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REVIEW

IgM nephropathy: is it closer to minimal change disease or to focal segmental glomerulosclerosis?

R. Brugnano[1] · R. Del Sordo[2] · C. Covarelli[2] · E. Gnappi[3] · S. Pasquali[3]

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Abstract Immunoglobulin (Ig)M nephropathy (IgMN), known since 1978, is a very controversial clinicopathological entity characterized by IgM diffuse deposits in the mesangium at immunofluorescence whereas light microscop identifies minimal glomerular lesion, hypercellularity and expansion of the mesangium or sclerotic focal, segmental lesion. Clinically, it is a nephrotic syndrome, especially in pediatric patients, or asymptomatic proteinuria and/or isolated hematuria. These characteristics narrowly define IgMN between minimal change disease and focal segmental glomerulosclerosis, so it is not often recognized as a separate pathology. Homogeneous epidemiologic, pathogenetic, clinical or histological data are not available. Recent research on the pathogenetic role of mesangial IgM has, however, renewed interest in IgMN and naturally the controversies.

Keywords IgM nephropathy · Minimal change disease · Focal segmental glomerulosclerosis · Nephrotic syndrome · Controversy

✉ R. Brugnano
rbrugnano@libero.it

[1] Department of Nephrology and Dialysis, S. Maria della Misericordia Hospital, Piazza Menghini, 1, San Sisto, 06156 Perugia, Italy

[2] Department of Experimental Medicine-Section of Pathological Anatomy and Histology, Medical School, University of Perugia, Perugia, Italy

[3] U.O.C Nephrology and Dialysis, S. Maria Nuova Hospital, Reggio Emilia, Italy

Introduction

Immunoglobulin (Ig)M nephropathy (IgMN) is a clinicopathological entity characterized by dominant diffuse and granular IgM deposits within the mesangium at immunofluorescence (IF), and the histological picture varies from no glomerular abnormalities to proliferation of mesangial cells, accumulation of extracellular mesangial matrix and segmental or global sclerosis. IgMN was first described in 1978 by Cohen et al. and Bhasin et al. [1, 2] as a distinct entity, but thus far there is no consensus about the significance of the presence of IgM deposits in the context of minimal change disease (MCD), mesangial proliferative glomerulonephritis (MePGN), and focal segmental glomerulosclerosis (FSGS), without associated systemic disorders [3–5]. The interpretation of IF findings is controversial in that some authors have described cases with IgM trace positivity on IF as IgMN while others have described cases with 1+ or 2+ IgM deposits as MCD. The significance of IgMN in the range of idiopathic MCD or FSGS glomerular disease and the epidemiology of IgMN are controversial. The frequency of IgMN in native renal biopsy series in children or adults varies from 2 to 18.5 % [6–8]. The disease is more common in children than in adults. In Italy, the annual frequency of IgMN over the period 1987–1993 was 1.9 % [9], but in the Italian Registry of Renal Biopsies (IRRB) from 1996 to 2000 [10] MCD, FSGS and MePGN without IgA deposits were considered as primary glomerulonephritis. The greatest prevalence of IgMN was reported in Thailand (45.8 % of 2154 biopsies) with a decline in frequency to 16.9 % from 2003–2005 [11]. We believe this demonstrates that there was an initial interest in IgMN in the 1980s, while differences in policy of renal biopsy practice in different countries makes it difficult to compare the databases across countries. The

correlation with varying biopsy timing and indications or genetic or environmental factors has still to be clarified. The clinical characteristics of IgMN do not differ from MCD and FSGS since they are associated with nephrotic syndrome (NS), steroid-resistant nephrotic syndrome (SRNS), hematuria and/or asymptomatic proteinuria. These disorders may have similar immunopathological features but are distinguished in the clinical course, in the response to therapy and the progression to end-stage renal disease (ESRD). Are MCD, IgMN and FSGS separate entities or are they part of the same spectrum of disease with overlapping features? Is IgMN in children with minimal change nephrotic syndrome a marker of disease severity, useful for a more aggressive therapeutic approach, and a prognostic marker? To answer these questions we will consider the problem from different points of view.

