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Changes in Clinicopathological Characteristics of Patients with Idiopathic Membranous Nephropathy: A Single-Center Retrospective Study

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Abstract

Background: The prevalence of Idiopathic Membranous Nephropathy (IMN) among patients with Primary Glomerular Disease (PGD) has increased in China.

Objectives: This cross-sectional study aimed to investigate changes in the clinicopathological features associated with IMN in northeast China.

Methods: We analyzed clinical and pathological data of 1,198 patients with IMN among 4,083 patients hospitalized with PGD undergoing renal biopsy from January 1, 2005, to December 31, 2018 at the Second Hospital of Jilin University in northeast China. Enrollees were divided into two groups: those seen from 2005 to 2011 (Group 1) and those seen from 2012 to 2018 (Group 2). We compared the clinicopathological features between Group 1 and Group 2.

Results: The percentage of patients with IMN among those with PGD increased over the 14 years of the study ($P = 0.001$). The male-to-female ratio, prevalence of microscopic hematuria, and proteinuria levels were higher in Group 2 than in Group 1 ($P < 0.05$). Among those with PGD, the percentages of patients with IMN-total, IMN-I, IMN-II, and IMN-III+IV, as well as Tubulointerstitial Lesion (TIL) scores, were higher in Group 2 than in Group 1 ($P < 0.05$). Finally, age ($P < 0.001$), degree of proteinuria ($P < 0.001$), and serum triglyceride level ($P = 0.027$) were significantly associated with TIL scores among patients with IMN.

Conclusions: Membranous nephropathy is now the leading cause of PGD, with increased TIL scores during the study period. Advanced age, high proteinuria, and serum triglyceride levels represent the independent risk factors for severe TIL among patients with IMN.

Keywords: Clinical Pathology, Idiopathic Membranous Glomerulonephritis, Tubulointerstitial Lesion

1. Background

Membranous Nephropathy (MN) commonly affects adults with Primary Glomerular Disease (PGD). Approximately 80% of patients with MN have Idiopathic Membranous Nephropathy (IMN) (1). The scientific literature shows that the prevalence of IMN among patients with PGD has decreased in developed countries (2, 3). However, a nationwide survey of 71,151 individuals in China showed that the prevalence of IMN increased from 12.2% in 2004 to 24.9% in 2014 (4). Other studies of IMN incidence in China similarly found an increasing trend over time, but their findings regarding the spectrum of PGD often conflict (5-9). For example, IgA nephropathy remains the most common cause of PGD among individuals from Beijing (6, 7), Shanghai (5), and Zhejiang province (9), but IMN is the leading cause of PGD among those from Shandong (8) and Jilin province (10). However, all of the above studies have their shortcomings. First, none of the data from the Shandong and Jilin provinces has addressed the changes in the pathological stage or clinical features of patients with IMN and the relationship between the severity of disease in clinical and its specific pathological stage. Second, the main pathological changes of IMN are in the glomeruli, and there is little attention to renal interstitium changes.

2. Objectives

In the current study, we surveyed patients with IMN and then compared the clinicopathological data between different periods, by a specific focus on IMN pathological stages and renal interstitium changes.

3. Methods

3.1. Patient Enrollment

A cross-sectional study was conducted by collecting patients who underwent renal biopsy during the period from January 1, 2005, to December 31, 2018 at the Second Hospital of Jilin University. It is a large general and teaching hospital that admits all patients and kidney samples from other hospitals. The inclusion criteria were (1) confirmed IMN by electron microscopy and light microscopy, and (2) complete clinical and pathological data. The exclusion criteria were (1) age < 14 years and (2) the absence of glomeruli in immunofluorescent staining of biopsy specimens or fewer than 10 glomeruli visualized with light microscopy. Each patient signed an informed consent form before this study. The study was approved by the Ethics Committee of the Second Hospital of Jilin University, and Institutional Review Board approval (2020017) was provided. The IMN patients enrolled in the study from 2005 to 2011 were considered as Group 1, and those enrolled from 2012 to 2018 were considered as Group 2. Data from the medical records for these patients were analyzed after separation into three pathological groups (IMN-I, IMN-II, and IMN-III+IV) based on gender and age.

