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# Clinical Features and Outcomes in Patients With Membranous Nephropathy and Crescent Formation

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**Abstract:** Cases of membranous nephropathy (MN) with crescent formation, in the absence of lupus, hepatitis B virus infection, anti-glomerular basement membrane (GBM) nephritis, or antineutrophil cytoplasmic antibody (ANCA), are on record. Clinical presentation and treatment outcomes in these patients are unclear.

All patients with biopsy-proven MN diagnosed between years 2008 and 2014 and followed up were enrolled retrospectively. Patients with ANCA, anti-GBM antibodies, lupus, hepatitis B virus infection, or malignance were excluded. Clinical features and outcomes were compared between MN patients with and without crescent.

Out of 401 consecutive patients with idiopathic MN, 28 (6.9%) showed crescent formation in 4.9% (2.2%–16.7%) of glomeruli. Mean age of these patients was 50.1 ± 11.1 years, and they presented with heavy proteinuria (6.5 ± 4.8 g/24 h) and hematuria; 21.4% of these patients had declined estimated glomerular filtration rate (<60 mL/min/1.73 m<sup>2</sup>) on biopsy. Anti-phospholipase A<sub>2</sub> receptor antibody was detectable in 79.7% of these patients. These clinical features were comparable to the MN patients without crescent ( $P > 0.05$ ). Twelve (42.9%) patients received steroids plus immunosuppressive therapy similar to that in patients without crescent (41.3%). Fewer patients with crescents achieved remission (67.9% vs 86.7%,  $P = 0.029$ ). Crescent formation was a risk factor for no response to the treatments (odds ratio [OR] = 3.1,  $P = 0.033$ ). Higher percentage of crescents predicted more risk for no remission (OR = 1.2,  $P = 0.038$ ). Patients with crescents presented more frequencies of abnormal serum creatinine during follow-up (10.7% vs 1.3%,  $P = 0.031$ ). Crescent formation was

also a risk factor for worse renal outcome (relative risk = 10.2,  $P = 0.046$ ).

MN patients with crescents showed unfavorable therapeutic response and tended to have worse renal outcomes. More aggressive treatments and renal protection might be considered to improve the outcomes.

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**Abbreviations:** ANCA = antineutrophil cytoplasmic antibody, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, GBM = glomerular basement membrane, MN = membranous nephropathy, OR = odds ratio, SLE = systemic lupus erythematosus.

## INTRODUCTION

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults,<sup>1–3</sup> and our center suggests that the frequency of idiopathic membranous nephropathy (iMN) has doubled over the last 10 years.<sup>4</sup> Kidney histomorphology shows thickened glomerular basement membrane (GBM), granular staining for IgG and complement along the periphery of glomerular capillary loops, and electron-dense subepithelial deposits with associated diffuse podocyte foot-process effacement.<sup>5</sup> In most idiopathic MN, the M-type phospholipase A<sub>2</sub> receptor (PLA<sub>2</sub>R) protein constitutive expression on podocyte surface has been identified as a major target antigen.<sup>6,7</sup> The natural history of the disorder is variable. Twenty-five percent of the patients may experience a complete spontaneous remission of proteinuria within 5 years, whereas 35% may progress to end-stage renal disease (ESRD) by 10 years.<sup>8</sup> Patients with persistent proteinuria and overtly declining renal function are at a higher risk for progressive renal deterioration.

Crescent formation is the most aggressive glomerular structure injury that can be resulted from various causes and pathogenic mechanisms.<sup>9</sup> Histologically, it is characterized by the accumulation of cells derived from proliferating and de-differentiated visceral and parietal cells in the Bowman's space.<sup>10,11</sup> Crescentic glomerulonephritis usually presents with the clinical picture of rapidly progressive glomerulonephritis; early treatment is of paramount importance for these patients. The current approach is based on a combination of corticosteroids and cytotoxic drugs with the aims of quenching the active inflammation and abating the cellular response and the antibody production.<sup>10</sup>

In idiopathic MN patients, crescent formation is rare unless there is concurrent anti-GBM disease or antineutrophil cytoplasmic antibody (ANCA) disease.<sup>12–14</sup> There are several reports on the combination of MN and anti-GBM antibody or ANCA.<sup>15–17</sup> Their clinical phenotypes are well described,<sup>16,18</sup> and in some

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studies distinct disease mechanisms are proposed.<sup>13,19,20</sup> However, crescents may also be encountered in MN patients lacking anti-GBM, ANCA, or clinical manifestations of lupus or chronic infections. Very few cases have been documented.<sup>15,21–24</sup> The clinical and pathological presentation of this disorder is still unclear. The effect of crescent formation on renal outcomes and its indication for the optimal treatment approach is yet to be defined. The present study was aimed at assessing the prevalence, clinical features, and outcomes of idiopathic MN with crescent formation in a large consecutive cohort.