The morphological point of view

IgMN to date is still far from being determined based on strict pathological criteria. In his review, published in 1988, Border claimed that MePGN, MCD and idiopathic focal sclerosis are three separate disorders but they overlap because the morphological alterations of MCD appear similar to the minimal changes found in early MePGN and focal sclerosis is similar to the findings in the late stage of MePGN [12]. According to Border, the central role of the mesangium is where the immune complex is localized and the earliest histologic lesion may be segmental mesangial proliferation, which can progress to generalized mesangial hypercellularity with matrix expansion, and ultimately to segmental or diffuse sclerosis [13–15]. The distinction between the three entities is based on IF with high inter-observer variability. The light microscopy (LM) and electron microscopy (EM) pictures can be identical to that of MCD or characterized by FSGS. In several series, the diagnosis of IgMN required examination of renal biopsy by LM, IF, and EM. Some investigators consider this entity as a transitional form between MCD and FSGS [16, 17]. The International Study of Kidney Disease in Children (ISKDC) did not differentiate MCD with IgM-positive immunofluorescence from IgM-negative MCD in childhood with nephrotic syndrome [18].

Immunofluorescence

IgMN is characterized by the presence of granular, diffuse and global IgM deposits in the glomerular mesangium. However, in MCD the IgM intensity is always minimal while in FSGS IgM is segmentally and focally distributed in sclerosis areas, not diffuse, as in IgMN [7, 19, 20]. Complementary fragments of C3 are found in the majority of cases, co-localized with IgM deposits of variable intensity [1, 8, 21].

Light microscopy

The spectrum of LM findings is quite heterogeneous. The morphologic alterations range from minor changes, to variable degrees of mesangial proliferation (usually of mild to moderate degree), to an FSGS pattern accompanied by adhesion formation with the Bowman's capsule [1, 4, 20, 22]. Some authors have also reported cellular crescents [23, 24]. It is difficult to distinguish an MCD pattern on the basis of LM examination alone, and IF and EM were required to describe the picture reported in numerous series [7, 8, 17, 25–28]. An FSGS pattern as the morphologic expression of IgMN is the most controversial feature. Many studies have excluded cases with this morphology from the IgMN category, while others have observed this lesion in a significant number of cases characterized by global IgM mesangial positivity in contrast to nonspecific, segmental IgM trapping in the idiopathic form of FSGS. The reports on prevalence of this morphologic pattern in biopsies of IgMN vary widely from 9 to 65.2 % of cases [20]. Focal global sclerosis is also quite common but it can be missed due to biopsy sampling error. Some researchers have noted progression of IgMN with minor changes or mesangial proliferation to FSGS on repeated biopsies in a variety of cases [19, 20, 25, 28]. Tubulointerstitial lesions such as tubular atrophy and interstitial scarring are also commonly observed at diagnosis and are usually mild [8, 19–21].

Electron microscopy

There are very few studies on the ultrastructural features of IgMN [20]. In the majority of cases, no EM was done and the diagnosis was made on the basis of IF microscopy. The few studies that have carried out EM examination have noted small, granular to short linear electron-dense deposits in the mesangium and paramesangium, along with variable degrees of mesangial cell proliferation and mesangial matrix expansion. Variable degrees of podocyte foot effacement, segmental or diffuse, have also been observed [20, 21, 25, 26, 28]. To confirm the difficulty of defining pathological criteria, we report in Tables 1 and 2 the most frequent biopsy findings from the most relevant series in the English-language international literature between 1991 and 2014.

