IgM Nephropathy: Clinical Picture and Long-Term Prognosis

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• ***Background:*** **Immunoglobulin M (IgM) nephropathy is an idiopathic glomerulonephritis with mesangial hypercellularity and diffuse IgM deposits.** ***Methods:*** **We studied clinical presentation, morphological findings, and prognostic factors in 110 patients with IgM nephropathy without systemic diseases. The series included both pediatric and adult patients with nephrotic syndrome (NS) or minor urinary abnormalities.** ***Results:*** **Mean postbiopsy follow-up was 8 years. During 15 years of follow-up, 36% of patients developed renal insufficiency and 23% reached end-stage renal failure. In multivariate analysis, hypertension at the time of renal biopsy was the only significant risk factor for renal insufficiency. Of histological parameters, interstitial fibrosis had the strongest prognostic value. Hypertension was diagnosed in 50% of patients with a postbiopsy follow-up of 15 years. Twenty-nine percent of nephrotic patients had disease resistant to corticosteroids, whereas 80% of patients with steroid-sensitive disease were steroid dependent. Eleven patients, 8 patients with NS and 3 patients with asymptomatic proteinuria, underwent repeated renal biopsy. In five samples, typical morphological characteristics of focal and segmental glomerulosclerosis were seen.** ***Conclusion:*** **We propose that IgM nephropathy can be divided into two subgroups with similar renal biopsy findings, but differences in sex distribution and initial presentation.** ***Am J Kidney Dis*** **41:343-350.**

INDEX WORDS: Immunoglobulin M (IgM) nephropathy; mesangial glomerulonephritis; focal and segmental glomerulosclerosis (FSGS); hematuria (HU); proteinuria (PU); nephrotic syndrome (NS).

IN 1978, TWO INDEPENDENT research groups described a new type of glomerulonephritis, immunoglobulin M (IgM) nephropathy.[1,2] Characteristic of this disease is diffuse, granular, and mesangial deposition of IgM. Although other immunoglobulins also may be deposited in the mesangium, IgM is predominant. IgM often is associated with complement, especially C3.[3-5] Light microscopy usually indicates diffuse proliferation of mesangial cells and accumulation of extracellular mesangial matrix. However, the histological picture can vary from no glomerular abnormalities to mesangial hyperplasia of varying degrees associated with segmental or global sclerosis.[4,6] Because of its varying morphological characteristics, IgM nephropathy as an independent entity has been questioned. Its extreme forms resemble two previously described disorders: minimal change disease (MCD) and focal and segmental glomerulosclerosis (FSGS).[4,7] In view of these overlaps, some investigators have argued that IgM nephropathy is a transitional form between these two conditions,[8,9] whereas others regard it as a distinct clinicopathological entity.[1,3,10,11] The main differences between IgM nephropathy and MCD are the poorer response to corticosteroid (CS) therapy and prominent mesangial IgM in IgM nephropathy.[4,12]

In most studies of IgM nephropathy, series have consisted of patients with nephrotic syndrome (NS). However, IgM nephropathy also is associated with hematuria (HU) and asymptomatic proteinuria (PU).[6,13,14] HU has been a marker of benign course, whereas patients with NS have developed deterioration of renal function more frequently.[14] Conversely, HU also has been proposed to be an independent risk factor in the progression of IgM nephropathy.[6]

There are only a few long-term longitudinal studies of IgM nephropathy. In those in which repeated biopsies have been performed because of deterioration of renal function, findings have been typical of FSGS.[14-16] In the present investigation, we studied the long-term prognosis of IgM nephropathy. The main goal is to identify factors that predict the natural course of IgM nephropathy. Attention also focuses on the incidence of FSGS and markers that favor IgM nephropathy changing to FSGS.

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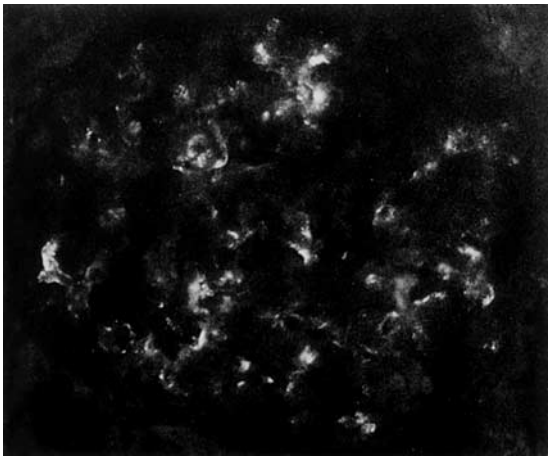

Fig 1. Glomerular fluorescent IgM in a granular mesangial pattern. (Original magnification ×510.)