## MATERIALS AND METHODS

### Patients and Sera

A total of 401 consecutive patients with biopsy-proven idiopathic MN diagnosed between the years 2008 and 2014, and followed up for at least 1 year at our center, were enrolled retrospectively. Patients with known secondary MN, such as hepatitis B/C virus infection, lupus, malignancy, rheumatoid arthritis, medications, and heavy metal poisoning, were excluded. Patients with ANCA, anti-GBM antibodies, lupus, or other identified likely causes of crescentic MN (eg, syphilis or concurrent postinfectious glomerulonephritis) were also excluded. Clinical data of the patients were collected at the time of diagnosis as well as during follow-up. The research was in compliance of the Declaration of Helsinki and approved by the ethics committee of Peking University First Hospital. Informed consent was obtained for sampling tissue and blood.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels using the Modification of Diet in Renal Disease Study equation adjusted for Chinese populations<sup>12</sup>:  $eGFR = 175 \times (\text{plasma creatinine})^{-1.234} \times \text{age}^{-0.179} \times 0.79$  (if female). Decreased eGFR was defined as  $<60 \text{ mL/min/1.73 m}^2$ .

### Renal Biopsies

Renal biopsy was performed at the time of diagnosis in all patients with the methods described previously.<sup>25</sup> The methods for renal biopsies specimen examinations are performed according to the standard operating procedure at our center.<sup>25</sup>

Glomerular MN lesions were classified into 4 stages according to the Ehrenreich and Churg's classification criteria.<sup>26</sup> Tubular atrophy and interstitial fibrosis were graded semiquantitatively from normal to severe (normal, no tubular or interstitial lesions; mild, 5%–25% of interstitial tissue affected; medium, 25%–50% of interstitial tissue affected; severe, >50% of interstitial tissue affected).

### Detection of Circulating Anti-PLA<sub>2</sub>R Antibodies

Plasma samples were collected on the day of renal biopsy, and then stored in aliquots at  $-80^\circ\text{C}$  until use. Circulating anti-PLA<sub>2</sub>R antibodies were detected by a commercial direct immunofluorescence assay (FA1254-1005-50; EUROIMMUN AG, Lübeck, Germany), with the use of a human embryonic kidney cell line (HEK293) that was transiently transfected with full-length complementary DNA encoding a PLA<sub>2</sub>R1 isoform as cell substrates. The detection was performed on an immunofluorescent assay Mosaic slide following the standard instructions.<sup>27</sup> Antibody positivity was defined as positive staining at plasma dilution of 1:10.

### Treatment and Follow-Up

The use of steroids and immunosuppressive agents at our center was in compliance with the 2012 KDIGO (Kidney

Disease: Improving Global Outcomes) guideline for glomerulonephritis.<sup>13</sup>

For evaluation of the therapeutic response of these patients, complete remission was defined as urinary protein excretion  $<0.3 \text{ g/d}$ , accompanied by a normal serum albumin concentration, and a normal serum creatinine. Partial remission was defined as urinary protein excretion  $<3.5 \text{ g/d}$ , and a 50% or greater reduction from peak values, accompanied by an improvement or a normalization of the serum albumin concentration and stable serum creatinine. Patients who did not meet the definitions above were considered to be no remission. For evaluation of the renal outcomes, the idiopathic endpoint was ESRD; the second endpoint was the abnormal of serum creatinine  $>133 \mu\text{mol/L}$ .

### Statistical Analysis

Statistical analysis was performed using statistical software SPSS 13.0 (SPSS Inc, Chicago, IL). Patients without crescent were randomly selected with the use of simple random selected function in SPSS without specific standard. Parametric data were presented as means  $\pm$  standard deviation. Nonparametric data were presented as median values with their intervals from the 25th to 75th percentile. Intergroup differences with respect to quantitative parameters were assessed using *t* test for normally distributed data. Differences of semiquantitative data were tested with the Kruskal-Wallis test and the Mann-Whitney *U* test. Differences of qualitative data were compared using the  $\chi^2$  test/Fisher exact test. Kaplan-Meier curves were used to analyze renal outcomes. Univariate survival analysis was performed using the log-rank test. Multivariate Cox regression models were built up without selection processes. Results were expressed as odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI). Considering the small sample size of patients with crescents, penalized regression was used to improve the accuracy of risk prediction, using glmnet package in R language (R 3.1.0).<sup>28,29</sup> All probabilities were 2-tailed, and the level of significance was set at 0.05.

