Clinicopathological features of atypical membranous nephropathy with unknown etiology in adult Chinese patients

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Abstract
Membranous nephropathy is typically classified as idiopathic and secondary, but nowadays the number of atypical membranous nephropathy (aMN) is increasing, many of which cannot determine its etiology in China. In this study, we compared the clinical and pathological characteristics of idiopathic membranous nephropathy (iMN) with aMN with unknown etiology from a single center in China. We retrospectively reviewed the clinical data of 577 patients with iMN and aMN at Peking University People’s Hospital from January 2006 to December 2015 over a 10-year period, and analyzed their clinical and pathological characteristics. The level of serum phospholipase A2 receptors (PLA2R) antibody was detected in 106 iMN and 162 aMN patients.

There were 278 iMN patients and 299 aMN patients who were included into this study in 3210 cases of renal biopsy during a 10-year period in our hospital. The average age of patients with iMN was significantly older than those with aMN (54.77 ± 13.01 vs 47.13 ± 16.16, P < .001). Around 75 patients (27%) were smokers in iMN patients, and 111 patients (37.1%) in aMN patients (P = .009). The main clinical manifestation of these 2 groups was nephrotic syndrome (61.5% in iMN group vs 58.4% in aMN group), but there were more patients accompanied with nephritis syndrome in aMN group than iMN group (17.1% vs 6.1%, P < .001). The immunofluorescence of renal biopsy showed "full house" in aMN group; and IgG subclass of the glomeruli demonstrated IgG4 (90.4%) was commonest in iMN group, but IgG1 (94.6%) in aMN group. 51 (48.1%) patients with iMN were detected positive PLA2R antibody in their serum, and 93 (57.4%) in aMN patients (P = .168). The patients with positive PLA2R antibody had higher positive rate of microscopic hematuria and urinary protein, lower albumin.

The aMN patients are younger, higher smoking rate, its main clinical manifestation is nephrotic syndrome, but more of them accompanied with nephritis syndrome than those in iMN patients. Serum PLA2R antibody could not distinguish aMN from iMN. aMN could be a special glomerular disease in China, and need a further research on a larger scale.

Abbreviations: ALT = glutamic-pyruvic transaminase, aMN = atypical membranous nephropathy, ANA = antinuclear antibodies, AST = glutamic oxalacetic transaminase, CTLD = C-type lectin domains, CysR = cysteine-rich, eGFR = estimated glomerular rate filtration, FNI = fibronectin type II, FRA = fibrin-associated antigen, iMN = idiopathic membranous nephropathy, MN = membranous nephropathy, NAG = N-acetyl-beta-D-glucosaminidase, PLA2R = phospholipase A2 receptors, SLE = systemic lupus erythematosus, SMN = secondary membranous nephropathy.

Keywords: atypical membranous nephropathy, clinical manifestation, idiopathic membranous nephropathy, phospholipase A2 receptor antibody, renal pathology

1. Introduction
Membranous nephropathy (MN) remains a leading cause of the nephrotic syndrome in adults, and is a common etiology of end-stage renal disease.[1,2] According to published data, the percentage of MN among renal biopsy specimen was increasing worldwide.[3-5] MN can be classified into idiopathic membranous nephropathy (iMN) without identified causes and secondary membranous nephropathy (SMN) attributed to systemic lupus erythematosus (SLE), hepatitis B, drugs, toxins, other infections, or malignancy. The most important process in diagnosis of MN is to determine it as idiopathic or secondary according to the clinical manifestations, serological examination and renal biopsy, which in turn guides the treatment and evaluating prognosis. Beck et al[6] found a IgG4 PLA2R antibody existed in 70% of MN patients, many studies have found that PLA2R antibody was associated with iMN, which was now a major autoantibody cause podocyte damage in iMN patients.[7] and it is significant to diagnose MN. In recent years, a kind of “secondary membranous nephropathy” which show “full house” in immunofluorescence but no clinical evidence of secondary cause is increasing in China. In 1982, Jones and Magil[8] reported 5 MN patients with mesangial proliferation and “full house” immunofluorescence, after 10 to 58 months of follow-up, none evidence of systemic disorder could be identified.
Jennette et al. [9] studied a group of patients with renal pathology mimicking membranous lupus nephritis but without clinical evidence for lupus, and found only a small percentage (67/8) showed the clinical evidences of SLE during later follow-up. This category of “secondary membranous nephropathy” is currently temporarily diagnosed as atypical membranous nephropathy [10] (aMN), lupus-like membranous nephropathy [11] or “full house” membranous nephropathy [12] and so on. It is not clear whether aMN is a special type of iMN, or the early performance of the so called secondary membranous nephropathy that can be attributed to SLE or hepatitis B, or caused by other unclear secondary factors, or a separate type of MN. Our research reviewed 577 patients who had been diagnosed as iMN and aMN in clinical and renal biopsies from 2006 to 2015, compared the clinical and pathological characteristics, we detected serum PLA2R antibody levels in some patients, and analyze the characteristics of the disease to provide the basis for clinical practice.