3.2. Data Collection

We collected the following clinical data of IMN patients at the time of biopsy: Age, gender, microscopic hematuria, proteinuria, serum albumin (40 - 55 g/L), creatinine (57 - 111 μmol/L), cholesterol (2.90 - 5.17 mmol/L), triglyceride (0.56 - 1.71 mmol/L), blood urea nitrogen (3.60 - 9.50 mmol/L), uric acid (90 - 410 μmol/L for males, 89 - 375 μmol/L for females), and estimated glomerular filtration rate (eGFR, > 90 mL/min). Biochemical indicators were detected by a HITACHI LABOSPECT 008 AS automatic analyzer. We also collected pathological data, including pathological grades and Tubulointerstitial Lesion (TIL) scores for analysis.

We classified the pathological stages of IMN under electron microscopy based on previous studies (11), as follows: Stage I (IMN-I): few sub-epithelial electron-dense areas, without significant Basement Membrane (BM) changes (except for podocyte fusion); Stage II (IMN-II): many sub-epithelial electron-dense areas causing glomerular capillary thickening accompanied by extensive podocyte fusion; Stage III (IMN-III): glomerular BM exhibiting a "worm-eaten" appearance in regions surrounding the electron-dense areas; and Stage IV (IMN-IV): most deposited electron densities absorbed and close to the density of BM. The TIL score (IMN-TIL) was evaluated based on the Katafuchi semi-quantitative score evaluation criteria, including interstitial inflammatory cell infiltration, interstitial fibrosis, and renal tubule atrophy (12).

3.3. Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or median (interquartile range). Time series analysis was used to analyze the change trend of IMN in PGD from 2005 to 2018. The *t*-test, χ^2-test, Mann-Whitney U, correlation analysis, and multiple linear regression were performed by SPSS V. 19.0 software for Windows (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant. In the process of data collection, very few data were missing. The method of the linear trend of points was used to replace the missing values.

4. Results

Finally, 4,083 patients with PGD and 1,198 patients with IMN were included. Among patients with IMN, the mean age was 50.92 ± 12.97 years, and the male-to-female ratio was 1.70:1. The numbers of patients with IMN and PGD and those undergoing renal biopsy overall had a similar trend of change (Figure 1). The incidence of IMN in PGD increased from 8.82% in the first quarter of 2005 to 52.33% in the fourth quarter of 2018. By time series analysis, we found that the overall trend of the IMN prevalence rate was upward over the past 14 years (P = 0.001) (Figure 2).

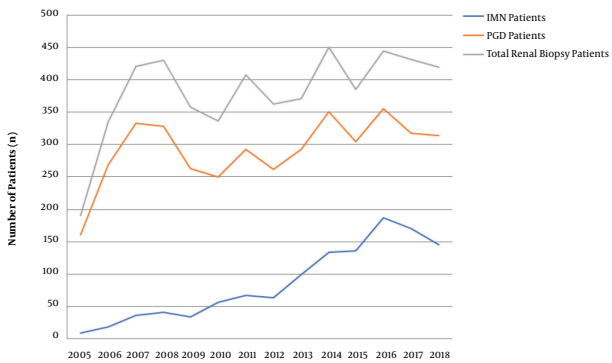

Figure 1. Changes in the numbers of patients with IMN and/or PGD and those who underwent renal biopsy from 2005 to 2018

4.1. Comparison of Clinical and Pathological Characteristics Between Groups

As shown in Table 1, we found that the male-to-female ratio, the prevalence of microscopic hematuria, and the proteinuria level were significantly higher in Group 2 than in Group 1 (P < 0.05). Representative images of various pathological stages of IMN are shown in Figure 3. As shown in Table 2, the percentages of patients with IMN-total, IMN-I, IMN-II, and IMN-III+IV among those with PGD, as well as IMN-TIL scores, were significantly higher in Group 2 than in Group 1 (P < 0.05).

