3	M	47	1	130/70	98	97	4	+
4	M	18	3.5	130/80	80	106	3.1	+[c]
5	M	37	7	160/100[b]	98	89	2.5	+[c]
6	M	25	5	110/60	98	105	1.4	+
7	M	13	3	140/70	89	95	1	+
8	M	19	0	125/80	89	100	2.4	+
9	F	44	2	130/70	53	99	5	−
10	F	26	9	130/85	80	66	1.5	+
11	M	13	17	160/100[b]	80	120	13[d]	+
12	F	14	3	110/70	68	90	1.2	+
			7	120/70	150	44	2	−
13	M	18	1	160/100[b]	230	40	1	−
14	M	23	1	130/80	92	138	2	+
			6	190/110[b]	90	130	4.3[d]	+

[a] Cr, creatinine concentration; CrCl, creatinine clearance; P, proteinuria; H, microscopic hematuria. Patients 1, 12, and 14 underwent two consecutive renal biopsies.
[b] With antihypertensive treatment.
[c] Macroscopic hematuria.
[d] Nephrotic syndrome.

C virus antibody assays yielded negative results for eight tested patients.

Pathologic Findings

Renal Biopsy at Referral

Light Microscopy Mesangial deposits were detected in all cases (Figure 1) and were particularly intense in five cases. Varying degrees of mesangial matrix expansion were present in all cases. Mesangial cell proliferation was not a predominant feature, being mild or absent. Subendothelial deposits were noted for seven patients. Subepithelial deposits of varying abundance were observed for nine patients, including humps in five cases. In all cases, parietal deposits were fewer and smaller than mesangial deposits (Table 2). Silver methenamine staining revealed the presence of spikes in seven cases and demonstrated a segmental "double-contour" appearance in only one case (patient 12). Segmental glomerular scars were present in six cases. Interstitial fibrosis was observed for 12 patients, and vascular sclerosis was noted for nine patients. Congo red staining was negative in all cases.

IF Analyses Diffuse and granular mesangial IgG deposits (graded + to +++) were present in all cases (Figure 2). Less intense mesangial IgM deposits were noted in five cases, but there were no IgA deposits (Table 3). Mesangial C3, C4, and C1q were detected in 14, eight, and 10 cases, respectively. Deposits in the capillary walls were observed for all patients and consisted of IgG (all cases), IgM (three cases), IgA (two cases), C3 (12 cases), C4 (three cases), and C1q (seven cases). Subepithelial deposits (mainly IgG and C3) were present in nine cases. IgG, C3, C4, and C1q deposits along the tubular basement membrane were observed in only one case (patient 1).

Light Chain and IgG Subclass Analyses IgG subclass and light chain type analyses were performed for six patients. Positive γ_1 staining was detected in five cases, γ_2 in one, γ_3 in five, and γ_4 in three. IgG1 and -3 were predominant. Both κ and λ light chains were present in all cases. No monoclonal γ or μ deposits were detected (Table 4).

Electron Microscopy Electron-microscopic findings were available in seven cases. All biopsies revealed the presence of large, electron-dense, granular deposits in the mesangial and perimesangial regions (Figure 3). No organized structure was detected within the deposits. For three patients (patients 3, 6, and 8), similar large subepithelial deposits were also present. Mesangial cell proliferation was mild or absent.

Repeated Renal Biopsy. Three patients (patients 1, 12, and 14) underwent two consecutive renal biopsies (17, 4, and 5 yr apart, respectively). In all three cases, mesangial deposits and mesangial matrix expansion persisted in the second renal biopsy. The number of sclerotic glomeruli had increased in all cases, whereas tubulointerstitial lesions remained stable. In contrast to the first biopsy, mild mesangial cell proliferation was noted in the second biopsy for one patient (patient 13) and was associated with segmental double contours in some glomeruli. Subepithelial deposits were more abundant in the second biopsy for another patient (patient 14). The IF study for patient 14 demonstrated that the distribution of IgG subclasses