## RESULTS

### Clinical and Laboratory Data

Among the 401 consecutive patients with biopsy-proven idiopathic MN, there were 28 (6.9%) patients having crescent formation in glomeruli on the renal biopsy specimens. Any case of MN with glomeruli having at least one cellular or fibrocellular crescent on light microscopy was included. Patients with ANCA, anti-GBM antibodies, lupus, or other identified likely causes of crescentic MN (eg, syphilis or concurrent postinfectious glomerulonephritis) were excluded. Out of 373 patients having idiopathic MN without crescent formation, 75 were randomly selected for comparison (Figure 1).

Among the 28 patients with crescentic MN, 11 patients were male and 17 were female, with a mean age of  $56.0 \pm 11.1$  years. Twenty (71.4%) of these patients had nephrotic syndrome. All patients presented with proteinuria ( $6.5 \pm 4.8 \text{ g/24 h}$ ) and 89.3% of patients had microscopic hematuria. The mean albumin and serum creatinine levels were  $26.8 \pm 7.7 \text{ g/L}$  and  $66.2 \pm 20.5 \mu\text{mol/L}$  ( $0.7 \pm 0.2 \text{ mg/dL}$ ), respectively, at the time of renal biopsy. The demographic and clinical data are shown in Table 1.

Patients with idiopathic MN with and without crescents had comparable levels of serum creatinine, serum albumin, and urinary protein excretion at the time of renal biopsy (Table 1).

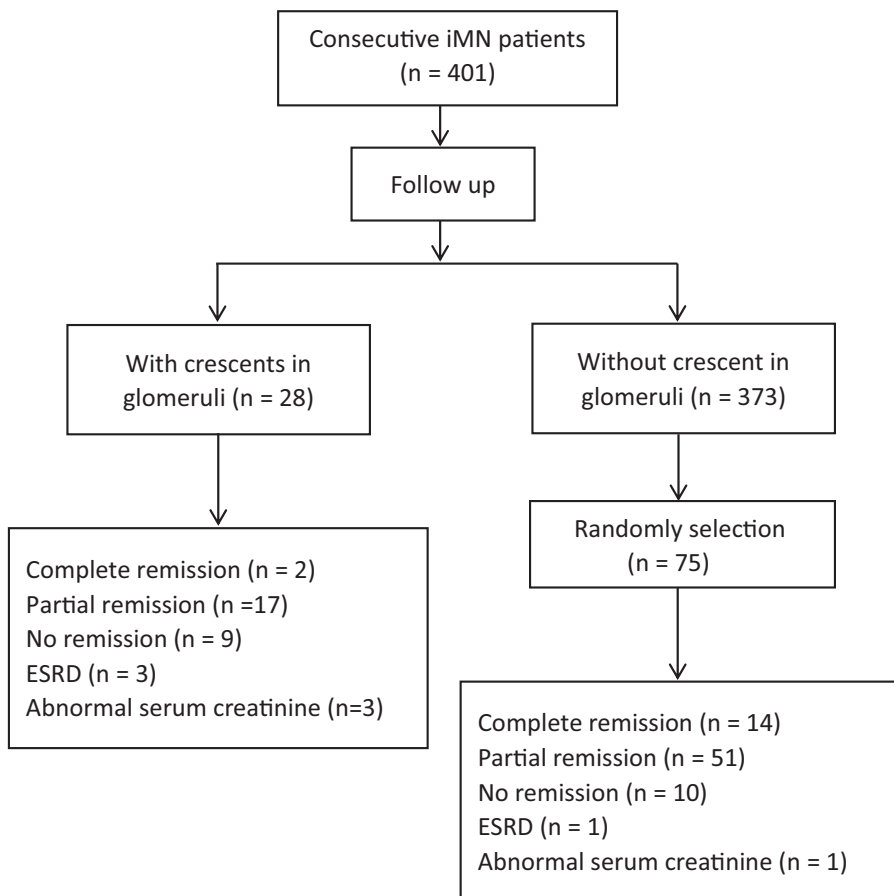


FIGURE 1. Schematic illustration of the study design.

The level of hemoglobin in iMN patients with crescent formation was lower than that in iMN patients without crescents ( $127.4 \pm 14.8$  g/L vs  $139.4 \pm 17.6$  g/L,  $P = 0.002$ ).

Circulating anti-PLA<sub>2</sub>R autoantibodies were detected by direct immunofluorescence assay at the time of renal biopsy. There were 79.7% of patients with MN and crescents contained positive anti-PLA<sub>2</sub>R antibodies, with no significant difference from that in MN patients without crescents (64.3%,  $P = 0.737$ ) (Table 1).

### Renal Histological Features

The glomeruli of patients with MN and crescents showed on average 4.9% (range, 2.2%–16.7%) involvement of crescents (Table 2); 17.9% of these crescents were small crescents, whereas 82.1% were large crescents. There was no circumference in the kidney specimens. Among the 28 patients with crescents, 6 (21.4%) biopsy specimens showed cellular crescents, 12 (42.9%) specimens showed fibrocellular crescents, 9 (32.1%) specimens showed fibrous crescents, whereas only 1 (3.6%) specimen showed cellular and fibrocellular crescents.

