Clinical characteristics and outcomes of idiopathic membranous nephropathy with glomerular IgM deposits

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Abstract
Glomerular IgM deposition is commonly shown in idiopathic membranous nephropathy, but the clinicopathological features and outcomes of IMN with IgM deposition are unclear. This single-center prospective cohort study enrolled 210 patients with biopsy-proven IMN from January 2016 to December 2018. Clinicopathological features, treatment responses, and kidney outcomes were compared between patients with and without IgM deposition. In total, 76 (36.2%) patients show glomerular IgM deposition. Patients with IgM deposition were younger (45 ± 13.30 vs. 50.59 ± 13.65 years, \(P = 0.006\)), had a higher estimated glomerular filtration rate (eGFR) (100.03 [81.31–111.37] vs. 92.67 [74.71–106.63] mL/min/1.73 m², \(P = 0.041\)), and had a lower proportion of nephrotic syndrome (60.5% vs. 75.4%, \(P = 0.024\)) at the time of kidney biopsy. Patients with IgM deposition had a significantly higher proportion of focal segmental glomerular sclerosis (FSGS) lesions (27.6% vs. 13.4%, \(P = 0.011\)) and C1q deposition (72.4% vs. 57.5%, \(P = 0.032\)). Although the treatments and initial treatment responses were comparable, patients with glomerular IgM deposition had a significantly greater proportion of eGFR decline of ≥ 5 mL/min/1.73 m² per year (log-rank test, \(P < 0.001\)) and eGFR decrease of ≥ 10% from baseline (log-rank test, \(P = 0.003\)). Cox regression analysis showed that IgM deposition was an independent risk factor of eGFR decline of ≥ 5 mL/min/1.73 m² per year (HR, 2.442; 95% CI, 1.550–3.848, \(P < 0.001\)) and eGFR decline by ≥ 10% from baseline (HR, 2.629; 95% CI, 1.578–4.385, \(P < 0.001\)) during follow-up. IgM deposition in the glomeruli is an independent risk factor for decreased renal function in patients with IMN.

Keywords IgM deposition · Idiopathic membranous nephropathy · Clinicopathological features · Renal outcomes

Background
Idiopathic membranous nephropathy (IMN) is the most common cause of nephrotic syndrome in adults [1, 2] and has become the most common primary glomerular disease following IgA nephropathy (IgAN) in China [3]. IMN is mediated by a variety of autoantibodies against podocytes and is clinically characterized by proteinuria or nephrotic syndrome and pathologically characterized by granular deposits of IgG and C3 subepithelial deposits, diffuse thickening of the basement membrane, and extensive fusion of podocyte foot processes [1, 4, 5].

Complement activation is confirmed to be an indispensable link in the pathogenesis of IMN [1, 6–8]. However, the main pathogenic antibodies of IMN are the anti-M-type phospholipase A2 receptor (PLA2R) antibody [9] and the thrombospondin type-1 domain-containing 7A (THSD7A) antibody [10], which are dominated by the IgG4 subtype. Although some studies have suggested that IgG4 may mediate podocyte injury by activating complement through the lectin pathway [11, 12], most studies indicate that IgG4 has a very limited capability to activate the complement system, and it is believed that IgG4 cannot activate complement through the classical and alternative pathways [13, 14].
Traditionally, deposition of other types of immune complexes (IgM, IgA, C1q) in the glomeruli is usually considered to be a feature of secondary membranous nephropathy [15]. In clinical practice, however, we have found that many patients who have IMN with positive anti-PLA2R antibodies also have IgM deposition in the glomeruli. Whether glomerular IgM deposition has an impact on the clinicopathological features and outcomes of IMN is currently unknown. In this study, we investigated the clinicopathological characteristics and clinical outcomes of IMN with glomerular IgM deposition.