Table 1 Histopathological pattern reported in patients with IgMN

	O'Donoghue et al. [23] (UK)	Zeis et al. [25] (GR)	Myllymaki et al. [19] (FIN)	Singhai et al. [8] (IND)	Vanikar et al. [27] (IND)	Mokhtar et al. [21] (SA)	Kanemoto et al. [26] (J)	Mubarak et al. [30] (PK)	Spreitzer et al. [28] (SLO)
IgM+ biopsies/ series of biopsies	54/599[a]	64/683[b]	110/2217[a]	117/2928[a]	28/236[b]	36/200[a]	30/70[c]	41/1753	19/55[b]
Age of IgM+ patients, years (range)	31[d] (14–69)	6.5[e] (2–14)	29[e] (1–75)	29[e] (13–68)	10 ± 3.6[e]	7.2[e] (1–39)	7.6 ± 3.4[e]	30.21 ± 10.12[e]	4.8[d]
Study design	R	R	R	R	R	R	R	R	R
MCD	0	20	nr	11	8	nr	21	nr	19
	54	nr	nr	87	17	nr	6	nr	–
FSGS	19	7	nr	19	3	4	3	nr	–
Re-biopsies	12	16	11	–	–	–	–	–	15
MCD	0	–	1	–	–	–	–	–	–
MePGN	12	–	–	–	–	–	–	–	–
FSGS	0	16	5	–	–	–	–	–	1
IgMN	–	–	4	–	–	–	–	–	–

IgMN Immunoglobulin M nephropathy, *MCD* minimal change disease, *MePGN* mesangioproliferative glomerulonephritis, *FSGS* focal segmental glomerulosclerosis, *NS* nephrotic syndrome, *PU* proteinuria, *H* hematuria, *nr* not reported, *R* retrospective study

[a] Total biopsies

[b] Biopsies in children with NS or PU and or H

[c] Biopsies in children with steroid-dependent or steroid-resistant NS

[d] Median age

[e] Mean age

The clinical point of view

In general, clinical manifestations of IgMN are variable and the commonest presentation in the pediatric population is NS; nephropathy can occur, also, in young adults and at any age presenting as steroid-resistant nephrotic syndrome, proteinuria and/or hematuria. The natural history and the prognosis of IgMN, like its presentation and morphology, are also quite varied; probably this is in part due to the variable length of follow-up and differences in the classification criteria across studies. There are only a few long-term longitudinal studies on IgMN and the majority are retrospective. In most studies, the number of patients was relatively small and the follow-up period short. Corticosteroids remain the mainstay of therapeutic strategies in these patients, as in MCD or primary FSGS [12]. The steroid response varies considerably across the studies. Many reports have demonstrated increased steroid resistance and a less-favorable outcome in IgMN compared to MCD and, thus, they consider it as a distinct clinicopathological entity [12, 19, 20, 25, 29, 30]. In 1983, Tejani and coworkers compared two groups of nephrotic patients, both with minimal changes in association or not with IgM deposits at LM. The patients with IgM deposits were older and 60 % were steroid-dependent compared to only 14 % of those without IgM [31]. In 2003, Myllymaki et al. in Finland published one of the largest and longest follow-up studies including 110 pediatric and adult patients with IgMN and NS [19]. During a 15-year follow-up, 36 % of patients developed renal insufficiency and 23 % reached ESRD. Hypertension was diagnosed in 50 % of patients, and at multivariate analysis was the only significant risk factor for renal failure. Among histological parameters, interstitial fibrosis had the strongest prognostic value. Twenty-nine percent of nephrotic patients were resistant to corticosteroids whereas 80 % of patients with steroid-sensitive disease were steroid-dependent. In this study, 5/11 repeated biopsies for NS showed a typical histopathologic pattern of FSGS [19]. There is controversy, however, in the literature about the clinicopathological correlation and outcome. Prasad et al. and Al-Eisa et al. concluded that MCD and IgMN are clinically indistinguishable in children who are biopsied for NS [32, 33] while Zeis et al. and Swartz et al. showed a worse response to therapy in IgMN, suggesting IgM positivity at IF as a surrogate marker for severity of MCD [25, 34].