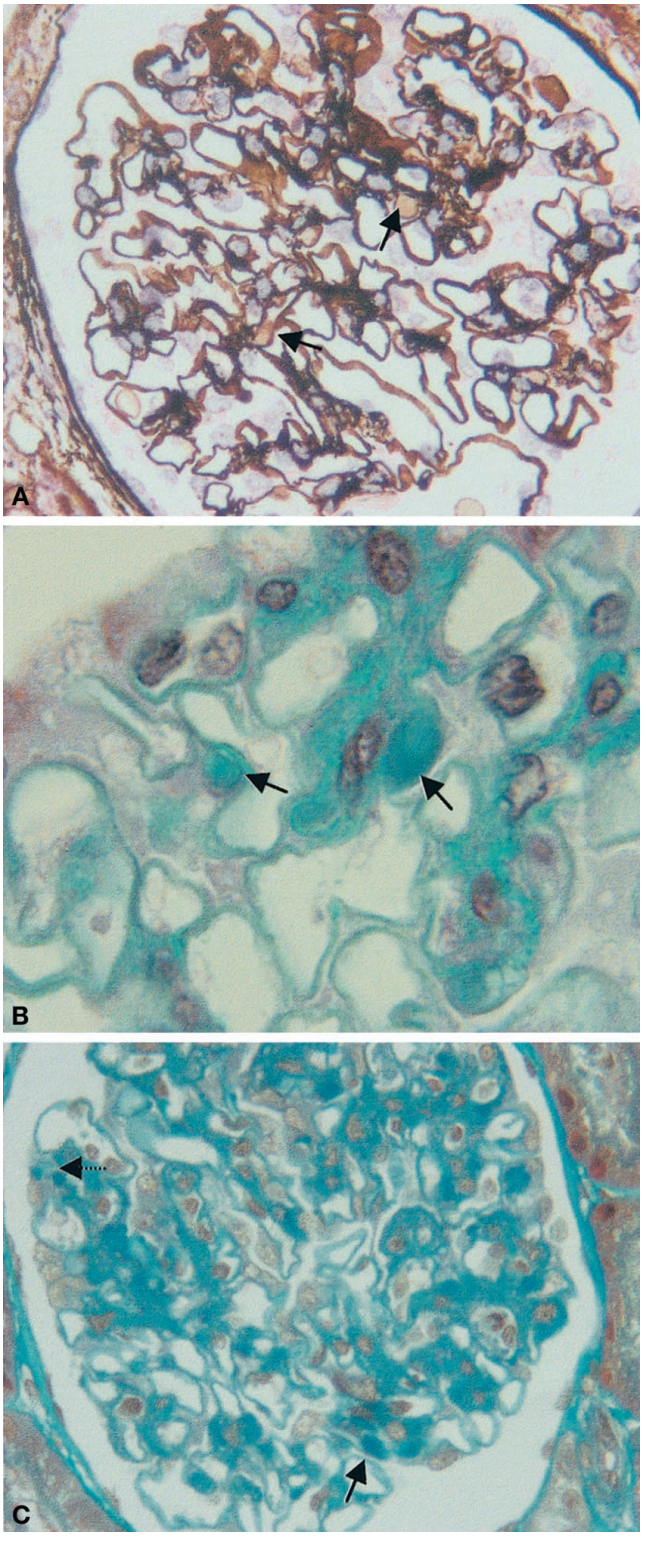

Figure 1. Light-microscopic findings. (A) Patient 4. Initial biopsy; silver methenamine staining. The presence of mesangial deposits (arrows) and mesangial matrix expansion can be observed. The absence of mesangial cell proliferation should be noted. (B) Patient 4. Renal graft biopsy performed 4 yr after renal transplantation. The recurrence of mesangial deposits (arrows) and mesangial matrix expansion can be observed. (C) Patient 14. The presence of mesangial (solid arrow) and subepithelial (dashed arrow) deposits can be observed. Magnifications: ×400 in A and C; ×1000 in B.