**Methods**

**Study population**

This study consecutively enrolled 210 patients with biopsy-proven IMN from January 1, 2016, to December 31, 2018, in the First Affiliated Hospital of Sun Yat-Sen University. Patients with known secondary MN such as that caused by a tumor, rheumatic immune disease (e.g., systemic lupus erythematosus, Sjögren’s syndrome, rheumatoid arthritis, antineutrophil cytoplasmic antibody-associated vasculitis), infectious-related nephritis (e.g., hepatitis B-related nephritis, hepatitis C, syphilis), a clear history of nephrotoxic drug use or history of heavy metal exposure, and diabetic nephropathy were excluded. The pathological data and clinical data of 210 patients with IMN who met the inclusion criteria were collected and followed up until December 31, 2019, for at least 6 months or until they developed end-stage renal disease or died (Fig. 1). This research complied with the Declaration of Helsinki and was approved by the Ethics Committee of Sun Yat-Sen University (EC No. 2019482).

**Clinical and pathological data**

Nephrotic syndrome is defined as a urinary protein concentration of > 3.5 g per 24 h and a serum albumin concentration of < 30 g/L. The estimated glomerular filtration rate (eGFR) was calculated using the formula established by the Chronic Kidney Disease Epidemic Collaboration [16]:

\[
eGFR = 144 \times \frac{\text{serum creatinine}}{0.7}^{0.329} \\
\times (0.993)^{\text{Age}} \quad \text{if female: serum creatinine} \leq 62(0.7) \\
\]

\[
eGFR = 144 \times \frac{\text{serum creatinine}}{0.7}^{1.209} \\
\times (0.993)^{\text{Age}} \quad \text{if female: serum creatinine} > 62(0.7) \\
\]

\[
eGFR = 141 \times \frac{\text{serum creatinine}}{0.9}^{0.411} \\
\times (0.993)^{\text{Age}} \quad \text{if male: serum creatinine} \leq 80(0.9) \\
\]

\[
eGFR = 141 \times \frac{\text{serum creatinine}}{0.9}^{1.209} \\
\times (0.993)^{\text{Age}} \quad \text{if male: serum creatinine} > 80(0.9) \\
\]

Glomerular membranous nephropathy lesions were classified into four stages according to the Ehrenreich–Churg staging system. Chronic tubulointerstitial injury lesions were graded semi-quantitatively from 0 to 2 according to the percentage of tubular atrophy injury: 0, ≤ 5%; 1, 6–25%; and 2, > 25%. The degree of interstitial fibrosis was defined as absent, mild, moderate, or severe. The fluorescence intensity of the IgG, IgM, IgA, C3, C1q, and IgG subclass was determined as negative or positive. Non-physiological glomerulosclerosis was defined as a proportion of glomerulosclerosis exceeding ((age / 2) − 10) × 100% [17, 18].
Treatment and follow-up

The use of corticosteroids and immunosuppressive agents was in compliance with the 2012 KDIGO guidelines [19]. Complete remission was defined as proteinuria of ≤ 0.3 g per 24 h and a serum albumin concentration of ≥ 35 g/L regardless of creatinine clearance [20]. Partial remission was defined as a reduction in proteinuria of ≥ 50% from baseline plus final proteinuria of 0.3 to 3.5 g per 24 h and a serum albumin level of ≥ 30 g/L regardless of creatinine clearance [20]. Clinical remission included complete remission and partial remission. Non-response, deterioration, and remission did not reach the level of partial remission; all were defined as no response. The primary endpoint event was renal function decline of ≥ 5 mL/min/1.73 m² per year and a ≥ 10% decline of eGFR from baseline. The secondary endpoint event was clinical remission.

Statistical analysis

Statistical analysis was performed using SPSS version 25 software (IBM Corp., Armonk, NY, USA), and P < 0.05 was considered statistically significant. Normally distributed variables are expressed as mean ± standard deviation, and non-normally distributed continuous variables are expressed as median with interquartile range. Categorical variables are expressed as absolute value and percentage. For continuous variables, comparisons between two groups were made using Student’s t test for normally distributed data and the Wilcoxon rank-sum test for nonparametric data. For categorical variables, the Chi-square test was used (Fisher’s exact test was used when the theoretical frequency was < 5). The correlation of IgM deposition with focal segmental glomerulosclerosis (FSGS) lesions and C1q deposition was tested using Pearson’s Chi-square analysis. Kaplan–Meier survival analysis was used to compare survival between the IgM-positive and IgM-negative groups, and a Cox proportional hazards model was used to analyze the correlation between IgM deposition and renal outcomes.