Table 2 Elementary lesions in patients with IgMN

	O'Donoghue et al. [23]	Zeis et al. [25]	Myllymaki et al. [19]	Singhai et al. [8]	Vanikar et al. [27]	Mokhtar et al. [21]	Kanemoto et al. [26]	Mubaraket al. [30]	Spreitzeret al. [28]
Total IgM+/biopsies	54/599	64/683	110/2217	117[a]/2928	28/236	36/200	30/70	41/1753	19/6240
Light microscopy									
Normal glomeruli or minimal lesions	–	20	38	nr	nr	10	nr	5	nr
Mesangial hypercellularity (variable degree)	54	64	37	nr	nr	26	nr	28	2
Mesangial matrix expansion	54	nr	nr	nr	nr	36	nr	28	nr
Focal and segmental glomerulosclerosis	19	7	40	nr	nr	4	nr	4	nr
Interstitial inflammation	nr	nr	7	nr	nr	11	nr	nr	nr
Interstitial fibrosis tubular atrophy (variable degree)	nr	nr	30	99	nr	11 3	nr	22	nr
Hyaline arteriolosclerosis/fibrointimal proliferation	nr	nr	45	99	nr	3	nr	5	nr
Immunofluorescence microscopy									
Only IgM+	2	33	32	126/142[b]	22	14	23	35	19
IgM+ C3	41	18	35	7/142[b]	3	12	–	28	–
IgM+ C3/IgG	–	–	–	7/142[b]	–	9	1	–	–
IgM+ IgA/C3/C1q/F	–	13	–	2/142[b]	–	1	1	–	–
IgM+ C1q	–	–	18	–	3	–	5	21	–
Arteriolar C3	–	–	69	–	–	–	–	–	–
IgM+ IgA/IgG/F	11	–	25	–	–	–	–	6	–
Electron microscopy									
N[a]	–	4	–	–	–	36	6	–	13
Electron dense mesangium deposits	–	4	–	–	–	22	1	–	5
Podocyte foot effacement	–	nr	–	–	–	–	–	–	11

Nr Not reported

[a] Total IgMN between 13–68 years

[b] Total IgMN

In Table 3 we report the main clinical presentation observed in various studies, with the different renal biopsy criteria, comprising, most frequently, idiopathic nephrotic syndrome and, rarely, isolated hematuria and/or proteinuria. Available clinical data at follow-up are reported in Table 4.

There are few data available on the use and response rate of immunosuppressive agents in patients with IgMN. Oral cyclophosphamide has been used in a small number of steroid-resistant or steroid-dependent patients with a response rate of up 50 % [20]. Kanemoto et al. in 2013 reviewed the clinical course of 70 children with steroid-dependent or steroid-resistant NS and observed that 30 IgM positive and/or C1q positive NS had good responses to cyclosporine, regardless of the histological pattern [26]. Also Spreitzer et al. in 2014 concluded that IgM IF-positive MCD did not signify a worse prognosis in children in comparison to C1q IF-positive MCD or IF-negative MCD [28]. Moreover, the proportion of patients in their study who received adjuvant immunosuppressive therapy (cyclophosphamide or levamisole or cyclosporine or mycophenolate mofetil) and the median of relapse-free survival time after initiation did not differ statistically between groups [28].

In contrast to FSGF, which is well known to recur early after a renal graft, there are only a few cases describing the recurrence of IgMN after transplantation [35–37]. In all cases, renal failure progressed to ESRD within several years after the diagnosis of NS, and the patients were steroid- dependent or -resistant. Rituximab was effective in two cases in combination with plasma exchange and immunoglobulins [36, 37].