PATIENTS AND METHODS

Patients

Our material was selected from patients with renal biopsy specimens evaluated in Tampere University Hospital (Tampere, Finland) during a period of 21 years from October 1977 to July 1998. Of 2,217 biopsy specimens, 110 specimens met criteria for IgM nephropathy (Fig 1). The definition of IgM nephropathy in this study is the same as in the study of Helin et al[3] in 1982. We excluded patients with systemic disease (systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and paraproteinemia). Of patients studied, there were 63 males (57%) and 47 females (43%). Mean age was 29 years (range, 1 to 75 years); 36 patients (33%) were younger than 16 years.

The study was approved by the Ethics Committee of Tampere University Hospital, the Ethics Commitee of the City of Tampere, and the Ministry of Social Affairs and Health.

Clinical Definitions

NS is defined as PU with 3.5 g/24 h of protein or greater, decreased levels of serum total protein (<6 g/dL [<60 g/L]) and albumin (<3 g/dL [<30 g/L]), and edema. PU is defined as urinary total protein greater than 0.15 g/24 h. The definition of HU is 3 or more erythrocytes/high-power field (HPF) of urinary sediment. Of 23 patients with HU, 7 patients had erythrocyte counts of 3 to 5 cells/HPF; 7 patients, 6 to 10 cells/HPF; and 9 patients, greater than 10 cells/HPF. Renal insufficiency is defined as a serum creatinine concentration greater than 1.41 mg/dL (>125 μmol/L) in men, greater than 1.19 mg/dL (>105 μmol/L) in women, and greater than +2 SDs of the mean of healthy children of corresponding age in pediatric patients. End-stage renal disease (ESRD) was in question when the patient needed chronic renal replacement therapy. A patient was regarded as hypertensive if resting blood pressure was 145/95 mm Hg or greater in adults. In children, classification of hypertension was made taking age and sex into account.[17] All patients administered antihypertensive drugs also are defined as hypertensive. Prebiopsy follow-up is defined as time from the first symptoms and signs of kidney disease to renal biopsy, and postbiopsy follow-up is the time from the diagnosis of IgM nephropathy to the last available control check.

Renal Biopsies and Laboratory Studies

Paraffin sections for light microscopy (LM) were stained by hematoxylin and eosin, periodic acid–Schiff reaction, Masson trichrome, and periodic acid–silver methenamine methods. Specimens were evaluated for mesangial cell proliferation and sclerosis, tubular atrophy, interstitial fibrosis and inflammation, arteriolar hyalosclerosis, and arterial intimafibrosis. Changes were graded as normal, mild, moderate, or marked (0 to 3, respectively). Also, the distribution of morphological changes and single glomerular and interstitial changes, such as relative amount of obliterated glomeruli, were taken into account. A specimen was considered representative if it contained four or more glomeruli.

For direct immunofluorescence (IF) studies, we used monospecific antisera against the heavy chains of human immunoglobulins (IgG, IgM, IgA), complement (C3, C1q), fibrinogen, light chains (kappa, lambda), and albumin. Glomerular IF findings were graded as −, +/−, +, ++, and +++.

CS Treatment

Prednisone or methylprednisolone has been the primary drug therapy for nephrotic patients in Tampere University Hospital.[18] Patients were distributed into three classes according to level of response to CS therapy: (1) steroid responsive; complete remission of urinary abnormalities persisting for at least 2 months after termination of therapy; (2) steroid dependent; complete remission during CS therapy, but recurrence when the dosage was reduced under a critical level or within 2 months after discontinuing the treatment; and (3) steroid resistant; no remission during 10 consecutive weeks of treatment. Remission is defined as a reduction in urinary protein concentration to less than 0.15 g/24 h and reduction of erythrocytes to less than 3 cells/HPF.

Statistics

Mann-Whitney *U* test was used to compare means between two independent groups. When there were more than two groups, we used analysis of variance. Differences between categorical factors were tested by chi-square test or Fisher's exact test, when appropriate. Logistic regression analysis was used for multivariate analysis in detecting independent risk factors. *P* less than 0.05 is considered significant for all tests. SPSS for Windows software (SPSS, Andover, MA) was used for statistical analysis.