Table 1. Demographic and Clinical Characteristics of Patients with Idiopathic Membranous Nephropathy[a]

	Total (N = 4083)	2005 - 2011 (N = 1891)	2012 - 2018 (N = 2192)	P Value
Gender (male)	755 (18.49)	165 (8.73)	590 (26.92)	< 0.001
Age (y)	50.92 ± 12.97	50.63 ± 14.92	50.99 ± 12.62	0.761
Microscopic hematuria, No. (%)	537 (13.15)	95 (5.02)	442 (20.16)	< 0.001
Proteinuria (g/day)	5.44 (4.61)	5 (3.75)	5.56 (4.96)	0.041
Serum albumin (g/L)	26.63 ± 9.58	25.01 ± 6.57	26.92 ± 9.97	0.057
Serum creatinine (μmol/L)	74.00 (28.70)	75.00 (28.00)	74.00 (39.00)	0.318
Serum cholesterol (mmol/L)	7.94 (3.42)	8.16 (3.70)	7.91 (3.33)	0.968
Serum triglyceride (mmol/L)	2.42 (2.05)	2.49 (2.35)	2.39 (1.88)	0.392
Blood urea nitrogen (mmol/L)	4.56 (2.31)	4.39 (2.32)	4.61 (2.34)	0.251
Serum uric acid (μmol/L)	345.75 ± 94.42	348.00 ± 85.27	345.23 ± 96.47	0.746
eGFR (mL/min/1.73 m^2)	96.38 ± 35.06	97.48 ± 31.78	98.22 ± 31.37	0.797

[a] Values are expressed as mean ± SD or No. (%).

Table 2. Pathological Features of Patients with Idiopathic Membranous Nephropathy Among Those with Primary Glomerular Disease

	Total (N = 4083)	2005 - 2011 (N = 1891)	2012 - 2018 (N = 2192)	P Value[a]
IMN-Total (n1%)	1198 (29.34)	263 (13.91)	935 (42.66)	< 0.001
IMN-I (n1%, n2%)	358 (8.77, 29.88)	71 (3.75, 26.99)	287 (13.09, 30.70)	< 0.001
IMN-II (n1%, n2%)	751 (18.39, 62.69)	161 (8.51, 61.22)	590 (26.92, 63.10)	< 0.001
IMN-III+IV (n1%, n2%)	89 (2.18, 7.43)	31 (1.64, 11.79)	58 (2.65, 6.20)	0.028
IMN-TIL score	2.42 ± 1.81	2.01 ± 1.72	2.64 ± 1.81	< 0.001

Abbreviations: n1%, percentage of IMN in PGD; n2%, percentage of IMN in IMN-Total.
[a] Comparison of n1% between the two periods.

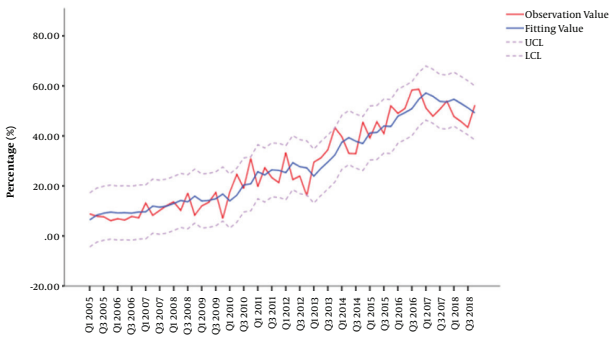

Figure 2. The quarterly percentages of patients with IMN among those with PGD, between 2005 and 2018

4.2. Variation in Pathological Features According to Age and Gender

The percentages of patients with IMN-total, IMN-I, IMN-II, and IMN-III+IV, as well as IMN-TIL scores, among those in the 45 - 59-year stratum, were significantly higher in Group 2 than in Group 1 (Table 3). In the other age strata, the percentages of patients with IMN-total, IMN-I, and IMN-II were also higher in Group 2 than in Group 1 ($P < 0.001$). As shown in Table 4, for both males and females, the percentages of patients with IMN-total, IMN-I, and IMN-II among those with PGD, as well as IMN-TIL scores, were significantly higher in Group 2 than in Group 1 ($P < 0.05$).

4.3. Factors Associated with IMN-TIL Scores

Correlation analyses showed that the IMN-TIL scores were positively correlated with age, proteinuria, serum creatinine, triglyceride, and blood urea nitrogen, but negatively correlated with serum albumin and eGFR. The results of multiple linear regression showed that age, proteinuria, and serum triglyceride were significantly associated with IMN-TIL scores (Table 5).

5. Discussion

By analyzing the clinical and pathological data of 4,083 patients with PGD from Jilin, China, we found a link between the IMN pathological stage and clinical features.