Results

Patients’ baseline clinical and pathological characteristics

Among the 210 patients with biopsy-proven IMN, 126 (60.0%) were males and their median age was 50.00 (40.00–59.25) years. The urinary protein excretion rate was 6.25 (3.09–9.16) g per 24 h, the median serum albumin concentration was 23.85 (19.80–28.18) g/L, the median serum creatinine concentration was 76.00 (62.00–95.00) μmol/L, and the median eGFR was 94.57 (76.55–108.50) mL/min/1.73 m² (Table 1).

In total, 41 (19.5%) patients presented with non-physiological glomerulosclerosis, 39 (18.6%) patients showed FSGS lesions, and 15 (7.1%) patients exhibited crescent formation. Additionally, 209 (99.5%) patients presented with granular staining of IgG, and IgG subclass staining was available in 139 (66.2%) patients. Of these 139 patients, 60 (43.2%) had IgG2 deposition, 135 (97.1%) had IgG4 deposition, and 124 (89.2%) had predominant IgG4 deposition. Moreover, 76 (36.2%) patients presented with IgM deposition and 181 (86.2%) patients showed C3 staining along the glomerular capillary walls. A total of 139 patients had available glomerular PLA2R staining; of them, 131 (94.2%) showed positive PLA2R staining in the glomerular basement membrane (Table 2).

| Parameters                                | n = 210 |
|-------------------------------------------|---------|
| Age (years)                               | 50.00 (40.00–59.25) |
| Gender (M), n (%)                         | 126 (60.0) |
| Hypertension, n (%)                       | 75 (35.7) |
| Diabetes, n (%)                           | 23 (11.0) |
| Nephritic syndrome, n (%)                 | 147 (70.0) |
| Proteinuria (g/24 h)                      | 6.25 (3.09–9.16) |
| Serum albumin (g/L)                       | 23.85 (19.80–28.18) |
| Serum creatinine (μmol/L)                 | 76.00 (62.00–95.00) |
| eGFR (mL/min/1.73 m²)                     | 94.57 (76.55–108.50) |
| eGFR < 60 mL/min/1.73 m²                  | 23 (11.0) |
| eGFR < 30 mL/min/1.73 m²                  | 8 (3.8) |
| Treatments                                |         |
| ACEI/ARBs only, n (%)                     | 83 (39.5) |
| Immunosuppressive therapies, n (%)        | 127 (60.5) |
| Corticosteroids only, n (%)               | 57/127 (44.9) |
| Corticosteroids + CNIs, n (%)             | 61/127 (48.0) |
| Corticosteroids + CTX, n (%)              | 9/127 (7.1) |
| Follow-up duration (months)               | 25.00 (15.75–37.00) |
| Treatment responses                       |         |
| Complete remission, n (%)                 | 92/210 (43.8) |
| Partial remission, n (%)                  | 45/210 (21.4) |
| No response, n (%)                        | 73/210 (34.8) |
| Death, n (%)                              | 5/210 (2.4) |
| ESRD(eGFR < 15 mL/min/1.73 m²), n (%)     | 1/210 (0.5) |
| eGFR decline ≥ 50%, n (%)                 | 9/210 (4.3) |
| eGFR decline ≥ 30%, n (%)                 | 26/210 (12.4) |
| Creatinine double, n (%)                  | 3/210 (1.4) |

| Parameters                                | n = 210 |
|-------------------------------------------|---------|

IMN idiopathic membranous nephropathy, M male, eGFR estimated glomerular filtration rate, ACEI/ARB angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, CNIs calcineurin inhibitors (including cyclophosphamide A and tacrolimus), CTX cyclophosphamide, ESRD end-stage renal disease
For the initial treatment, 83 (39.5%) patients were treated conservatively and 127 (60.5%) were treated with immunosuppressants. Of these 127 patients, 57 (44.9%) were treated with corticosteroids only, 61 (48.0%) were treated with corticosteroids plus calcineurin inhibitors, and 9 (7.1%) were treated with corticosteroids plus cyclophosphamide (Table 1).