RESULTS

Clinical Findings at Biopsy

Clinical findings in 110 patients with IgM nephropathy at time of renal biopsy are listed in Table 1. Of 36 pediatric patients, 32 patients had NS, whereas biopsy indications in the adult group

Table 1. Clinical Data at Time of Renal Biopsy

	Clinical Manifestation							
	NS		PU		PUHU		HU	
	Adults	Children	Adults	Children	Adults	Children	Adults	Children
No. of patients	18	32	33	4	5		18	
Sex (M/F)	10/8	25/7	18/15	2/2	2/3		6/12	
Age (y)								
Median	52	6	36	11	34		39	
Range	17-69	1-15	18-75	6-15	19-57		25-58	
Prebiopsy follow-up (y)								
Median	0.5	1	1	1	2		4	
Range	0-30	0-6	0-28	0-0.5	0-20		0-20	
Renal function								
Normal	11	29	28	4	5		17	
Impaired	7	3	5	0	0		1	
Hypertensive	9	7	13		2		7	
PU (g/24 h)								
Mean	13.4	6.8	0.9	1.2	0.7		—	
Range	4.6-30	3.5-39	0.2-4.0	0.6-1.9	0.3-1.1		—	

were distributed more evenly, with asymptomatic PU the most common (45%). In the HU group, women predominated. At the time of biopsy, the prevalence of renal insufficiency was 15%, and hypertension, 35%.

Renal Pathological Evaluation

A summary of LM findings is listed in Table 2. A dominant finding in LM evaluation was minimal or mild mesangial cell proliferation and/or mild mesangial sclerosis. In only 2 specimens was cell proliferation of moderate or marked degree seen. In 38 specimens, mesangial sclerosis was seen, but in only one specimen was the degree of sclerosis moderate or marked. The only significant difference in histological findings among the different groups (NS, PU, PUHU, and HU) was significantly milder hyalosclerosis in patients with NS ($P < 0.01$).

Table 2. Histological Findings in 110 Patients With IgM Nephropathy

Finding	No. of Patients
Glomeruli	
Normal or minimal lesions	38
Mesangial hypercellularity	
Mild	35
Moderate or marked	2
Mesangial sclerosis	
Mild	39
Moderate or marked	1
Tubulointerstitial tissue	
Tubular atrophy*	22
Interstitial fibrosis*	8
Interstitial inflammation*	7
Vascular tissue	
Arteriolar hyalosclerosis*	21
Arterial intimafibrosis*	7
Obliterated glomeruli	17

*Mild, moderate, or marked.

In addition to IgM, the other glomerular IF findings were IgG in 8 specimens, IgA in 12 specimens, C3 in 35 specimens, C1q in 18 specimens, and fibrinogen in 5 specimens. In all specimens, the intensity of IgA was no more than of minimal degree, and the distribution of IgA often was segmental. Positive staining for C3 in arterioles was noted in 69 cases.

Immunosuppressive Pharmacotherapy

Forty-seven of 50 patients with NS and two of 37 patients with PU were treated with CSs (prednisone or methylprednisolone). The response of nephrotic patients to CS treatment is listed in Table 3. CS response correlated significantly with progression to renal insufficiency ($P < 0.05$). Patients with CS-sensitive disease had more marked interstitial inflammation and fibrosis on renal biopsy ($P < 0.05$). Secondary medi-

Table 3. Response to CS Therapy in Patients With NS

	No. of Adults	No. of Children	All Patients
Patients	17	33	50
Treated with steroids	14	33	47
Steroid-responsive	5	1	6
Steroid-dependent	5	23	28
Steroid-resistant	4	9	13

cation for those evincing a poor response to CS was usually oral cyclophosphamide. Of 22 patients administered cyclophosphamide therapy, 11 patients reached complete remission lasting for at least 4 months (range, 4 months to 8 years). Ten patients remained dependent on CSs or had disease resistant to CSs.