2. Materials and methods

2.1. Study participants

This was a retrospective study. We collected all the patients diagnosed as membranous nephropathy by clinical data and renal biopsy in Beijing University People’s Hospital from January 2006 to December 2015 for this research. Inclusion criteria: iMN group: MN patients with unknown etiology and characterized glomerular lesions of only immune complex deposited under the epithelial and thickening glomerular basement membrane. aMN group: MN patients with unknown etiology in clinical, its renal pathology showed cell proliferation and multiple locations immune complex deposition in addition to the glomerular basement membrane lesions, and excluded lupus nephritis, hepatitis B virus (HBV)-related glomerulonephritis and MN secondary to drugs, toxins, other infections, or malignancy. In all cases, MN accompanied with other pathological pattern, such as diabetic nephropathy, IgA nephropathy, and so on, were ruled out. This study was approved by the ethics committee of Peking University People’s Hospital (2017PHE141-01).

2.2. Method

2.2.1. Data collection. General information: sex, age, blood pressure, and smoking status (smoke more than 1 cigarette per day for 6 consecutive or accumulated months) at the time of biopsy. Clinical manifestation: patients were divided into the following 4 categories according to the existence of hematuria, proteinuria, edema, hypertension, hypoalbuninemia, hyperlipidemia or not: Simple proteinuria and hematuria, nephrotic syndrome, nephritis syndrome, nephritic syndrome accompanied with nephritis syndrome. Also they were divided into the following 3 categories according to estimated glomerular rate filtration (eGFR) level (calculate with CKD-EPI formula) and the condition of clinical and pathology: eGFR > 60 mL/min 1.73 m², chronic renal insufficiency (eGFR < 60 mL/min 1.73 m²) and acute kidney injury (acute/subacute renal tubular and/or interstitial injury in pathology with declined eGFR). Laboratory examination: Kidney damage indicators: hematuria, 24-hours urinary protein, renal tubular function quantitative (urine retinol binding protein, urine beta 2-microglobulin, urine N-acetyl-beta-D glucosaminidase [NAG]), serum creatinine, urea, uric acid, eGFR level, serum albumin, blood lipid; Immunological indicators: Serum complement (C3 and C4), antinuclear antibodies (ANA), serum IgG, IgA, and IgM; Glutamic-pyruvic transaminase (ALT) and glutamic oxaloacetic transaminase (AST).

Pathology of renal biopsy: all renal tissue was performed optical microscopy (HE, Masson, PAS/M staining), immunofluorescence (IgA, IgG, IgM, C1q, C3, fibrin-associated antigen [FRA]) and electron microscope test, and additional HBsAg and HBeAg immunochemistry test if the kidney pathology of the patient showed aMN. The pathological diagnosis came from pathologists. There were 269 patients detected IgG subtypes of renal tissue by immunofluorescence method. ELISA method was used to detect the antibody levels of phospholipase A2 receptors (PLA2R) in patients’ serum, and then the patients in the 2 groups above were taken into PLA2R serum antibody positive and negative groups, respectively, based on antibody positive or not, and compared their clinical and pathological data again. The Anti-PLA2R ELISA (IgG) kits were purchased from EURO-IMMUN Medizinische Labordiagnostika AG, the results were considered as negative for < 20 relative units (RU)/mL and positive for ≥ 20 RU/mL.

2.2.2. Statistical analysis. SPSS 22.0 statistical software was used for data analysis. Quantitative variables with normal distribution were expressed in x ± s and compared by t-test and data with abnormal distribution were expressed in median and compared by nonparametric test. Categorical variables were compared by χ² test. P < .05 was considered statistically significant, P < .01 was considered notably statistically significant.

3. Result

From January 2006 to December 2015, there were 3210 cases of renal biopsy in our center and membranous nephropathy accounted for 820 (25.5%) cases of total, including 351 (10.9%) iMN patients, 105 SMN patients (lupus nephritis type V and HBV associated membrane nephritis), 364 (11.3%) aMN patients. Data of renal biopsy showed that iMN accounted for 11.93% of the total in the previous 5 years, and 10.20% in the latter 5 years; however, aMN increased from 3.88% in the previous 5 years to 16.87% in the latter.