Table 3 Clinical presentation and steroid response in patients with IgMN with different patterns

	O'Donoghue al. [23]	Zeis et al. [25]	Myllymaki et al. [19]	Singhai et al. [8]	Vanikar et al. [27]	Mokhtar et al. [21]	Kanemoto et al. [26]	Mubarak et al. [30]	Spreitzer et al. [28]
Total patients	54	64	110	117	28	36	30	41	19
Average follow-up (range, years)	3–10	1–12	1–15	0–6	4	1–7	3.3–6.7	≥18	1–31.1
NS	31	20	50	111	28	32	30	34	19
PU	19	14	37	6	–	2	–	2	–
HUPU	–	12	5	–	–	–	–	3	–
HU	20	18	18	–	–	18	5	26	12
24 h urinary protein, mean (gr)	6.5 (0–34)	nr	13.4 ANS 6.8 CNS 0.9 APU 1.2 CPU 0.7 APUHU	0.95 MCD 2.54 MePGN 5.3 FSGS	47.2 MCD 85.96 MePGN 139.9 FSGS m/kgBW	8.22	nr	nr	nr
Hypertension	15	nr	38	12	nc	5	3	10	9/17[a]
SCr mg/dl (range) in MCD	1.07 (0.57–5.11)	nr	–	1.46 ± 1.6	0.67 ± 0.41	nr	–	1.19 ± 0.74	–
SCr mg/dl (range) in FSGS/MePGN					0.49 ± 0.2 1.17 ± 1.88				
RF normal	–	nr	94	–	–	36	–	28	12/17[a]
RF decreased	–	nr	16	–	–	–	–	13	3/17[a]
Steroid responsive	20	14	6/47	11 MCD 31 MePGN 0 FSGS	7 MCD 8 MePGN 0 FSGS	3	–	nr	17
Steroid resistant	–	0	13/47	–	10	21	14	nr	1
Steroid dependent	–	–	28/47	–	–	8	10	nr	–

IgMN Immunoglobulin M nephropathy, *NS* nephrotic syndrome, *PU* proteinuria, *HUPU* hematuria and proteinuria, *HU* hematuria, *SCr* serum creatinine, *MCD* minimal change disease, *MePGN* mesangioproliferative glomerulonephritis, *FSGS* focal segmental glomerulosclerosis, *RF* renal function, *nr* not reported, *ANS* adult nephrotic syndrome, *CNS* child nephrotic syndrome, *APU* adult proteinuria, *CPU* child proteinuria, *APUHU* adult proteinuria and hematuria, *nc* not comparable to others

[a] Data available for 17 patients

Table 4 Available clinical data at follow-up in IgMN

	O'Donoghue et al. [23]	Zeis et al. [25]	Myllymaki et al. [19]	Singhai et al. [8]	Vanikar et al. [27]	Mokhtar et al. [21]	Kanemoto et al. [26]	Spreitzer et al. [28]
Total patients	54	64	110	117	28	36	30	19
Hypertension	30	3	49	nc	nc	nr	nr	10
24 h urinary protein mean (gr)	–	–	nc	nc	nc	nc	nr	nr
SCr mg/dl (range) in MCD	–	–	–	0.81	nc	nr	nr	nr
SCr mg/dl (range) in FSGS/MePGN	–	–	–	3.65/1.08	nc	nr	nr	nr
RF normal	20	13	83	–	25	nr	nr	nc
RF decreased	20	51	21	–		nr	nr	nc
ESRD	14	–	6	5	2	1/23	1	0