All biopsy specimens from patients with MN and crescents showed a membranous pattern of glomerular injury without fibrinoid necrosis. Among the 28 patients, 16 (57.1%) patients were diagnosed as MN stage I, 11 (39.3%) patients as MN stage

II, and 1 (3.6%) patient as MN stage III. None of the patients showed overt mesangial hypercellularity or endothelial proliferation. These glomerular lesions were similar to those of MN without crescents (Table 2).

Tubular atrophy was more common in the patients with crescentic MN (96.3% vs 78.6%,  $P = 0.016$ ). Twenty-six (92.8%) patients showed mild tubular atrophy in interstitial area, and 1 patient had medium tubular atrophy in interstitial area, no one had severe tubular atrophy. Among the 28 patients with crescents, 25 (89.3%) patients had mild interstitial fibrosis plus monocyte and lymphocyte infiltration, and 1 patient had medium interstitial fibrosis with monocyte and lymphocyte infiltration. The interstitial monocyte and lymphocyte infiltration was more common in patients with crescents ( $P = 0.036$ ) (Table 2).

Immunofluorescence staining performed on renal biopsies from all patients with MN and crescents showed granular capillary loop IgG and C3 staining with intensity >1+ (– to 4+). The intensity of IgG (96.42% vs 97.33%,  $P = 0.596$ ) and C3 (89.28% vs 94.66%,  $P = 0.634$ ) deposits was comparable between patients with and without crescents. The immunofluorescence staining of IgA (14.28%), IgM (35.71%), C1q (32.14%), and fibrin-related antigen (7.14%) was shown in the patients with crescents, which was comparable to that in patients without crescent.

**TABLE 1.** Clinical and Laboratory Features From Patients of Idiopathic MN With and Without Crescents

	MN + Crescents (n = 28)	MN (n = 75)	P
Age	56.0 ± 11.1	51.8 ± 13.5	0.143
Sex (M/F)	11/17	40/35	0.205
Urinary protein, g/24 h	6.5 ± 4.8	5.3 ± 3.2	0.231
Albumin, g/L	26.8 ± 7.7	27.7 ± 5.7	0.514
Nephrotic syndrome, n (%)	20 (71.4%)	52 (69.3%)	0.837
Microscopic hematuria, n (%)	25 (89.3%)	68 (90.7%)	0.833
Serum creatinine, μmol/L	66.2 ± 20.5	66.8 ± 17.5	0.878
Serum creatinine, mg/dL	0.7 ± 0.2	0.8 ± 0.2	
Declined eGFR (<60 mL/min/1.73 m <sup>2</sup> ), n (%)	6 (21.4%)	11 (14.7%)	0.492
Hemoglobin, g/L	127.4 ± 14.8	139.4 ± 17.6	<b>0.002</b>
Cholesterol, mmol/L	6.7 ± 2.1	7.6 ± 2.3	0.073
Uric acid, μmol/L	346.1 ± 79.1	365.4 ± 90.3	0.322
Hypertension, n (%)	18 (64.3%)	36 (48.0%)	0.141
Anti-PLA <sub>2</sub> R antibody positive, n (%)	19/24 (79.7%)	45/70 (64.3%)	0.737

eGFR = estimated glomerular filtration rate, MN = membranous nephropathy, PLA<sub>2</sub>R = M-type phospholipase A<sub>2</sub> receptor.  
The bold values are the factors that have statistical significance.

### Treatment Responses and Renal Outcomes

Of the 28 idiopathic MN patients with crescents, 12 patients (42.9%) received immunosuppressive treatment that included cyclophosphamide, ciclosporin, or tacrolimus, combined with prednisone, which was similar to that in patients without crescents (41.3 %) (Table 3).

On follow-up (22.7 ± 19.5 months), out of 28 patients with crescents, 19 (67.9%) patients achieved complete remission (n = 2) or partial remission (n = 17), the frequency of which was lower than that in MN patients without crescent (86.7%,  $P = 0.029$ ) over a comparable duration of follow-up (27.2 ± 20.9 months,  $P > 0.05$ ) (Table 3). Crescent formation