3.1. iMN and aMN

3.1.1. General information. Around 278 patients in iMN group and 299 patients in aMN group were included in this study, and the patient’s general information as shown in Table 1. The average age was 54.77 ± 13.01 years old (17–82 years old) in iMN group, and 47.13 ± 16.16 years old (14–80 years old) in aMN group, with significant difference (P < .001). Patients were divided into different groups according to age (Fig. 1), there were 205 patients (73.7%) with the age of 41 to 70 in iMN group, especially 51 to 60 years old (33.1%); and 184 patients (61.5%) with the age of 41 to 70 in aMN group. The percent of patients younger than 40 in aMN group (99 cases, 33.1%) was significantly more than those of iMN group (42 cases, 15.1%) (P < .001). The ratio of male to female in patients with iMN was 1:1, the average age was 56.11 ± 13.00 years old in men, and was 53.42 ± 12.93 years old in women, with no significant difference; the ratio of male to female was 1.34:1 in patients with aMN, the average age was 45.50 ± 15.79 years old in men, and 49.30 ± 16.45 years old in women, with significant difference (P = .05).

There were 75 smokers (27%) in iMN group, and 111 smokers (37.1%) in aMN group (P = .009).
3.1.2. Clinical manifestations. The clinical manifestations of patients were shown in Table 2. In iMN group, there were 46 cases (16.6%) with simple proteinuria and hematuria, 171 cases (61.5%) with nephrotic syndrome, 17 cases (6.1%) with nephrotic syndrome accompanied with nephritis syndrome; and 33 cases (11.1%) accompanied with nephritis syndrome, 17 cases (6.1%) with nephrotic syndrome accompanied with nephritis syndrome and atypical membranous nephropathy, iMN group respectively, and the patients with nephrotic syndrome and atypical membranous nephropathy, aMN group respectively, there was no significant difference (X² = 2.17, P = .14). About renal function, in iMN group, there were 252 patients (90.6%) whose eGFR was more than 60mL/min 1.73 m², 10 cases (3.6%) accompanied with chronic renal insufficiency, 16 patients (5.8%) accompanied with acute kidney injury; and 265 patients (88.6%), 8 patients (2.7%), 26 patients (8.7%) in aMN group, respectively, there was no significant difference (X² = 2.169, P = .34) about the composition of renal function between the 2 groups.

3.1.3. Laboratory examination. To compared these kidney damage indicators and immunological indices of the iMN and aMN groups (Table 3): there were significant differences in eGFR (92.31 ± 22.32 vs 97.56 ± 27.26 mL/min 1.73 m², P = .01), microscopic hematuria (65.3% vs 69.6%, P = .28), uric acid (353.46 ± 100.97 vs 373.20 ± 103.68 mmol/L, P = .02), ALT (18.07 ± 11.24 vs 20.50 ± 13.70 U/L, P = .02), triglyceride (2.61 ± 1.95 vs 2.90 ± 2.17 mmol/L, P = .09), cholesterol (7.38 ± 2.31 vs 7.30 ± 3.40 mmol/L, P = .69), urine retinol binding protein (7.50 vs 6.28 mg/L, P = .03), urine β2-microglobulin (1199.62 vs 1113.67 μg/L, P = .001), urine NAG (60.18 vs 45.70 U/L, P = .02), serum complement C3 (1.11 ± 0.25 vs 1.07 ± 0.24 g/L, P = .04) and C4 (0.30 ± 0.18 vs 0.27 ± 0.09 g/L, P = .02), and there was no significant difference about microscopic hematuria, 24hours urinary protein, serum creatinine, blood urea, albumin, blood lipid, ANA, serum IgA, IgG, IgM between the 2 groups. But the level of serum immunoglobulin IgG was lower than the normal value (7.2–16.8 g/L).