Clinicopathological characteristics of patients with IMN with IgM deposition

Among the 210 patients with IMN, 76 had IgM deposition in the glomeruli. Of these 76 patients, 54 had glomerular PLA2R immunofluorescence information, and 52 (96.3%) PLA2R staining was positive. Compared with patients without glomerular IgM deposition, patients with IgM deposition were younger (45 ± 13.30 vs. 50.59 ± 13.65, P = 0.006), had a higher eGFR (100.03 [81.31–111.37] vs. 92.67 [74.71–106.63], P = 0.041), and showed a lower proportion of nephrotic syndrome (60.5% vs. 75.4%, P = 0.024) at the time of kidney biopsy (Table 3).

Pathologically, patients who had IMN with IgM deposition had a higher proportion of concurrent FSGS lesions (27.6% vs. 13.4%, P = 0.011) and C1q deposition (72.4% vs. 57.5%, P = 0.032) (Table 4), and there was no statistically significant difference in treatments or treatment responses between the two groups (Table 3).

Correlation of IgM deposition with FSGS lesions and C1q and C3 deposition

Of the 39 patients with FSGS lesions, 23 (59.0%) presented with C1q deposition and 35 (89.7%) had C3 deposition. All patients with FSGS + C1q deposition had C3 deposition. Moreover, correlation analysis showed a significant correlation between IgM deposition and FSGS lesions (r = 0.175, P = 0.011), C1q deposition (r = 0.148, P = 0.032), and FSGS + C1q deposition (r = 0.244, P < 0.001) (Table 5).

IgM deposition and renal outcomes

Kaplan–Meier survival curves preliminarily showed that compared with patients without glomerular IgM deposition, more patients with glomerular IgM deposition had an eGFR decline of ≥ 5 mL/min/1.73 m² per year (log-rank test, P < 0.001) and an eGFR decrease of ≥ 10% from baseline (log-rank test, P = 0.003) (Fig. 2).

After adjusting for age, sex, urinary protein level, eGFR, glomerulosclerosis, FSGS lesions, crescents, chronic interstitial tubular injury, hyalinization, stage of membranous nephropathy, C1q deposition, treatment regimen, and treatment response factors, multiple Cox regression analysis showed that the risk of an eGFR decline of ≥ 5 mL/min/1.73 m² per year and an eGFR decline of ≥ 10% from baseline was 2.442 times higher (95% confidence interval, 1.550–3.848, P < 0.001) and 2.629 times higher (95% confidence interval, 1.578–4.385, P < 0.001) in patients with than without IgM deposition during the follow-up period (Table 6).

Discussion

This study involved 210 adult patients with biopsy-proven IMN from 2016 to 2018, of whom 76 (36.2%) had IgM deposition in the glomeruli. We found that patients who had...
IMN with glomerular IgM deposition were younger, had better renal function, and had a lower proportion of nephrotic syndrome than those without IgM deposition at the time of kidney biopsy. Pathologically, patients who had IMN with glomerular IgM deposition had more C1q deposition and more FSGS lesions. Although there was no significant difference in treatment regimens and clinical remission between the two groups, the risk of renal function deterioration was higher in the IgM deposition group. Though our results cannot verify the cause–effect relationship of IgM deposition and those clinical findings, taking into account the results of Cox regression, we suppose IgM deposition is an independent risk factor for FSGS lesion, C1q deposition, and deterioration of renal function. For the reason that more young IMN patients accompanied with IgM deposition on renal biopsy, we suggested that FSGS may cause more prominent glomerular hematuria which leading clinicians to perform renal biopsy right away; for elderly patients with renal syndrome, clinicians are more inclined to perform PLA2R examination; first, then some of them may clinically diagnosed as IMN and caused the postpone of renal biopsy.

Similar to our study, previous studies have shown that among patients with FSGS [21] and IgAN [22], those with IgM deposition were younger (FSGS positive vs. negative, 24.5 [18.8–39.0] vs. 46.5 [26.0–64.0] years; IgAN moderate vs. no or trace, 31.71 ± 10.21 vs. 34.82 ± 11.03 years), but patients with IgM deposition showed heavier proteinuria. The reason for these differences may be that IMN is a podocyte lesion disease, which itself is characterized by massive proteinuria, and the podocyte-induced massive proteinuria covered up the enhanced proteinuria caused by IgM deposition damage.