Table 2. Light-microscopic findings in 17 renal biopsies from 14 patients with IgG nephropathy[a]

Patient No.	Mesangial Lesions			Parietal Lesions				Glomerular Sclerosis		Tubulo-interstitial Fibrosis	Vascular Lesions
	Cellular Proliferation	Mesangial Matrix Expansion	Deposits	Deposits		Double Contour	Spikes	Focal	Global		
				Subend.	Subepith.						
1	−	+++	+++	++	+	−	+/−	0 (13)[b]	1 (13)	+[c]	−
	+/−	+++	+++	++	+/−	−	−	0 (40)	16 (40)	+[c]	−
2	−	+++	+++	−	+[d]	−	−	0 (16)	4 (16)	+	+
3	−	++	+++	−	+[d]	−	−	0 (11)	0 (11)	+	++
4	+	++	++	−	−	−	−	2 (20)	1 (20)	+	−
5	+/−	++	++	−	−	−	−	1 (10)	3 (10)	+	++
6	−	++	++	−	+[d]	−	+	3 (24)	6 (24)	+	+
7	+	++	++	−	−	−	−	2 (20)	0 (20)	+	+
8	+/−	++	++	+	+	−	+	0 (13)	1 (13)	−	−
9	+/−	+	++	+/−	+[d]	−	+	0 (10)	0 (10)	−[e]	−
10	+[f]	++	++	+/−	+	−	+/−	0 (13)	3 (13)	+	+
11	−	+	+	−	−	−	−	3 (11)	5 (11)	++	++
12	−	++	++	++	+[d]	−	−	0 (34)	8 (34)	++[c]	+/−
	+	++	+	+	−	+[f]	+	30 (37)	29 (37)	++[c]	−
13	−	+	+	−	−	−	−	0 (6)	3 (6)	++[c]	++
14	−	+	+++	+/−	+[d]	−	+/−	0 (13)	0 (13)	−	−
	−	+	++	+/−	++	−	+	3 (18)	2 (18)	+[e]	+

[a] Subend., subendothelial; Subepith., subepithelial.
[b] Numbers in parentheses, total numbers of glomeruli.
[c] Interstitial cellular infiltrate.
[d] Humps.
[e] Interstitial foam cells.
[f] Segmental.

in the mesangial deposits remained identical to that noted in the first renal biopsy (IgG1 and IgG3).

Patient Outcomes

Six patients (patients 1, 5, 7, 11, 13, and 14) received antihypertensive therapy. Patients 1, 7, 9, 11, and 14 received an angiotensin-converting enzyme inhibitor or an angiotensin II AT1 receptor antagonist. No patient received corticosteroids or immunosuppressive drugs.

Four patients (patients 3, 5, 6, and 10) were lost to follow-up monitoring. For the remaining 10 patients, the mean follow-up period was 12 yr (range, 3 to 25 yr) (Table 5). At the last follow-up examination, six patients were hypertensive. Four patients (patients 2, 4, 12, and 13) reached end-stage renal disease within 3 to 15 yr after diagnosis, and chronic renal failure developed in three additional patients (patients 1, 7, and 11). Three patients (patients 8, 9, and 14) exhibited persistently normal renal function 7 to 25 yr after the recognition of MIG.