3.1.4. Renal pathology. Patients with iMN were characterized by glomerular lesions with only immune complex deposited under the epithelial and thickening glomerular basement membrane, and patients with aMN were associated with cell proliferation and multiple locations immune complex deposition in addition to the glomerular basement membrane lesions. As shown in Table 4, the renal immunofluorescence test of patients.

| Table 1 | The general information of idiopathic membranous nephropathy group and atypical membranous nephropathy group. |
|---------|----------------------------------------------------------------------------------------------------------|
|          | iMN group (n = 278) | aMN group (n = 299) | P       |
| Sex (cases)  | Male 139 (50%)   | Male 171 (67.2%)   | .08     |
|            | Female 139 (50%) | Female 128 (42.8%) |         |
| Age, years  | 54.77 ± 13.01    | 47.13 ± 16.16      | <.001   |
| Prodromic infection (cases) | 24 (8.72%) | 24 (8.03%) | .79 |
| Systolic pressure, mm Hg | 131.55 ± 19.22 | 133.25 ± 19.46 | .29 |
| Diastolic pressure, mm Hg | 81.23 ± 11.20 | 82.12 ± 11.15 | .34 |
| Smoking rate (total) | 75 cases (27.0%) | 111 cases (37.1%) | .009 |
| Smoking rate (male) | 73 cases (52.52%) | 103 cases (60.23%) | .17 |
| Smoking rate (female) | 2 cases (1.44%) | 8 cases (6.25%) | .04 |

aMN = atypical membranous nephropathy, iMN = idiopathic membranous nephropathy.

We compared the categorical variables with χ² test.

| Table 2 | The composition of clinical manifestation in idiopathic membranous nephropathy group and atypical membranous nephropathy group. |
|---------|----------------------------------------------------------------------------------------------------------|
|          | iMN group (n = 278) | aMN group (n = 299) | P   | P   |
| Simple proteinuria and hematuria | 46 (16.6%) | 33 (11.1%) | .05 | <.001 |
| Nephrotic syndrome | 171 (61.5%) | 175 (58.4%) | .45 |
| Nephritis syndrome | 44 (15.8%) | 40 (13.4%) | .41 |
| Nephritis syndrome accompanied with nephritis syndrome | 17 (6.1%) | 51 (17.1%) | .001 |

aMN = atypical membranous nephropathy, iMN = idiopathic membranous nephropathy.

We compared the total data and found the significant difference between the 2 groups (P = 16.712, P < .001).

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Table 3

|                        | IMN group (n = 278) | aMN group (n = 299) | P  |
|------------------------|---------------------|---------------------|----|
| Microscopic hematuria (cases) | 177 (65.3%)          | 204 (69.6%)         | .28|
| 24 hours urinary protein, g/L | 6.01 (4.77)           | 5.91 (4.83)         | .89|
| Urine retinol binding protein, mg/L | 7.50 (0.41)         | 6.28 (0.62)         | .003|
| Urine β2-microglobulin, μg/L | 119.62 (184)         | 111.67 (384)        | .001|
| urine NAG, UL | 60.18 (46.43)         | 45.70 (54.73)       | .01|
| blood urea, mmol/L | 5.61 (5.03)           | 6.94 (8.07)         | .82|
| Serum creatinine, umol/L | 74.40 (66)            | 79.79 (70)          | .27|
| sGFR, mL/min 1.73 m² | 92.31 ± 22.32         | 97.56 ± 27.26       | .01|
| Uric acid, mmol/L | 353.46 ± 100.97       | 373.20 ± 103.68     | .02|
| Albumin, g/L | 28.02 ± 7.06           | 27.55 ± 8.38        | .46|
| ALT, U/L | 18.07 ± 11.24          | 20.50 ± 13.70       | .02|
| AST, U/L | 21.56 ± 12.03          | 21.94 ± 9.96        | .68|
| Triglyceride, mmol/L | 2.67 ± 1.95           | 2.90 ± 2.17         | .09|
| Cholesterol, mmol/L | 7.38 ± 2.31           | 7.30 ± 3.40         | .69|
| LDL-C, mmol/L | 4.53 ± 1.85            | 4.51 ± 2.08         | .93|
| HDL-C, mmol/L | 1.32 ± 0.50            | 1.43 ± 1.74         | .35|
| ANA (1/160) | 19.91                  | 24.04                | .28|
| Blood IgA, g/L | 2.23 ± 0.96            | 2.24 ± 1.05         | .88|
| Blood IgG, g/L | 7.35 ± 3.66            | 7.03 ± 3.16         | .08|
| Blood IgM, g/L | 1.24 ± 0.67            | 1.17 ± 0.61         | .49|
| Blood C3, g/L | 1.11 ± 0.25            | 1.07 ± 0.24         | .04|
| Blood C4, g/L | 0.30 ± 0.18            | 0.27 ± 0.09         | .02|

ALT = glutamic-pyruvic transaminase, aMN = atypical membranous nephropathy, ANA = antinuclear antibody, AST = glutamic-oxaloacetic transaminase, sGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, iMN = idiopathic membranous nephropathy, LDL-C = low-density lipoprotein cholesterol, NAG = N-acetyl-beta-D-glucosaminidase.