Our study also showed that patients with IgM deposition presented with more glomerular C1q deposition and FSGS lesions. Meanwhile, 59.0% (23/39) of patients with FSGS lesions had C1q deposition. Although there was no significant difference in immune complex deposition in the glomeruli in patients with typical FSGS lesions, thin basement membrane nephropathy, and mild glomerular lesions, but one study showed that patients with FSGS lesions had a significantly higher IgM deposition rate than patients with thin basement membrane nephropathy and mild glomerular lesions (55.4% vs. 30.0%) [23]. In addition, other studies have shown that patients with IgM nephropathy who present with only IgM deposits in the mesangial area

| Parameters                  | With IgM deposition | Without IgM deposition | P value |
|-----------------------------|---------------------|------------------------|---------|
| Gender (male/female)        | 42/34               | 84/50                  | 0.291   |
| Age (years)                 | 45±13.30            | 50.59±13.65            | 0.006   |
| Proteinuria (g/24 h)        | 4.50 (2.26–9.04)    | 6.58 (3.51–9.5)        | 0.149   |
| Serum albumin (g/L)         | 24.55±6.802         | 24.30±6.017            | 0.785   |
| Nephrotic syndrome, n (%)   | 46 (60.5)           | 101 (75.4)             | 0.024   |
| Serum creatinine (μmol/L)   | 72.50 (58.50–89.75) | 78.00 (64.00–95.75)    | 0.239   |
| eGFR (ml/min /1.73 m²)      | 100.03 (81.31–111.37)| 92.67 (74.71–106.63)  | 0.041   |
| Hypertension, n (%)         | 22 (28.9)           | 53 (39.6)              | 0.123   |
| Diabetes, n (%)             | 14 (10.4)           | 9 (11.8)               | 0.756   |
| Treatment                   |                     |                        | 0.135   |
| ACEI/ARBs only, n (%)       | 31 (40.8)           | 52 (38.8)              |         |
| Corticosteroids, n (%)      | 22 (28.9)           | 35 (26.1)              |         |
| Corticosteroids + CNIs, n (%)| 17 (22.4)          | 44 (32.8)              |         |
| Corticosteroids + CTX, n (%)| 6 (7.9)             | 3 (2.2)                |         |
| Spontaneous remission, n (%)| 19 (25.0)           | 32 (23.9)              | 0.856   |
| Treatment response, n (%)   |                     |                        | 0.852   |
| Complete remission, n (%)   | 31 (40.8)           | 61 (45.5)              |         |
| Partial remission, n (%)    | 20 (26.3)           | 25 (18.7)              |         |
| No response, n (%)          | 25 (32.9)           | 48 (35.8)              |         |

Bold values suggested that the P <0.05

*IMN* Idiopathic membranous nephropathy, *eGFR* estimated glomerular filtration rate, *ACEI/ARBs* angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, *CNIs* calcineurin inhibitors (including cyclophosphamide A and tacrolimus), *CTX* cyclophosphamide.
are more likely to progress to FSGS lesions as confirmed by repeat renal biopsy [24–26]. In patients with primary FSGS lesions, the presence of concurrent IgM and C3 deposition has been shown to be an independent risk factor for renal insufficiency (hazard ratio, 5.67) [21]. Some studies have suggested that IgM deposition in the mesangial region is a transitional state between minimal change disease and FSGS [25, 27]. All of the above studies suggested that glomerular IgM deposition may be associated with FSGS lesions.

IgM is mainly secreted and synthesized by plasma cells in the spleen and lymph nodes, accounting for 5% to 10% of the total serum immunoglobulins. IgM exists as a pentamer and is the largest immunoglobulin in the human circulatory system.
A commonly accepted view is glomerular IgM deposition represents passive trapping of the large IgM macromolecule within areas of sclerosis. It was recently proposed that in kidney disease, antibodies mainly exert their pathogenic effects by activating complement. Activation of C1q is the first step in activation of the classical complement pathway. C1q has six sites that can bind to immunoglobulin molecules, and it is activated only when more than two sites are bound. As a pentamer, IgM has a higher ability to activate C1q than monomer-form IgG [28–30]. Numerous studies have confirmed that IgM deposition in the glomeruli is often accompanied by C3, C4, and C1q deposition [22, 31–33]. Animal models have demonstrated that IgM deposited within the glomerulus mediates glomerulosclerosis by activating the classical and alternative complement pathways [29, 34]. Panzer et al. [35] established a mouse model of non-sclerotic glomerulonephritis and found that special IgM that recognizes phospholipids became bound to glomerular epitopes and contributed to the progression of glomerular damage. Strassheim et al. [29] found that depletion of peritoneal B lymphocytes by hypotonic shock had no effect on plasma IgM levels in a mouse model of adriamycin-induced FSGS but could prevent both glomerular IgM and C3 deposition; additionally, they found that C3 and IgM co-localized within the glomeruli. These results suggest that the IgM deposited in the glomeruli may be secreted by innate immune B-1a cells that recognize non-protein antigens [29, 36, 37].