Postbiopsy Course

Clinical course. The clinical course of the disease during postbiopsy follow-up (mean, 8 years) is listed in Table 4. One hundred six patients were followed up for at least 1 year; 64 patients, at least 5 years; 44 patients, at least 10 years; and 22 patients, 15 years or more. The prevalence of renal insufficiency at the end of follow-up was 19%. Six of the total patients (5%) reached ESRD, whereas in the group with 15 years of follow-up, the prevalence was 23%

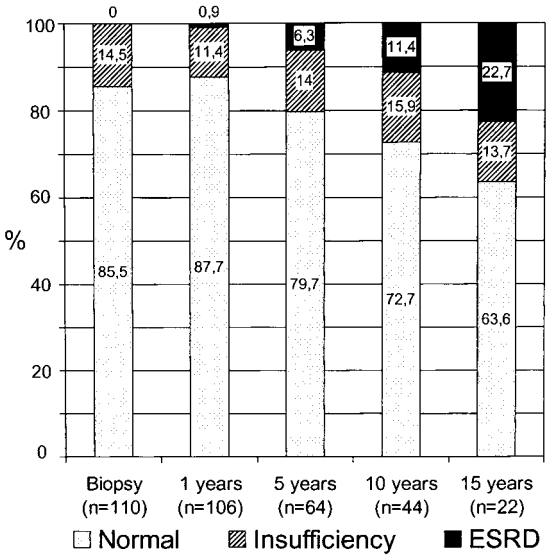

Fig 2. Renal insufficiency and ESRD in patients with IgM nephropathy at time of biopsy and in postbiopsy follow-up.

(Fig 2). Five of the 6 patients with ESRD had NS as their initial clinical manifestation, and 1 patient had PU. In all but 1 patient with HU with or without PU, renal function remained normal.

The prevalence of hypertension at the end of follow-up was 45% in the entire material and 50% in the group with 15 years of follow-up (Fig 3). Patients with asymptomatic PU became hyper-

Table 4. Clinical Data at the End of Follow-Up

	Initial Clinical Manifestation							
	NS		PU		PUHU		HU	
	Adults	Children	Adults	Children	Adults	Children	Adults	Children
No. of patients	18	32	33	4	5		18	
Postbiopsy follow-up (y)								
Median	4	5	11	3	5		11	
Range	0.5-21	1-22	0-20	1-18	3-19		0-20	
Renal insufficiency	7	3	9	1			1	
ESRD	3	2	1					
Hypertensive	11	6	21	1	2		8	
PU								
Increased			3	1	1			
Stable			22		3			
Decreased			8	3	1			
HU								
Persistent					2		12	
Disappeared					3		6	
Clinical remission	7	22	8	3	1		6	

Abbreviations: Increased, asymptomatic PU doubled; Decreased, PU decreased to protein less than 0.15 g/24 h.

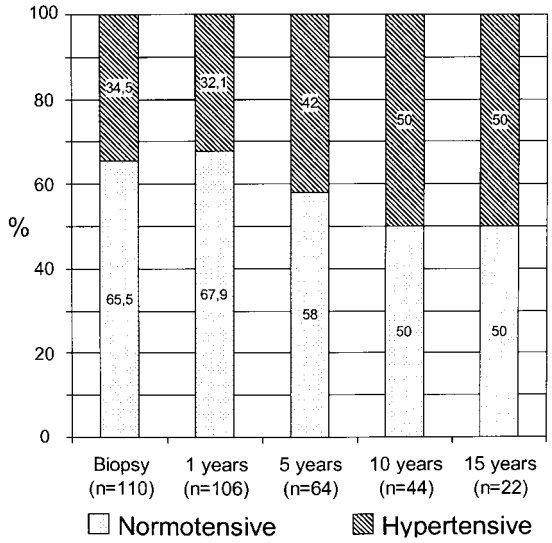

Fig 3. Hypertension in patients with IgM nephropathy at time of biopsy and in postbiopsy follow-up

tensive significantly more frequently (60%) than those in the other groups ($P < 0.05$). In 5 patients (12%) with PU with or without HU, the initial amount of PU had doubled by the end of follow-up. The persistence of PU in patients with PU or PUHU did not affect the prognosis of IgM nephropathy. In 14 patients (61%) with HU with or without PU, HU persisted. Of all patients, 48 patients (44%) were in complete remission at the end of follow-up. Children reached remission more frequently than adults ($P < 0.001$).