Table 4

|                        | IMN group (n = 278) | aMN group (n = 299) | P  |
|------------------------|---------------------|---------------------|----|
| Positive rate | IgA | 23 (8.4%)           | 237 (80.6%)        | <.001|
|                        | IgG | 266 (97.4%)         | 283 (96.3%)        | .42|
|                        | IgM | 173 (63.1%)         | 245 (83.6%)        | <.001|
|                        | C1q | 23 (8.4%)           | 238 (81.0%)        | <.001|
|                        | C3  | 245 (89.4%)         | 281 (95.0%)        | .003|
|                        | C4  | 75 (80.4%)          | 167 (89.3%)        | .79|

3.2. MN with serum PL2AR antibodies

Collected 268 patients serum specimens in the biological sample bank of our hospital (106 cases with IMN, 162 cases with aMN), and the levels of serum PL2AR antibodies were detected by ELISA. The positive rate of serum PL2AR antibodies in iMN group was 48.1% (51 cases), and was 57.4% (93 cases) in aMN group, with no significantly different (P = .168). Regrouped the patients into 4 subgroups according to serum PL2AR positive antibodies or not and then their clinical and pathological characteristics were analyzed.

3.2.1. General information. As shown in Table 5, in iMN group, there were 33 male patients (64.7%) with positive serum PL2AR antibodies, 24 male patients (42.6%) with negative antibodies (P = .05). The average age was not significant different between antibodies positive and antibodies negative patients in iMN group (P = .93), but in aMN group with significant different (P = .02).

3.2.2. Laboratory examination. Laboratory results between the 4 groups are shown in Table 6. There was significantly heavier microscopic hematuria (in iMN group: 82.4% vs 54.5%, P = .002; in aMN group: 77.4% vs 60.9%, P = .02), urinary protein (in iMN group: 7.58 g vs 5.10 g, P = .01; in aMN group: 6.51 g vs 4.88 g, P = .002), and lower serum albumin, IgG, complement C4 in the patients with positive PL2AR antibodies whether in IMN or aMN group.

Table 5

|                        | IMN group (n = 106) | aMN group (n = 162) | P  |
|------------------------|---------------------|---------------------|----|
| Sex (cases) | Male 57 (61.3%)     | Male 37 (53.6%)     | .33|
|                        | Female 49 (38.7%)   | Female 35 (46.4%)   | .01|
| Age, years | 58.69 ± 14.33        | 53.42 ± 12.94       | .05|
|                        | 57 (35.3%)           | 31 (57.4%)          | .002|
| Predominant infection (cases) | 7 (13.3%)            | 3 (6.5%)            | .261|
|                        | 134.94 ± 19.71       | 132.28 ± 20.51      | .43|
| Smoking rate (male) (cases) | 17 (33.3%)           | 14 (25.5%)          | .735|
|                        | 37 (39.8%)           | 25 (36.2%)          | .65|
| Smoking rate (female) (cases) | 16 (48.5%)           | 14 (25.8%)          | .482|
|                        | 34 (59.6%)           | 22 (50.5%)          | .99|
| Smoking rate (male) (cases) | 1 (5.6%)             | 0                   | .380|
|                        | 3 (8.3%)             | 3 (9.4%)            | 1.00|

ALT = atypical membranous nephropathy, ANA = antinuclear antibody, AST = glutamic-oxaloacetic transaminase, sGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, iMN = idiopathic membranous nephropathy, aMN = atypical membranous nephropathy.

*We compared the categorical variables with χ² test.
Blood C4, g/L 0.36 ±
Blood IgG, g/L 6.71 ±
aMN patients between antibodies positive group and antibodies negative group.

3.2.3. Renal pathology. There were 48 patients with PLA2R antibodies positive and 55 patients with PLA2R antibodies negative in iMN group, 91 and 67 patients in aMN group respectively, with no significant difference (X² = 3.027, P = .08). Only the positive rate of IgG1 (P = .04) and IgG4 (P = .002) of aMN patients between antibodies positive group and antibodies negative group had a significant difference (Table 7).