Patients 5 and 13 underwent two consecutive renal transplantations (RT). For patient 5, surgical complications led to rapid loss of the renal graft after the first RT. Four years after the second RT, renal graft dysfunction and proteinuria (1.5 g/d) were observed. A renal graft biopsy demonstrated the recurrence of mesangial deposits and mesangial matrix expansion in the absence of mesangial cell proliferation (Figure 1). Mild

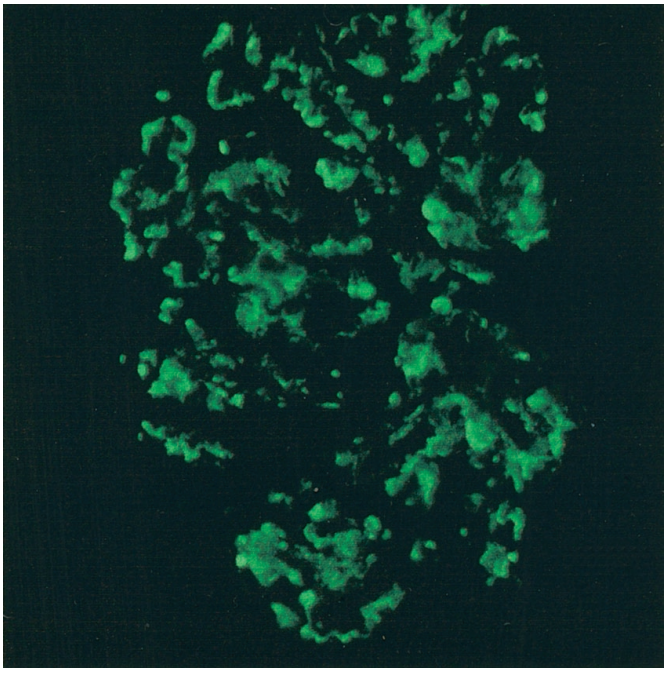

Figure 2. Immunofluorescence study findings for patient 14, demonstrating positive glomerular staining with anti-IgG monoclonal antibodies.

Table 3. Characteristics of IF staining in glomeruli from 14 patients (16 biopsies) with IgG nephropathy[a]

Patient No.	IgG		IgA		IgM		C3		C4		C1q		Subepithelial Deposits
	Mg	Cw	Mg	Cw	Mg	Cw	Mg	Cw	Mg	Cw	Mg	Cw	
1	+++	++	−	+	−	+/−	+++	++	+	+	++	++	+
	++	+	−	−	−	−	+	+	+	−	+	+	+
2	++	−	−	−	−	−	+	+	+	−	ND	ND	+
3	++	−	−	−	−	−	+	+	+	−	ND	ND	+
4	++	+	−	−	−	+/−	++	+	+	−	++	+	−
5	+	−	−	−	+/−	−	+	+	−	−	ND	ND	−
6	+	−	−	−	−	−	+	−	−	−	+	+	+
7	+	−	−	−	+	−	+	−	ND	ND	+	−	−
8	+	−	−	−	−	−	+	+	+	−	+	−	+
9	+	+	−	−	−	−	+	+	−	−	+	+	+
10	+	+	−	−	−	−	+	+	−	−	+	+	+
11	+	−	−	−	−	−	+	+	+	+	−	−	−
12[b]	+	+	−	−	+/−	−	+	+	+	−	+	+	+
13	++	+	−	−	+/−	−	++	+	−	−	+	−	−
14	++	+	−	−	−	−	++	+	+/−	+/−	++	+	+
	++	++	−	+	+	−	++	++	ND	ND	+	+	+

[a] Mg, mesangium; Cw, capillary wall; ND, not done.
[b] Data shown for the second renal biopsy. There was an absence of glomeruli in the first renal biopsy sample for immunofluorescence (IF) analysis.

interstitial and vascular sclerosis was present. No glomerular or interstitial cellular infiltrate was noted. In IF studies, mesangial and parietal IgG (scored ++), C3 (scored ++), C4, and C1q deposits were detected. No mesangial IgA or IgM deposits were noted.

Patient 13 lost her first renal graft because of severe acute rejection 1.5 yr after RT. Her second RT has been uneventful to date, and no renal graft biopsy has been performed.

Discussion

MIG as a Distinct Pathologic Entity

Glomerular mesangial IgG deposition occurs in various types of primary and secondary glomerulonephritides, including lupus nephritis (10) and mesangiocapillary nephropathy (11). In IgAN, the most common type of primary glomerulonephritis, IgG (mainly IgG1 and IgG3) is codeposited with IgA in up to 40% of cases (12).