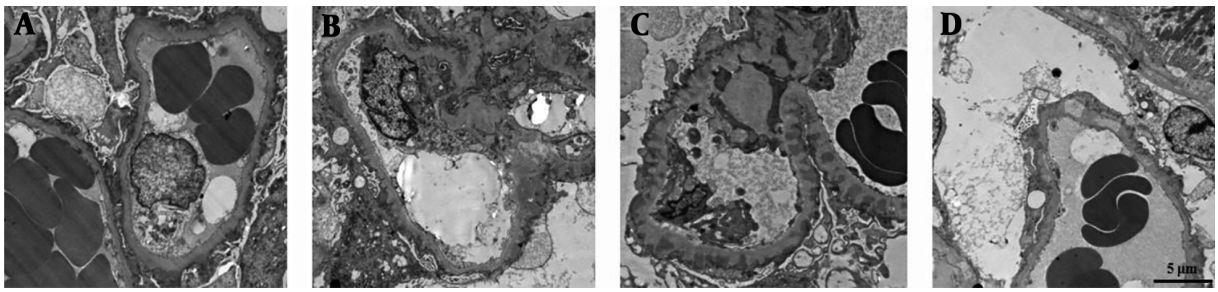

Figure 3. Various pathological stages of IMN under electron microscopy. A, stage I; B, stage II; C, stage III; D, stage IV. (6000×).

Table 3. Pathological Features of Patients with Idiopathic Membranous Nephropathy Based on Age

Age	Total (N = 4083)	2005 - 2011 (N = 1891)	2012 - 2018 (N = 2192)	P Value[a]
14 - 44 years				
IMN-Total (n1%)	363 (8.89)	103 (5.45)	260 (11.86)	< 0.001
IMN-I (n1%, n2%)	111 (2.72, 30.58)	26 (1.37, 25.24)	85 (3.88, 32.70)	< 0.001
IMN-II (n1%, n2%)	223 (5.46, 61.44)	64 (3.38, 62.14)	159 (7.25, 61.15)	< 0.001
IMN-III+IV (n1%, n2%)	29 (0.71, 7.98)	13 (0.69, 12.62)	16 (0.73, 6.15)	0.872
IMN-TIL score	1.91 ± 1.68	1.67 ± 1.82	1.97 ± 1.64	0.302
45 - 59 years				
IMN-Total (n1%)	519 (12.71)	99 (5.24)	420 (19.16)	< 0.001
IMN-I (n1%, n2%)	154 (3.77, 29.67)	33 (1.75, 33.33)	121 (5.52, 28.82)	< 0.001
IMN-II (n1%, n2%)	326 (7.98, 62.81)	54 (2.86, 54.55)	272 (12.41, 64.76)	< 0.001
IMN-III+IV (n1%, n2%)	39 (0.96, 7.52)	12 (0.63, 12.12)	27 (1.23, 6.42)	0.050
IMN-TIL score	2.58 ± 1.84	1.69 ± 1.44	2.78 ± 1.86	< 0.001
≥ 60 years				
IMN-Total (n1%)	316 (7.74)	61 (3.22)	255 (11.63)	< 0.001
IMN-I (n1%, n2%)	93 (2.28, 29.43)	12 (0.63, 19.67)	81 (3.70, 31.77)	< 0.001
IMN-II (n1%, n2%)	202 (4.95, 63.92)	43 (2.27, 70.49)	159 (7.25, 62.35)	< 0.001
IMN-III+IV (n1%, n2%)	21 (0.51, 6.65)	6 (0.32, 9.84)	15 (0.68, 5.88)	0.102
IMN-TIL score	3.03 ± 1.71	2.86 ± 1.79	3.07 ± 1.69	0.470

Abbreviations: n1%, percentage of IMN in PGD; n2%, percentage of IMN in IMN-Total.
[a]Comparison of n1% between the two periods.

Also, the changes in renal interstitium were related to the clinical courses of IMN patients. Prior studies showed that the frequency of IMN among patients with PGD has decreased over recent decades in the United Kingdom (2), the United States (3), France (13), and Brazil (14). An opposite trend has been observed in many developing countries, such as Pakistan (15), Czech Republic (16), and India (17, 18). Our results suggested that the percentage of patients with IMN among those with PGD increased from 5.63% to 53.63% over the past 14 years in northeast China, with IMN ultimately becoming the leading cause of PGD. This trend may be attributed to the increased number of cases with IMN-I (9.34%) and IMN-II (18.41%).