4. Discussion
More than 50 years ago, people found a kind of membranous nephropathy patients, whose pathological characteristics similar to lupus nephritis, but unable to make a clinical diagnosis of SLE. In 1964, Simenhoff and Merrill[13] considered that “lupus nephritis may present as a renal syndrome only, without any of the other manifestations of SLE,” but with the knowledge of SLE, many and many scholars regarded the SLE as a kind of “systemic disease,” whose pathological changes not only confined to a certain organs, and such type of “lupus nephritis” with only kidney injury in the subsequent follow-up only a small number of these patients can be diagnosed as SLE. Previous literature reported in 101 patients with similar MN, only 12 people in an average follow-up of 3 years to be testified the clinical diagnosis of SLE[10,12,13]. This kind of MN (“full house” in immunofluorescence, no clinical disease.

Table 6
Laboratory examination of serum phospholipase A2 receptors antibody positive group and negative group.

| IMN group (n = 106) | PLA2R antibody positive (n = 51) | PLA2R antibody negative (n = 55) | P |
|---------------------|----------------------------------|----------------------------------|---|
| Microscopic Hematuria | 42 (82.4%) | 30 (54.5%) | .002 |
| 24 hours urinary protein, g/L | 7.58 (6.00) | 5.10 (4.00) | .01 |
| Urine Retinol binding protein, mg/mL | 10.71 (1.29) | 6.48 (0.44) | .00 |
| Urine β2-microglobulin, μg/L | 1665.55 (351.00) | 851.78 (338.80) | .57 |
| Urine NAG, UL | 51.40 (29.90) | 82.77 (41.44) | .51 |
| Blood urea, mmol/L | 5.96 (5.33) | 6.12 (4.83) | .14 |
| Serum creatinine, μmol/L | 87.12 (82.00) | 79.36 (69.00) | .02 |
| eGFR mL/min 1.73 m² | 82.75 ± 23.81 | 88.97 ± 21.43 | .16 |
| Uric acid, mmol/L | 376.20 ± 110.64 | 346.53 ± 113.40 | .18 |
| Albumin, g/L | 25.03 ± 6.26 | 28.99 ± 7.08 | .006 |
| ALT, UL | 16.45 ± 11.04 | 18.45 ± 9.79 | .33 |
| AST, UL | 22.08 ± 9.03 | 21.06 ± 9.80 | .58 |
| Triglyceride, mmol/L | 2.31 ± 1.28 | 2.15 ± 0.90 | .45 |
| Cholesterol, mmol/L | 8.29 ± 2.98 | 7.39 ± 2.21 | .09 |
| LDL-C, mmol/L | 5.23 ± 2.37 | 4.68 ± 1.52 | .16 |
| HDL-C, mmol/L | 1.40 ± 0.66 | 1.40 ± 0.52 | .99 |
| ANA, 1/titer† | 4.35 (0) | 14.90 (0) | .23 |
| Blood IgA, g/L | 2.02 ± 0.83 | 2.31 ± 0.95 | .11 |
| Blood IgG, g/L | 6.71 ± 2.79 | 7.77 ± 3.54 | .09 |
| Blood IgM, g/L | 1.00 ± 0.45 | 1.28 ± 0.81 | .03 |
| Blood C3, g/L | 1.09 ± 0.27 | 1.06 ± 0.25 | .58 |
| Blood C4, g/L | 0.36 ± 0.53 | 0.28 ± 0.15 | .09 |

ALT = glutamic-pyruvic transaminase, aMN = atypical membranous nephropathy, ANA = antinuclear antibodies, AST = glutamic oxalacetic transaminase, eGFR = estimated glomerular rate filtration, HDL-C = high-density lipoprotein cholesterol, iMN = idiopathic membranous nephropathy, LDL-C = low-density lipoprotein cholesterol, NAG = N-acetyl β-D glucosaminidase.
† Showed with the form of average (median), and compared with t test.
‡ Showed with the form of average (median), and compared with nonparametric test.

Table 7
Immunofluorescence of renal biopsy of idiopathic membranous nephropathy group and atypical membranous nephropathy group serum phospholipase A2 receptors antibody positive group and negative group.