The first adult cases of primary glomerulonephritis characterized by exclusive or predominant mesangial IgG deposits were observed in Japan by Sato *et al.* (7). Subsequently, Yoshikawa *et al.* (8) reported 10 pediatric cases of MIG. The report by Sato *et al.* (7) included only six adult patients, with a relatively benign course of MIG after a median follow-up period of 4.9 yr (Table 6). This small number of reported adult cases, the relatively limited follow-up periods, and probably the indolent course of nephropathy were the limiting factors for the characterization of MIG as a distinct primary glomerulonephritis. Here we report the largest series of MIG cases to date, including 14 cases. Ten of our patients underwent extended follow-up monitoring, with a mean follow-up period of 11.5 yr; four patients were monitored for >15 yr. In our series, the course of MIG was far from benign, inasmuch as chronic renal failure occurred in one-half of the patients. In addition, we describe the first recurrence of mesangial IgG deposits in a

Table 4. Light chain and γ subclass analysis for six patients with IgG nephropathy

Patient No.	IgG1	IgG2	IgG3	IgG4	κ Light Chain	λ Light Chain
1	++	−	−	+	++	+
3	−	−	++	−	++	+
7	++	+	+	−	++	+
12	+	−	+	+/−	+	+
13	+	−	+	+/−	+	+
14[a]	+	−	+	−	+	+
	+	−	+	−	+	+

[a] Patient 14 underwent two consecutive renal biopsies.

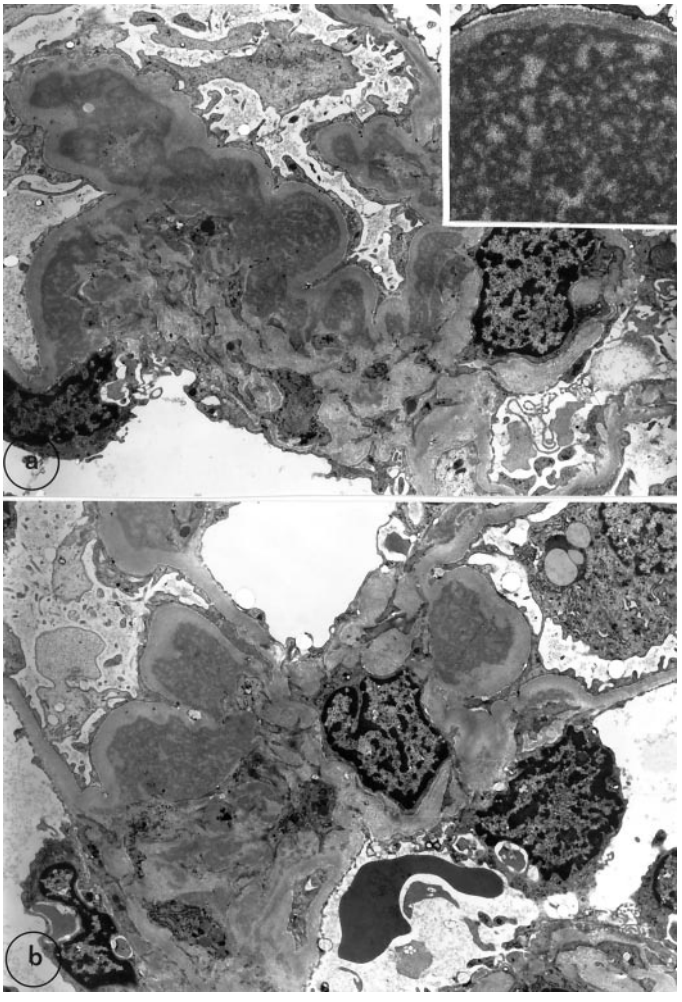

Figure 3. Electron-microscopic findings. (a) Patient 4. Large electron-dense deposits in the mesangium can be observed. (Inset) High-magnification view of mesangial deposits, with the peculiar appearance of a granular meshed network. (b) Patient 3. The same peculiar appearance of mesangial deposits as observed for patient 4 should be noted. The presence of rare subepithelial deposits should also be noted. Magnification: ×8500 in a; ×25,000 in inset.

renal graft. Such recurrence supports the notion that MIG is a distinct type of primary glomerulonephritis.