**TABLE 2.** Pathological Features From Patients of Idiopathic MN With and Without Crescents

	MN + Crescents (n = 28)	MN (n = 75)	P
Total no. of glomeruli	29.5 ± 10.7	25.5 ± 11.0	0.107
Globally sclerotic	1 (0, 2.5)	0 (0, 1)	0.079
Crescents (%)	4.88 (3.25, 7.08)	—	<b>&lt;0.001</b>
MN stages			0.816
MN-I, n (%)	16 (57.1%)	38 (50.7%)	
MN-II, n (%)	11 (39.3%)	33 (44.0%)	
MN-III, n (%)	1 (3.6%)	4 (5.3%)	
Mesangial proliferation (%)	0	0	1.000
Tubular atrophy			<b>0.016</b>
Normal	1 (3.6%)	16 (21.3%)	
Mild	26 (92.8%)	59 (78.6%)	
Medium	1 (3.5%)	0 (0%)	
Severe	0	0	
Interstitial fibrosis			0.058
Normal	2 (7.1%)	16 (21.3%)	
Mild	25 (89.3%)	59 (78.7%)	
Medium	1 (3.6%)	0 (0.0%)	
Severe	0	0	
Interstitial monocyte and lymphocyte infiltration			<b>0.036</b>
Normal	2 (7.1%)	18 (24.0%)	
Mild	25 (89.3%)	57 (76.0%)	
Medium	1 (3.6%)	0 (0.0%)	
Severe	0	0	
Intensity of IgG staining, median (range)	3 (2–3)	3 (2–3)	0.596
Intensity of C3 staining, median (range)	2 (1–2)	2 (1–2)	0.634

Tubular-interstitial lesions were semiquantified according to the percentage of involved area: “normal” as 0% of the cortical area or tubules; “mild” as 1% to 25% of the cortical area or tubules; “medium” as the 25% to 50% of the cortical area or tubules; and “severe” as >50% of the cortical area or tubules. MN = membranous nephropathy.

**TABLE 3.** Therapeutic Response and Renal Outcomes From Patients of Idiopathic MN With and Without Crescents

	MN + Crescents (n = 28)	MN (n = 75)	P
Steroids and immunosuppressive therapy, n (%)	12 (42.9%)	31 (41.3%)	0.889
Complete remission, n (%)	2 (7.1%)	14 (18.67%)	0.258
Partial remission, n (%)	17 (60.71%)	51 (68%)	0.487
No remission, n (%)	9 (32.1%)	10 (13.3%)	<b>0.029</b>
Relapse during follow-up, n (%)	8 (28.6%)	18 (24.0%)	0.635
Time from onset to remission, mo	14.4 ± 17.4	10.3 ± 13.8	0.217
Abnormal serum creatinine, n (%)	3 (10.7%)	1 (1.3%)	<b>0.031</b>
The survival time of normal renal function, mo	20.2 ± 16.7	27.4 ± 20.9	0.121
Follow-up time, mo	22.7 ± 19.5	27.2 ± 20.9	0.329

MN = membranous nephropathy.

was a risk factor for no remission of nephrotic syndrome after treatments (OR = 3.1, 95% CI 1.1–8.7, *P* = 0.033). Higher percentage of crescents in glomeruli was a predictor of difficulty in achieving clinical remission (OR = 1.2, 95% CI 1.0–1.3, *P* = 0.038) (Table 4). These results were also substantiated by penalized regression analysis (Table 5).

Among the 12 patients receiving steroids and immunosuppressive treatments, only 6 (50.0%) patients got remission during follow-up. Although among the 31 MN patients without crescent who received immunosuppressive treatment, 26 (85.3%) patients got remission (*P* = 0.038). Crescent formation was yet a risk factor for no remission of nephrotic syndrome in the patients receiving immunosuppressive treatments (OR = 4.7, 95% CI 1.1–19.6, *P* = 0.035).

After clinical remission, 8 (28.6%) out of the 28 MN patients with crescents relapsed, which was not significantly different from patients without crescents (24.0%, *P* = 0.635).

During follow-up, 8 (28.6%) patients with MN and crescents manifested a decline in eGFR, with the level decreased from 133.7 ± 26.8 to 42.2 ± 7.76 mL/min/1.73 m<sup>2</sup>. Among them, 3 patients progressed to ESRD and 5 patients had a decline of eGFR but without the need for renal replacement treatments. Compared with the patients without crescents, abnormal serum creatinine was more frequently occurred in patients with MN and crescents (10.7% vs 1.3%, *P* = 0.031). The renal outcomes in MN patients with crescents tended to be

worse than those in patients without crescent (*P* = 0.022) (Figure 2).

Crescent formation appeared to be a risk factor for renal dysfunction in patients with MN (RR = 10.2, 95% CI 1.0–100.5, *P* = 0.046). Higher level of urinary protein excretion (RR = 1.3, 95% CI 1.0–1.7, *P* = 0.046) and lower level of eGFR on renal biopsy (RR = 1.2, 95% CI 1.0–1.4, *P* = 0.040) also were predictors of worse renal outcomes in MN patients (Table 6). These results were substantiated on penalized regression analysis, which further indicated that the percentage of crescents was another determinant of worse renal outcomes (RR = 2.013, 95% CI 1.084–2.479, *P* = 0.045) (Table 7).