| Positive rate | PLA2R antibody positive (n = 48) | PLA2R antibody negative (n = 55) | P |
|---------------|----------------------------------|----------------------------------|---|
| IgA | 4 (8.3%) | 8 (14.5%) | .33 |
| IgG | 45 (93.8%) | 52 (94.5%) | .86 |
| IgM | 21 (43.8%) | 24 (43.6%) | .99 |
| C1q | 4 (8.3%) | 4 (7.3%) | .84 |
| C3 | 39 (81.3%) | 47 (85.5%) | .57 |
| FRA | 13 (27.1%) | 7 (12.7%) | .07 |
| IgG1 * | 13 (27.1%) | 8 (16.0%) | .10 |
| IgG2 | 0 (0%) | 0 (0%) | — |
| IgG3 | 10 (20%) | 0 (0%) | .28 |
| IgG4 | 0 (0%) | 0 (0%) | — |
| PLA2R antibody positive (n = 91) | PLA2R antibody negative (n = 67) | P |
| IgA | 68 (74.7%) | 54 (80.6%) | .39 |
| IgG | 67 (95.6%) | 62 (92.5%) | .41 |
| IgM | 72 (79.1%) | 60 (89.6%) | .08 |
| C1q | 70 (76.9%) | 57 (85.1%) | .20 |
| C3 | 88 (96.7%) | 61 (92.4%) | .23 |
| FRA | 23 (25.3%) | 26 (36.8%) | .07 |
| IgG1 * | 13 (27.1%) | 44 (61.7%) | .04 |
| IgG2 | 64 (75.6%) | 33 (48.8%) | .44 |
| IgG3 | 10 (16.4%) | 5 (10.4%) | .37 |
| IgG4 | 59 (69.7%) | 37 (77.1%) | .002 |

ALT = atypical membranous nephropathy, FRA = fibrin-associated antigen, iMN = idiopathic membranous nephropathy. Showed with the form of average (percent), and compared with χ test.
* The number of patients detected IgG subtypes in PLA2R antibody positive group and negative group in iMN group was 17 and 10, respectively, and was 61 and 48 in aMN group, respectively.

Jiang et al. Medicine (2018) 97:32 www.md-journal.com
evidence of secondary cause) was currently called aMN in China, and now we could not clear its cause and long-term a unique characteristics of clinical manifestation and laboratory examination, or whether its treatment and prognosis are different from iMN and SMN, these problems had been paid the attention more and more. In this study, we analyzed a decade of clinical and pathologic data of MN and found iMN accounted for 42.80% of MN, aMN accounted for 44.39%. The onset age of patients with aMN was younger than those with iMN (47.13 vs 54.77 years old), and the sex ratio was 1.34:1 in aMN group, but 1:1 in the iMN group. Some scholars also reported iMN accounted for 31.8% of membranous nephropathy, mean age was 43.9 ± 13.2 years old, and were mainly distributed between 40 to 60 years old, male and female ratio 1.53:1,[17] but some other data showed that in developed countries, iMN accounted for 60% to 80%, the sex ratio of MN patients was 1.3 to 2.3:1.[18,19] These results are different from our center that indicate that different country or different geographic environment in some country may have a certain geographic on the development of disease.

Our research found that the smoking rates of patients with aMN group were more than those of iMN group significantly (37.1% vs 27.0%, P = .009), indicates that patients with aMN could be more susceptible to environmental impact than those with iMN. The researcher from Japan have pointed out that smoking was a risk factor for disease progression of iMN, and the kidney function decline accelerated significantly in iMN patients smoking cumulative more than 40 bales each year.[20] so it is possible that the environmental factors play an important role of in onset and development of iMN. Besides smoking, air pollution was also paid more attention gradually. Hou et al[14] conducted the first study of the correlation between the air pollution and the pathogenesis of membranous nephropathy, they estimated the profile of temporal change in glomerular diseases in an 11-year renal biopsy series including 71,151 native biopsies in 938 hospitals spanning 282 cities in China from 2004 to 2014, and examined the association of long-term exposure to fine particulate matter of < 2.5 mμ (PM2.5) with membranous nephropathy, they found that higher 3-year average exposure to high concentrations of PM2.5 environment can increase the incidence of membranous nephropathy, and also found that each 10 μg/m3 increase in PM2.5 concentration associated with 14% higher odds for membranous nephropathy (OR, 1.14; 95% CI, 1.10 to 1.18) in regions with PM2.5 concentration > 70 μg/m3.

In our study, nephrotic syndrome was the main clinical manifestations in iMN and aMN groups, the patients with nephrotic syndrome accompanied with nephritis syndrome in aMN group (17.1%) was more than iMN group (6.1%) significantly. And the average serum IgG levels of patients with aMN were below normal lower limit but there was no significant difference in serum albumin level of 2 groups, suggested aMN patients’ immune disorder might be more serious than iMN patients, and some patients with aMN may exist the underlying cause which were not found yet such as virus infection, environmental factors, etc.[20,21] ALT and uric acid of aMN group were higher than iMN group, and serum C3 and C4 were lower than those in iMN group, these results were accord with some other literature before. Yang et al[10] found that the blood CRP, albumin and AST of patients with aMN is higher than iMN patients, and the C3 levels of aMN patients was higher than normal, and IgG level of iMN group is lower than normal. Rijnink et al[22] compared the idiopathic nonlupus “full house” nephropathy with lupus nephritis and found that the former had higher level of proteinuria (P < .01), but lower levels of hematuria (P = .04) and complement (P < .001), less C1q stained in glomeruli (P = .002). The results of laboratory tests in different research are not all the same, in addition to consider the difference of instruments, reagents, and methods in different hospitals, also need to consider environmental factors from different regions. In addition, our study found that the level of eGFR of aMN group patients was a little higher than the iMN group patients (P = .01), but the mean values of 2 groups were > 90 mL/min 1.73 m2.