The prevalence of MIG among primary glomerulonephritides diagnosed at our institution between 1972 and 2000 was approximately 0.5%. Our data are in accordance with the previous reports of incidences of 0.54% in adults (7) and 1.1% in children (8) and contrast with the high frequency of IgAN (13). However, the incidence of MIG may be underestimated, because patients with mild urinary abnormalities do not undergo renal biopsies. In our series, nine patients exhibited normal renal function at the time of referral, and renal biopsies were performed because of significant proteinuria and microscopic and/or macroscopic hematuria. Median proteinuria at referral was 2.5 g/d, with the nephrotic syndrome being noted for one patient. Our data are in contrast to the mild proteinuria ($\leq$0.7 g/L) noted in the six cases of IgG nephropathy reported by Sato *et al.* (7). Interestingly, in one case (patient 4), recurrent episodes of gross hematuria occurred during upper respiratory tract infections, producing a striking clinical resemblance to IgAN.

All 14 cases of MIG presented here share two prominent pathologic features, *i.e.*, the presence of exclusive or predominant mesangial IgG deposits and mesangial matrix expansion. IgG deposits exhibited a uniform appearance in light- and electron-microscopic studies. In a large control necropsy study by Sinniah (14), isolated mesangial IgG deposits were not detected, in contrast to IgA and IgM. Moreover, for three of our patients (patients 1, 12, and 14), repeated renal biopsies (performed 17, 4, and 5 yr, respectively, after the first biopsy) revealed persistent mesangial IgG deposits, with the presence of the same IgG subclasses in the only tested case (patient 14). Therefore, we think that IgG deposits were not coincidental in our cases and are pathogenically relevant.

Mesangial deposition of complement components, mainly C3 and C1q, was present in almost all cases. Similar patterns of complement component deposition in the mesangium were observed by Sato *et al.* (7) and Yoshikawa *et al.* (8). C3 mesangial deposition is a common pathologic feature of other Ig deposit-related, primary glomerulonephritides and occurs in almost all cases of IgAN (14). However, in contrast to MIG, C4 and C1q deposits are uncommon in IgAN.

In our series, as well as in previously reported cases (7,8), the extensive Ig and complement deposition contrasts with the absence of marked mesangial cell proliferation. This absence of endo- and extracapillary cell proliferation is in striking contrast to IgAN, in which mesangial cell proliferation and crescents are observed in 36 and 26% of cases, respectively (15,16).

Segmental parietal deposits (subendothelial and subepithelial) were detected in more than one-half of our patients. Parietal deposits were mild in all cases except in the second renal biopsy for patient 14. In contrast, in the report by Sato *et al.* (7), IgG deposits were exclusively located in the mesangium. In their pediatric series, Yoshikawa *et al.* (8) did not observe parietal deposits in IF analyses but observed subepithelial, subendothelial, and intramembranous deposits for nine of 10 patients in electron-microscopic studies.