## DISCUSSION

Idiopathic MN with crescents is a rare entity with only individual case reports<sup>12–14</sup> and one series of 19 patients reviewed by Rodriguez et al having been documented.<sup>9</sup> In the present study, we retrospectively examined a consecutive biopsy-proven idiopathic MN cohort and revealed the prevalence of 6.9% of MN patients who had crescent formation in the glomeruli. All of these patients were negative for ANCA, anti-GBM antibody, lupus, or other identified likely causes of crescentic glomerulonephritis. The absence of necrotizing lesions in all biopsy specimens and the absence of systemic

**TABLE 4.** Risk Factors for No Response to the Treatments in Patients With Membranous Nephropathy

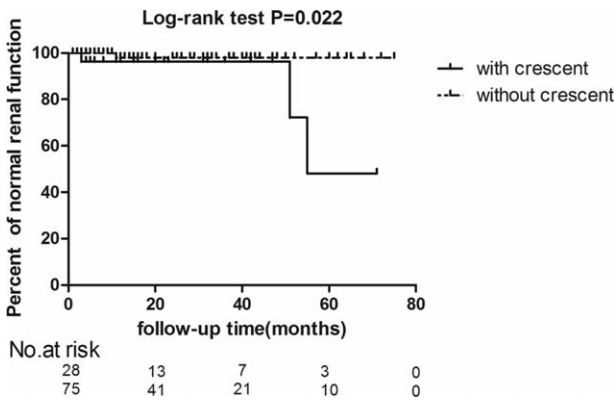
	OR	95% CI	P
Sex (male)	1.886	0.676–5.260	0.226
Age (increased by 1 y)	1.007	0.968–1.047	0.744
Crescent formation	3.079	1.093–8.672	<b>0.033</b>
Percentage of crescents (increased by 1%)	1.166	1.009–1.349	<b>0.038</b>
Tubular atrophy	0.687	0.196–2.400	0.556
Hypertension	1.010	0.373–2.738	0.984
Nephrotic syndrome	1.776	0.538–1.864	0.346
Hemoglobin (increased by 1 g/L)	0.989	0.961–1.018	0.456
Serum albumin (increased by 1 g/L)	0.917	0.838–1.004	0.062
eGFR (decreased by 1 mL/min/1.73 m <sup>2</sup> )	0.998	0.986–1.010	0.711
Urinary protein excretion (increased by 1 g/24 h)	1.038	0.910–1.184	0.583
Interstitial fibrosis	1.159	0.299–4.489	0.830

eGFR = estimated glomerular filtration rate, OR = odds ratio.

**TABLE 5.** Risk Factors for No Response to the Treatments in Patients With Membranous Nephropathy (Penalized Regression)

	Estimate	95% CI	P
Sex (male)	0.803	0.783–8.009	0.141
Crescent formation	1.569	1.081–8.767	<b>0.033</b>
Percentage of crescents (increased by 1%)	1.104	1.009–1.358	<b>0.038</b>
Tubular atrophy	0.731	0.079–1.850	0.145
Serum albumin (increased by 1 g/L)	-0.087	0.706–1.995	0.062

CI = confidence interval.



**FIGURE 2.** Kaplan-Meier analysis for abnormal serum creatinine with comparison between idiopathic membranous nephropathy (MN) patients with and without crescent. MN Patients with crescent formation in glomeruli had worse renal outcome during follow-up ( $P=0.022$ ).

vasculitis argued that the crescents may also not result from ANCA-negative vasculitis. Circulating anti-PLA<sub>2</sub>R antibody was screened in for all these patients with the positive rate being 79.2%. It was comparable with that in MN patients without crescent, and indicated that the mechanism of crescent formation may nevertheless be induced by the autoimmune disorders toward PLA<sub>2</sub>R, the major target antigen of idiopathic MN.<sup>4,6</sup> The involvement of crescent formation in the present

study was <50%, with an average of 4.9% (range, 2.2%–16.7%). We checked all our patients with immune-complex crescentic glomerulonephritis (crescents >50%) in the same period and found 5 patients with MN lesion. However, 2 patients were those of hepatitis B virus-associated MN and 3 patients had positive anti-GBM antibodies. No patient was diagnosed as idiopathic MN, which implies that severe crescent formation >50% is possibly due to secondary causes (Table 8).