PLA2R1 is a 180-kDa membrane receptor as the major podocyte antigen in iMN, with a large extracellular region namely a cysteine-rich domain (CysR), a fibronectin type II domain (FNIII), and 8 distinct C-type lectin domains (CTLD1–8),[23] Beck et al[6] found a IgG4 PLA2R antibody existed in 70% of MN patients firstly, which was now a major autoantibody cause podocyte damage by activating lectin and alternative complement pathway in MN patients.[24] In recent years, some scholars identified reactive epitopes in the CysR, CTLD1, and CTLD7 domains and confirmed the reactivity with soluble forms of each domain: CysR is a major antigen epitope of PLA2R antibodies, but the antigen epitope gradually spreading to CysRCTLD1 and CysRCTLD1CTLD7 with the progress of the disease, and the latter 2 were more closely with the activity of disease.[24] At present various studies reported serum PLA2R antibodies positive rate of iMN patients ranging from 48% to 82.3%.[25–29] In which the lowest positive rate (48%) was from Japan.[25] similar with our study, this phenomenon may have something to do with race and geographic environment. Some scholars pointed out that serum anti PLA2R antibodies even exist in SMN, and the positive rate ranging from 58.8% to 72.3%.[30,31] In our study, the positive rate of serum PLA2R antibodies in iMN group was 48.1% and 57.4% in aMN group with no statistical difference; and there was no significant different in immunofluorescence positive rate of IgG4, which indicates that there has no obvious advantage about serum PLA2R antibodies in distinguishing iMN from aMN.

In this study, the average age of PLA2R antibody positive patients was older than those of the antibody negative ones. The heavier microscopic hematuria and proteinuria were found in PLA2R antibody positive patients both in aMN and iMN group, and their albumin levels were lower, all above indicated that PLA2R antibody could lead to more severe proteinuria and hypoalbuminemia. Now some scholars found the similar results about proteinuria levels, especially when the positive serum PLA2R antibody level was above 180 RU/mL (P < .05)[27] and the higher the titer of PLA2R antibody, the poorer response to treatment and prognosis.[32,33]

Xu et al[34] reviewed the management of membranous nephropathy in Asia. The data from Asia showed that the prognosis of the patients with iMN was relatively good, overall renal survival rate was 81.1% to 86.6% at 15 years after diagnosis. The prognosis of patients with aMN may be different from the iMN and SMN patients. Sam et al[35] conducted a follow-up study, they retrospectively reviewed 98 patients with MN including 39 (40%) patients with iMN, 36 (37%) patients with lupus membranous GN and 23 (23%) patients with aMN (“lupus-like” MN). After average follow-up of 3.5 years, they found that proteinuria and serum creatinine level of the patients with membranous lupus nephritis were lower than those of iMN patients, “lupus-like” MN patients. In addition, during the follow-up period, 11 of 39 (28%) in iMN patients, 2 of 36 (6%) in lupus membranous GN, and 3 of 23 (13%) in “lupus-like” MN patients progressed to end-stage renal disease and were on
diagnosis. Similarly, Rijnink et al. found that idiopathic nonlupus "full house" nephropathy was an independent risk factor for end-stage renal disease (hazard ratio 5.31, 95% confidence interval 1.47–19.24).

Generally, our study indicated the clinical manifestations of aMN and iMN are different, the aMN patients are younger, higher smoking rate, its main clinical manifestation is nephrotic syndrome, but more of them accompanied with nephritis syndrome than those in iMN patients, but serum PLA2R antibody could not distinguish aMN from iMN. Certainly, our research still exists some limitations. Secondly, this research is still lack of follow-up data about aMN and iMN. Thirdly, our study lacks kidney tissues PLA2R status. Whether aMN is different from iMN as a particular disease is still not clear, which need further large scale clinical and basic researches on aMN.

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