Differential Diagnosis

The recognition of this disease as a new type of glomerulonephritis requires the careful exclusion of other types of glomerulonephritides. There was no marked mesangial cell proliferation in any case, and mesangial interposition was present in a single case (patient 12) in a repeat renal biopsy performed during advanced renal failure. These pathologic features exclude the diagnosis of mesangiocapillary glomerulonephritis, another type of primary glomerulonephritis associated with glomerular deposition of Ig and complement. We also excluded the diagnosis of membranous nephropathy, although subepithelial deposits and spikes were observed for nine of our patients. Indeed, the subepithelial deposits noted in some of our cases were focal, fewer in number, and smaller in size, compared with mesangial deposits. Similarly, such mild subepithelial deposits are common in IgAN, occurring in 18 to 56% of

Table 5. Long-term outcomes in mesangial IgG nephropathy[a]

Patient No.	Follow-Up Period (yr)	H	P (g/d)	BP (mmHg)	SCr (μM)	CrCl (ml/min)
1	20	+	2.3	150/100[b]	99	60
2	7	+	5.3	150/80[b]	ESRD	ESRD
4	15	−	11.7	140/100[b]	ESRD	ESRD[c]
7	23	−	0.45	110/90[b]	150	57
8	25	−		125/80	81	115
9	12	+	1.4	145/96[b]	70	78
11	6	+	10	120/80[b]	180	40
12	4	−	3.4	140/90	ESRD	ESRD[c]
13	3	−	0.5	150/90	ESRD	ESRD
14	7	+	2	132/80	82	124

[a] Patients 3, 5, 6, and 10 were lost to follow-up monitoring. H, microscopic hematuria; P, proteinuria; SCr, serum creatinine concentration; CrCl, creatinine clearance; ESRD, end-stage renal disease.
[b] With antihypertensive therapy.
[c] Underwent two consecutive renal transplantations.

cases (17,18). Moreover, several studies have established the IgG4 subclass as the most constantly present IgG subclass in glomerular deposits (19,20). This contrasts with our MIG cases, in which IgG4 deposits were observed in only one tested case. The humps noted in six of our cases may suggest the diagnosis of postinfectious glomerulonephritis. However, humps are not pathognomonic of postinfectious glomerulonephritis and are encountered in various nephropathies, including some cases of IgAN (17). No clinical or biologic features of ongoing infection were noted for any patient during extended follow-up monitoring. Marked mesangial proliferation and low complement levels, two main features of postinfectious glomerulonephritis, were absent in all of our cases. Finally, the recurrence of MIG in patient 5 argues against the diagnosis of postinfectious glomerulonephritis. Therefore, we rejected the possibility of postinfectious glomerulonephritis. Mesangial C1q deposits, which were detected in all of our cases, could suggest C1q nephropathy, as first described by Jennette *et al.* (21). However, C1q nephropathy is characterized by the glomerular deposition of C1q, as a predominant complement component, and various types of Ig. The opposite is true in our MIG cases and in those reported by Sato *et al.* (7) and Yoshikawa *et al.* (8), in which mesangial deposits consist of IgG, as a predominant or exclusive Ig, and various complement components (C3, C1q, and C4). Therefore, MIG is clearly different from C1q nephropathy. Mesangial IgG glomerular deposits are also encountered in lupus nephritis and fibrillary/immunotactoid glomerulopathy. Lupus nephritis is characterized by the extensive glomerular deposition of Ig and complement, leading to mesangial cell proliferation. Despite the prolonged duration of illness at the time of referral and/or follow-up examinations, clinical and serologic features of SLE (or any other systemic disease) were repeatedly absent among our patients. Moreover, the absence of any mesangial proliferation in MIG cases, contrasting with the severe renal abnormalities of some patients, argues against the diagnosis of lupus

Table 6. Clinical features and renal outcomes in reported series of MIG[a]

	No. of Patients	Age at Onset (yr)	HBP	Renal Function at Diagnosis	H and/or P	Follow-Up Period (yr)	Renal Function at Last Follow-Up Examination
Sato *et al.* ((7))	6	33 (7 to 52)[b]	1/6	Median CrCl, 98 ml/min (18 to 126 ml/min)	P, 6/6 (0.1 to 0.7 g/d); H, 6/6[c]	3.5	Stable, 6/6
Yoshikawa *et al.* ((8))	10	4.7 (1.9 to 15)	0/10	CRF, 0/10	Nephrotic syndrome, 4/10; H, 8/10	3.4 (0.4 to 8.4)	CRF, 0/10
Present report	14	19 (13 to 47)	6/14	CRF, 3/14	P, 14/14 (1 to 13 g/d); H, 12/14[c]	12 (3 to 25)[d]	ESRD, 4/14; CRF, 3/14