ESRD End-stage renal disease; for other abbreviations, see previous tables

The pathogenetic point of view

Since the first clinicopathological studies on MCD and FSGS in the 1970s, new insights derived from both animal models and genetic studies have enabled a better definition of these diseases, above all the identification of podocytes as the major cellular target. Injury of different kinds to the podocytes leads to a loss of interdigitating foot processes along the outer aspect of the glomerular capillary wall and podocyte depletion through detachment, apoptosis or necrosis and disruption of the glomerular charge-selective sieving barrier, leading to proteinuria [38, 39]. Clinical and experimental studies have suggested that MCD is an immune-mediated disease in which podocytes are affected by circulating cytokines produced by peripheral blood mononuclear cells or, more specifically, T-cells, pointing to a role of the immune system [40]. However, the molecular basis for MCD is still uncertain. FSGS is a pattern of injury, divided into forms based on: (1) gene disruption involving nephrin, podocin as cell-adhesion and cell-signaling proteins, and (2) extrinsic or systemic factors including viral infection, toxicity, complement activation, intracapillary hypertension, and metabolic storage diseases [39]. Studies on the biology of glomerular visceral epithelial cells have revealed the pathophysiology of cell–cell and cell–matrix interaction governing the integrity of the cell and the glomerular capillary filter and its malfunction in the nephrotic syndrome in MCD and FSGS [38, 39]. In patients with IgMN, some studies have found elevated serum IgM or IgM immune complex concentrations without structural or biochemical abnormalities of the IgM molecule, as observed in IgA nephropathy [17, 20]. The immune complex-mediated activation of the classical complement pathway has been suggested by observation of the co-localization of the complementary components along with IgM in the glomerular mesangium, in particular C3 [17, 20]. Strassheim et al. in 2013 hypothesized that IgM, as a "natural antibody", binds to endogenous neopitopes of glomerular cells after injury, as in other tissues, activating the complement system. The authors, in an experimental model of mice with adriamycin nephropathy, showed that the depletion of B cells prevented deposition of IgM and C3 in glomeruli reducing proteinuria and glomerulosclerosis and suggesting that IgM and C3 might be pathogenic and not only markers of immune injury. Also, in a subset of patients diagnosed with primary FSGS, the same authors showed that IgM and C3d co-localization indicate that IgM binds to specific glomerular epitopes and complement activation [41]; measurement of complement activation fragments in plasma from patients with FSGS further demonstrates that the complement system is activated in this disease [42]. Panzer et al., in the same group of researchers, in 2015 studied whether IgM can add to existing cellular damage, possibly by activating complement via the classical pathway (involving C1q, C4, and C2). They used an elegant murine model of non sclerotic glomerular disease. They argue that it is possible that glomerular injury simultaneously increases the classical pathway activation by natural IgM, which binds to injury-associated epitopes while also decreasing the ability of complement regulatory proteins within the glomerulus to control amplification of complement activation through the alternative pathway. Binding of IgM within the glomerulus can be a downstream event occurring secondary to glomerular damage as part of the repair process to help remove apoptic cells but it may also result in local tissue damage [43].

Discussion

The relationship between MCD, IgMN and FSGS remains controversial. Some researchers have proposed that IgMN is a transitional state between MCD and FSGS while others have suggested that in the course of time IgMN may convert to FSGS [15, 25, 31]. These hypotheses are

sustained by the low rate of response to therapy compared to MCD, the slow progression of renal failure and the low rate of recurrence post-transplantation compared to FSGS. Because patients with FSGS have a poor prognosis it is important to identify the clinical or pathological factors that predict the progression of IgMN to FSGS. It is difficult to obtain a homogeneous patient group: at the time of presentation, the duration of proteinuria varies and some patients may have already started treatment. Recently, there has been an increase in the number of publications on this disease and a renewed interest in this area to try and understand if IgM has any pathogenic role and, if so, what. Panzer and colleagues [40] studied an animal experimental model suggesting that IgM and C3 might be pathogenic and not markers of nonimmune injury: IgM bound to damaged glomeruli activated complement and amplified injury. The recent shift of attention to the pathogenic role of IgM leads to thinking that only with prospective studies and a general consensus regarding the pathological classification will it be possible to understand the etiology and pathogenesis of the disease.

In conclusion, it seems possible to describe IgMN from a clinical and morphological perspective as ranging from MCD to FSGS, but it is important to look at the immunopathogenic role of IgM to identify the subset of nephrotic patients in whom these molecular mechanisms are involved and so likely to benefit from treatment with newer drugs that target B cells or the complement system.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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