Patients with idiopathic MN and crescents presented with heavy proteinuria, usually nephrotic syndrome, microscopic hematuria, and mostly normal renal function at the time of renal biopsy. These features were similar to those in MN patients without crescent.<sup>9,23</sup> In contrast to the previous study,<sup>9</sup> the MN patients with crescents in our center did not present with more advanced stage of MN than the patients without crescent. The time duration from disease onset to renal biopsy was comparable between the 2 groups. These findings suggest that the mechanism of crescent formation may not be ascribed to a late diagnosis or advanced stage of glomerular injury. Arrizabalaga et al<sup>22</sup> reported individual cases of crescentic MN in patients lacking anti-GBM antibody, ANCA, lupus, or chronic infections, whom presented with markedly numerous interstitial inflammatory cell infiltrations. This morphological feature was also commonly shown in our patients with MN and crescents. It is implied that the cell-mediated inflammatory response may participate in the transformation of crescentic MN.

At the time of renal biopsy, the baseline level of eGFR was comparable between the MN patients with and without crescent. All patients received the same treatment irrespective of the presence of glomerular crescents. However, over a comparable

**TABLE 6.** Risk Factors for Abnormal Serum Creatinine in Patients With Membranous Nephropathy

	RR	95% CI	P
Sex (male)	0.316	0–47.682	0.372
Age (increased by 1 y)	1.089	0.964–1.231	0.168
Urinary protein excretion (increased by 1 g/24 h)	1.315	1.005–1.723	<b>0.046</b>
eGFR (decreased by 1 mL/min/1.73 m <sup>2</sup> )	1.182	1.008–1.387	<b>0.040</b>
Crescent formation	10.245	1.044–100.535	<b>0.046</b>
Percentage of crescents (increased by 1%)	1.238	0.984–1.557	0.068
Tubular atrophy	25.956	0–11 × 10 <sup>7</sup>	0.624
Interstitial fibrosis	26.135	0–10727.713	0.621
Hypertension	2.169	0.198–3.757	0.526
Nephrotic syndrome	1.596	0.135–5.934	0.711
Hemoglobin (increased by 1 g/L)	0.962	0.902–1.026	0.242
Serum albumin (increased by 1 g/L)	0.913	0.773–1.079	0.285

eGFR = estimated glomerular filtration rate.

**TABLE 7.** Risk Factors for Abnormal Serum Creatinine in Patients With Membranous Nephropathy (Penalized Regression)

	Exp.(Coef.)	95% CI	P
Age (increased by 1 y)	1.089	0.964–1.231	0.168
Urinary protein excretion (increased by 1 g/24h)	1.298	1.007–1.675	<b>0.044</b>
eGFR (decreased by 1 mL/min/1.73 m <sup>2</sup> )	1.182	1.021–1.992	<b>0.040</b>
Crescent formation	10.245	1.044–70.500	<b>0.046</b>
Percentage of crescents (increased by 1%)	2.013	1.084–2.479	<b>0.045</b>
Hypertension	2.199	0.101–16.654	0.843

eGFR = estimated glomerular filtration rate.

**TABLE 8.** Additional Clinical Features of Entire MN Patients With the Comparison Between Patients With and Without Crescents

	MN + Crescents (n = 28)	MN (n = 373)	P
Age	56.0 ± 11.1	53.0 ± 12.0	0.076
Sex (M/F)	11/17	210/163	0.081
Urinary protein, g/24 h	6.5 ± 4.8	5.8 ± 4.5	0.434
Albumin, g/L	26.8 ± 7.7	28.1 ± 15.1	0.656
Nephrotic syndrome, n (%)	20 (71.4%)	244 (65.4%)	0.518
Microscopic hematuria, n (%)	25 (89.3%)	311 (83.4%)	0.413
Serum creatinine (μmol/L) (mg/dL)	0.7 ± 0.2	0.8 ± 0.3	0.320
Declined eGFR (<60 mL/min/1.73 m <sup>2</sup> ), n (%)	6 (21.4%)	87 (23.3%)	0.819
Hemoglobin, g/L	127.4 ± 14.8	136.1 ± 17.4	0.684
Cholesterol, mmol/L	6.7 ± 2.1	7.7 ± 5.3	0.292
Uric acid, μmol/L	346.1 ± 79.1	351.5 ± 95.0	0.684
Hypertension, n (%)	18 (64.3%)	190 (50.9%)	0.173
Total no. of glomeruli	29.5 ± 10.7	26.8 ± 11.0	0.180
Globally sclerotic	1 (0, 2.5)	0 (0, 2)	0.203
Mesangial proliferation (%)	0	0	1.000
MN stages			
MN-I, n (%)	16 (57.1%)	192 (51.5%)	0.656
MN-II, n (%)	11 (39.3%)	151 (40.5%)	
MN-III, n (%)	1 (3.6%)	30 (8%)	
Tubular atrophy			0.003
Normal	1 (3.6%)	106 (28.4%)	
Mild	26 (92.8%)	257 (68.9%)	
Medium	1 (3.5%)	10 (0.03%)	
Severe	0	0	
Interstitial fibrosis			0.052
Normal	2 (7.1%)	52 (13.9%)	
Mild	25 (89.3%)	313 (83.9%)	
Medium	1 (3.6%)	8 (2.1%)	
Severe	0	0	
Interstitial monocyte and lymphocyte infiltration	0.010		
Normal	2 (7.1%)	106 (28.4%)	
Mild	25 (89.3%)	260 (69.7%)	
Medium	1 (3.6%)	7 (1.9%)	
Severe	0	0	
Intensity of IgG staining, median (range)	3 (2–3)	3 (2–3)	0.112
Intensity of C3 staining, median (range)	2 (1–2)	2 (1–2)	0.083
Steroids and immunosuppressive therapy, n (%)	12 (42.9%)	182/352 (51.7%)	0.367
Complete or partial remission, n (%)	19 (67.9%)	296/352 (84.1%)	0.575
No remission, n (%)	9 (32.1%)	56/352 (15.9%)	0.028
Relapse during follow-up, n (%)	8 (28.6%)	55/352 (15.6%)	0.076
Time from onset to remission (months)	14.4 ± 17.4	7.8 ± 10.8	0.056
Abnormal serum creatinine, n (%)	3 (10.7%)	11/352 (3.1%)	0.040
Survival time of normal renal function, mo	20.2 ± 16.7	23.8 ± 18.1	0.374
Follow-up time, mo	22.7 ± 19.5	19.5 ± 17.39	0.276