[a] MIG, mesangial IgG glomerulonephritis; HBP, high BP; CrCl, creatinine clearance; CRF, chronic renal failure; H, hematuria; P, proteinuria; ESRD, end-stage renal disease.
[b] Age at the time of renal biopsy.
[c] Including three patients who exhibited bouts of gross hematuria.
[d] Four patients were lost to follow-up monitoring.

nephritis. Therefore, the diagnosis of (latent) lupus nephropathy can be reasonably excluded for our patients.

Glomerular IgG deposits may occur as organized fibrillar (fibrillary glomerulonephritis) (22) or microtubular (immunotactoid glomerulonephritis) (23) deposits. The cases reported herein are clearly different from fibrillar/immunotactoid cases, for the following reasons. (*1*) Electron-microscopic studies for seven of seven of our patients revealed large electron-dense deposits in the absence of microtubular or fibrillary aggregates. (*2*) Whereas immunotactoid glomerulonephritis is characterized by monoclonal IgG deposits, mesangial IgG deposits were polyclonal in IF analyses for six of six of our patients (Table 4). (*3*) In contrast to fibrillary glomerulonephritis, in which IgG deposits are exclusively of the γ_4 subclass (24), γ_1 and γ_3 were the predominant subclasses within the mesangium for all of our tested patients. (*4*) For all of our patients, long-term follow-up monitoring failed to reveal monoclonal gammopathy or lymphoproliferative disorder, which are frequently associated with immunotactoid glomerulopathy.

The pathogenesis of MIG remains unclear. Mesangial IgG deposition does not seem to be related to increased serum IgG levels, because all non-nephrotic patients exhibited normal IgG levels. It may be speculated, as for IgA1 in IgAN (13), that specific biochemical abnormalities of IgG1 and -3 may lead to their deposition in the mesangium. This glomerular IgG deposition may lead to either immunotactoid glomerulonephritis or MIG, depending on the predominant IgG subtype(s).

MIG Prognosis

For our patients, treatment was purely supportive and consisted of an antihypertensive and/or antiproteinuric regimen, including angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists for five patients. In the report by Sato *et al.* (7), all patients presented with normal renal function and mild proteinuria and therefore did not receive immunosuppressive treatment. In a case report (25), the nephrotic syndrome in an adult patient with MIG was resistant to corticosteroid and cyclophosphamide treatment. In the report by Yoshikawa *et al.* (8), four children with MIG, nephrotic syndrome, and normal renal function were treated with a corticosteroid regimen, with complete or partial remission in two cases. It remains to be established whether steroid treatment could prevent or slow the progression of severe MIG, as recently reported for IgAN (26).

At the last follow-up examination, one-half of the patients had progressed to chronic renal failure and four had reached end-stage renal disease. These data are in sharp contrast to previous reports that suggested a relatively benign course for MIG (7,8). In our series, renal function remained normal in two patients, despite persistent urinary sedimentation abnormalities. Therefore, as for IgAN, the prognosis of MIG is highly variable among patients.

One of the most striking features of this series is the recurrence of MIG after RT in one patient (patient 4) (Figure 1). In light-microscopic and IF studies, mesangial deposits in the renal graft were very similar to those noted in the native kidney. This is the first report of MIG recurrence in a renal transplant recipient. As for IgAN, recurrence after RT was probably the last missing element of proof for the identification of MIG as a distinct type of glomerulonephritis.

In summary, MIG is a very rare but distinct type of primary glomerulonephritis that is characterized by exclusive or predominant mesangial IgG deposits. Its renal prognosis may be less favorable than previously reported. Nephrologists should be aware of the possibility of recurrence in renal grafts.

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