Table 5 Correlation of IgM deposition with FSGS lesions and C1q and C3 deposition

| Parameters | n      | r     | P    |
|------------|--------|-------|------|
| FSGS       | 18.6%  | 0.175 | 0.011|
| C1q        | 66.2%  | 0.148 | 0.032|
| C3         | 86.2%  | 0.014 | 0.835|
| FSGS + C1q | 11.0%  | 0.244 | < 0.001|
| FSGS + C3  | 16.7%  | 0.244 | < 0.001|
| FSGS + C1q + C3 | 11.0% (23/210) | 0.244 | < 0.001|

Bold values suggested that the P <0.05
All patients with FSGS + C1q deposition had C3 deposition

Table 5 Correlation of IgM deposition with FSGS lesions and C1q and C3 deposition

FSGS focal segmental glomerular sclerosis

Our study also showed no difference in short-term treatment responses between patients with and without IgM deposition under similar treatment (40.8% vs. 45.5%, 26.3% vs. 18.7%, and 32.9% vs. 35.8% for complete remission, partial remission, and non-response, respectively; P = 0.852). However, renal outcomes were worse in the IgM deposition group, and IgM deposition was an independent risk factor for poor renal function outcomes in patients with IMN. Similarly, a study of 106 patients with primary FSGS showed no statistically significant difference in the initial treatment response or relapse rate between patients with and without IgM deposition when the initial treatment was comparable, but the proportion of refractory nephrotic syndrome (defined as no response to treatment or steroid dependency) was higher in patients with IgM deposition (34.0% vs. 15.6%, P = 0.04; the proportion of non-response to treatment was 18.9% vs. 11.1%, P = 0.43), and IgM deposition was an independent risk factor for refractory disease (odds ratio, 3.97) and renal progression (hazard ratio, 4.75) [21]. Similarly, patients who had minimal change disease with IgM deposition showed a higher proportion of steroid-resistant disease (45.5% vs. 41.0%, P = 0.05), and more patients progressed to renal failure (10.4% vs. 1.7%, P = 0.05) [38]. In patients with IgAN, more severe IgM deposition is associated with heavier proteinuria (3.38 ± 3.14 vs. 2.52 ± 3.01 g per 24 h),

Fig. 2 Crude analyses of relationship between IgM deposition and renal function decline. Kaplan–Meier estimates of a eGFR decline of ≥ 5 mL/min/1.73 m2 per year and b eGFR decline of ≥ 10% from baseline. eGFR, estimated glomerular filtration rate
### Table 6 Relationship between IgM deposition and renal function prognosis

|                      | HR (95% CI) | P value |
|----------------------|-------------|---------|
| eGFR decline ≥ 5 ml/min /1.73 m²/year (cases = 96) |            |         |
| Model 1              | 2.063 (1.369, 3.109) | 0.001   |
| Model 2              | 2.355 (1.529, 3.628) | < 0.001 |
| Model 3              | 2.324 (1.508, 3.582) | < 0.001 |
| Model 4              | 2.442 (1.550, 3.848) | < 0.001 |

Model 1: Unadjusted
Model 2: Adjusted for age and sex
Model 3: Adjusted for Model 2 covariates, proteinuria, and eGFR
Model 4: Adjusted for Model 3 covariates, proteinuria, and eGFR

**Conclusion**

IgM deposition in the glomeruli is an independent risk factor for decreased renal function in patients with IMN.
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