eGFR = estimated glomerular filtration rate.

follow-up period, patients with crescents less frequently achieved remission in response to treatment, and had a higher tendency for renal dysfunction.

In the present study, we validated the following risk factors for prognosis of MN patients: higher level of urinary protein excretion and decreased eGFR at the time of renal biopsy.<sup>8,9,21</sup> Furthermore, we found that crescent formation was another risk factor for the worse renal outcome of MN patients. Compared with the patients without crescent, the OR for serum creatinine abnormality raised 10.2 times in the patients with crescents; 28.6% of the patients with crescents progressed to a decline in eGFR during follow-up, including 3 patients who went into ESRD. Poor prognosis was also reported in previous cases of MN with crescents.<sup>9,19</sup> These findings justify the case for closer attention to crescent formation in MN patients at the time of biopsy. Frequent monitoring of serum creatinine and eGFR, and more protection of renal function should be considered for these patients during follow-up.

We treated the patients with MN and crescents with the same strategies according to 2012 KDIGO guideline for glomerulonephritis,<sup>13</sup> with no regard to the crescents. Some patients (67.9%) did respond well, but the remission rate was much lower than that in patients without crescent (86.7%). The steroids and immunosuppressive treatments did not improve the responses as well. Logistic analysis identified that crescent formation and higher percentage of crescents were both risk factors for no response to the treatments. We proposed 2 explanations for this finding. 1. MN patients with crescent formation are proposed to be a distinct subgroup of idiopathic MN, with autoimmune mechanism toward PLA<sub>2</sub>R. Recent studies<sup>30,31</sup> performed epitope mappings on PLA<sub>2</sub>R and identified the N-terminal portion as immunodominant epitopic region. However, Fresquet et al<sup>30</sup> provided that 10% of the subjects possessed reactivity to C-terminal portion. Fine epitope mapping is also unclear for the N-terminus. In autoimmune mechanisms, the clinical phenotypes are often reported to be associated with different epitope reactions. Thus, the autoimmune characteristics of autoantibodies against PLA<sub>2</sub>R in MN patient with crescent formation might be responsible for the refractory response to the treatments. Another explanation is the retrospective observation in this study. The treatments for MN patients with crescents were the same as those without crescent. However, the regimens of steroids and immunosuppressive drugs for MN are insufficient for crescentic glomerulonephritis. Owing to the scarcity of published literature relating to MN patients with crescents,<sup>9,15,21–23</sup> there are no treatment recommendations for this entity. The intensive treatments for crescentic glomerulonephritis<sup>13,32,33</sup> would be referred, when the patients were under a condition of rapid deterioration of renal function. However, further investigations are required to ascertain the advantages and risks associated with such therapeutic strategies in these patients.

The limitation of the present study was a retrospectively observational study, thus a cause–effect relationship could not be established. Furthermore, the findings from this single-center study with limited number of patients require validation from multicenter studies with large cohort. The potential mechanisms for the crescent formation in MN lesions were also unclear.

In summary, we reported a distinct subgroup of MN patients with crescents, which was detected in 6.9% of idiopathic MN patients. This entity might be mediated by the autoimmunity toward PLA<sub>2</sub>R, but did not appear to be related to the known causes for crescentic glomerulonephritis.

Crescent formation was a risk factor for no response to treatments and renal dysfunction during follow-up. Studies on more aggressive treatments are required for the improvement of renal outcomes.

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