Repeated biopsies. Eleven patients underwent a repeated biopsy (Table 5); indications were deterioration in renal function, increasing PU, and/or poor response to pharmacotherapy. Five of the repeated biopsy samples showed typical histological characteristics of FSGS. In five of the repeated biopsy samples, minimal histological lesions were seen with mesangial IgM in four specimens and negative IF findings in one specimen. One patient developed typical lupus nephritis. Four patients with FSGS had renal insufficiency at the end of follow-up, and three patients had reached ESRD, whereas all patients with minimal lesions had normal renal function. Of patients with ESRD, two patients had been administered CS therapy, and both had disease resistant to CSs. There was no difference in known duration of disease between patients with FSGS and minimal lesions. We found no clinical or morphological indicator that would predict the development of FSGS.

Of six patients who reached ESRD, five patients underwent renal transplantation, and in one patient, IgM nephropathy recurred in the transplant.

Prognostic Factors

On the basis of univariate analysis, we selected age, hypertension, serum creatinine level, interstitial fibrosis, and arteriolar hyalosclerosis for the model for binary logistic regression anal-

Table 5. Clinical and Histological Findings of Patients Who Underwent Repeated Renal Biopsy

Patient No.	Sex M/F	Age (y)	Clinical Picture	dU-Prot (g/24 h)	IF-IgM (− to +++)	Prebiopsy (y)	Interbiopsy (y)	HT1/ HT2	Crea1/Crea2 (mg/dL)	CS Response	Rebiopsy Finding
1	F	1	PU	1.4	++	0.5	3	+/+	0.29/0.74*	Resistant	FSGS
2	F	11	NS	5.5	++	3	2	−/+	0.59/0.68	Resistant	FSGS
3	M	15	PU	0.8	++	0.5	17	−/+	0.74/2.0*	—	FSGS
4	F	28	PU	4.0	+	6	3	−/+	2.1*/1.3*	—	FSGS
5	M	55	PU	2.0	+/++	9	9	−/+	1.0/1.4*	—	FSGS
6	F	3	NS	35.1	++	0	4	+/−	0.35/0.55	Dependent	IgM nephropathy
7	M	4	NS	3.9	+/++	1	13	−/−	0.50/0.89	Dependent	IgM nephropathy
8	M	6	NS	5.4	+/++	4	2	−/−	0.26/0.63	Dependent	IgM nephropathy
9	F	51	NS	5.0	+	13	3	+/+	0.62/0.67	Resistant	IgM nephropathy
10	M	7	NS	16.5	+/++	4	4	−/−	0.41/0.66	Dependent	MCD
11	M	12	NS	3.5	+/++	0.5	2	−/+	0.72/0.62	Dependent	LED

NOTE. To convert serum creatinine to SI units (μmol/L), multiply mg/dL by 88.40.

Abbreviations: PU, isolated proteinuria; dU-Prot, 24-hour urine total protein at time of initial biopsy; IF-IgM, intensity of mesangial IgM in initial biopsy; Prebiopsy, time from first symptoms to initial biopsy; Interbiopsy, time from initial biopsy to repeated biopsy; HT1, hypertension at time of initial biopsy; HT2, hypertension at time of repeated biopsy; Crea1, serum creatinine level at time of initial biopsy; Crea2, serum creatinine level at time of repeated biopsy; LED, lupus nephritis.

*Greater than normal range.

ysis. Based on clinical experience, presence of PU or HU also was included in the model for multivariate analysis. Tubular atrophy was excluded from the model because it correlated strongly with interstitial fibrosis, and of these two morphological parameters, it had a weaker correlation with renal insufficiency. Multivariate analysis showed blood pressure ($P < 0.05$) to be the only independent risk factor for the development of renal insufficiency.

For a model exploring risk factors for ESRD in IgM nephropathy, we selected prevalence of hypertension, daily amount of PU, serum total protein, and positivity of glomerular C1q in the IF study. None of these parameters appeared to have independent prognostic value in multivariate analysis.

DISCUSSION

The present study of 110 patients with IgM nephropathy included both adults and children, and in addition to patients with NS, patients with minor urinary abnormalities also were included. The present is an expanded follow-up study of an earlier work of Saha et al,[14] with a larger number of patients and longer follow-up. This is the largest series and the longest postbiopsy follow-up study reported to date in the context of IgM nephropathy.

Indications for renal biopsy vary in different centers. This probably has influence on the incidences of renal insufficiency reported in different studies. Our policy has been to perform a renal biopsy in adult patients with minor urinary abnormalities. This may explain the favorable prognosis of IgM nephropathy in our series. Compared with the earlier work of Saha et al[14] in 1989, we have more patients with NS in the present study. This may have influenced the long-term course and conclusions in comparison to the earlier cohort. Controversy prevails about the independence of IgM nephropathy in the range of idiopathic glomerulopathies. Characteristic of IgM nephropathy is granular, diffuse, and global IgM deposition in the glomerular mesangium.

The morphological picture of the condition may resemble MCD or FSGS, which also may have glomerular IgM deposits. However, IgM IF in MCD is always of minimal intensity. In FSGS, IgM is segmentally and focally distributed in sclerosing areas, not diffusely, as in IgM nephropathy. A poorer response to CS therapy and more markedly increased proinflammatory cytokine production have been described in IgM nephropathy compared with MCD.[4,19]

The pathogenesis of IgM nephropathy remains unclear, although abnormal T-cell function or a disturbance in immunoaggregate clearance by mesangial cells have been suggested.[5,20] Many studies have reported increased serum IgM or IgM immunocomplex concentration in patients with IgM nephropathy, which would support the aforementioned concept.[3,21]

Some studies of IgM nephropathy have reported a predominance of men,[2,6,8,10,22,23] whereas others have found more women.[1,3,11,14,20,24] In the present study, the entire material was dominated by men, but there were significantly more women among patients with HU. A female majority rarely has been found in any glomerulonephritis.[25] It also has been reported that sex has a prognostic value in nondiabetic chronic renal diseases.[26] In our present study, we found no statistically significant difference between men and women in the prognosis of IgM nephropathy.

There are only few reports of patients with HU or asymptomatic PU as the initial clinical symptoms of IgM nephropathy. According to our findings and some previously published studies, patients with HU would appear to have a more favorable course of the disease compared with those with PU or NS.[12,14]

Previously reported steroid response rates in IgM nephropathy vary considerably; mean percentage of steroid resistance is 28%.[4] In our series, long-term complete remission was observed in only 14% of cases. More than half of both children and adults were CS dependent, and one third had disease resistant to CS therapy. Accordingly, the response to steroid therapy in IgM nephropathy is considerably worse than in MCD.[27] The long-term prognosis in steroid responders was good. The greatest prevalence of renal insufficiency at the end of follow-up was found in patients with PU. Only two patients with PU were treated with CSs. In IgA nephropathy, it was shown that glucocorticoid therapy may reduce renal injury and improve renal function in patients without nephrotic-range PU.[28,29] It is not known whether steroid therapy also

would improve the prognosis among patients with IgM nephropathy with isolated PU.

The prevalence of hypertension was 35% at the time of biopsy and 45% at the end of follow-up. These prevalences are similar to those previously reported in IgM nephropathy and also in IgA nephropathy in Finland.[14,30] The incidence of hypertension during follow-up was greatest in the PU group, which may have an influence on the clinical outcome of these patients.

In multivariate analysis, hypertension was found to be an independent risk factor for the development of renal insufficiency. However, no parameter prognosticated progression to ESRD, possibly because only six patients reached ESRD. In 1991, O'Donoghue et al[6] reported very different risk factors in their study of 54 patients with IgM nephropathy. They found mesangial cell proliferation, mesangial sclerosis, and HU to be independent risk factors for ESRD. Here, these markers had no significant prognostic value; HU was a safety rather than a risk factor.

Many investigators have suggested that in the course of time, IgM nephropathy converts to FSGS. In the present study, 5 of 11 repeated biopsies performed during the 8 years of postbiopsy follow-up showed a typical histopathologic picture of FSGS. Because patients with FSGS have a poor prognosis, it would be important to identify the clinical or pathological factors that predict the progression of IgM nephropathy to FSGS.[7] We found no such factors, possibly because only 10% of our patients underwent a repeated biopsy. Because all patients with FSGS were in the NS and PU groups, there may be an indication of greater risk for progression in these patients than in patients with HU or PUHU.

Judging from previous findings[12,14] and the present data, we suggest there are two subgroups of IgM nephropathy: a subgroup with a predominance of men is usually manifested by NS, and the other consists mainly of women with microscopic HU.

In conclusion, we propose that IgM nephropathy may be a more severe disease than suggested. Approximately one third of the patients developed renal insufficiency of some degree, and half the patients experienced hypertension at the postbiopsy follow-up of 15 years. Some patients, especially those with PU, seem to develop FSGS. We also suggest that even within the term IgM nephropathy, there may be two different diseases with similar morphological characteristics, but different sex distributions and clinical outcomes.

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