The pathogenesis of IMN is still unclear and is affected by multiple factors, including environmental factors and genetic susceptibility. In recent decades, particulate matter 2.5 (PM2.5) has become a major constituent of air pollution, leading to numerous adverse health effects. The highest concentrations of PM2.5 are reported in northern China, where the incidence of IMN appears to be highest, like Shandong province (4, 19). It has also been reported that exposure to mercury, formaldehyde, alkylating agents, and other unknown drugs may be associated with increased risk of MN (20, 21). Since our city is a heavy industry base, chemical pollutions should also be considered.

Furthermore, the IMN-TIL score, as an independent predictor of renal prognosis (22, 23), was significantly higher in all patients enrolled in Group 2 than those in Group

Table 4. Pathological Features of Patients with Idiopathic Membranous Nephropathy Based on Gender

Gender	Total (N = 4083)	2005 - 2011 (N = 1891)	2012 - 2018 (N = 2192)	P Value[a]
Male				
IMN-Total (n1%)	755 (18.49)	165 (8.73)	590 (26.92)	< 0.001
IMN-I (n1%, n2%)	203 (4.97, 26.89)	42 (2.22, 25.45)	161 (7.34, 27.29)	< 0.001
IMN-II (n1%, n2%)	499 (12.22, 66.09)	105 (5.56, 63.64)	394 (17.97, 66.78)	< 0.001
IMN-III+IV (n1%, n2%)	53 (1.30, 7.02)	18 (0.95, 10.91)	35 (1.60, 5.93)	0.069
IMN-TIL score	2.52 ± 1.88	2.13 ± 1.78	2.74 ± 1.88	0.003
Female				
IMN-Total (n1%)	443 (10.85)	98 (5.18)	345 (15.74)	< 0.001
IMN-I (n1%, n2%)	155 (3.80, 34.99)	29 (1.53, 29.59)	126 (5.75, 36.52)	< 0.001
IMN-II (n1%, n2%)	252 (6.17, 56.89)	56 (2.96, 57.14)	196 (8.94, 56.81)	< 0.001
IMN-III+IV (n1%, n2%)	36 (0.88, 8.12)	13 (0.69, 13.27)	23 (1.04, 6.67)	0.218
IMN-TIL score	2.35 ± 1.66	1.74 ± 1.85	2.47 ± 1.66	0.006

Abbreviations: n1%, percentage of IMN in PGD; n2%, percentage of IMN in IMN-Total.
[a]Comparison of n1% between the two periods.

Table 5. Relationship Between Idiopathic Membranous Nephropathy-Tubulointerstitial Lesion Scores and Clinicopathologic Indicators

Variables	Pearson/Spearman Correlation Analysis		Multiple Linear Regression Analysis		
	r	P Value	β (Standardized)	*t*	P Value
Gender	-0.055	0.083			
Age	0.272	< 0.001	0.261	7.531	< 0.001
Microscopic Hematuria	-0.032	0.366			
Proteinuria	0.185	< 0.001	0.142	3.867	< 0.001
Serum albumin	-0.088	0.013	-0.020	-0.568	0.571
Serum creatinine	0.265	< 0.001			
Serum Cholesterol	-0.026	0.470			
Serum Triglyceride	0.093	0.009	0.077	2.222	0.027
Blood urea nitrogen	0.176	< 0.001			
Serum uric acid	0.000	0.994			
eGFR	-0.294	< 0.001			
Stages of IMN	0.042	0.175			

1. This trend was also true among the stratum of middle-aged individuals, regardless of gender. The results also indicated that the IMN-TIL score was associated with multiple clinical features (Table 5). These findings suggest that advanced age and high levels of proteinuria and serum triglyceride play important roles in the pathogenesis of IMN-TIL. Therefore, effective treatments for proteinuria and high serum triglyceride may help slow down the progression of IMN-TIL.

In this study, we found significant differences over time among patients with IMN, including the gender ratio of those affected and the prevalence of microscopic hematuria and proteinuria. Overall, IMN was seen predominantly in male patients, with a male-to-female ratio of 1.70:1, which was higher than in previous reports (24, 25). The number of PGD patients with IMN increased by 18.19% and 10.56% among males and females of Group 2, respectively, compared to Group 1. The observed differences between male and female patients with IMN may be attributed to race and geographic region. In this study, the prevalence of IMN increased most over time (13.92%) among patients of middle age (45 - 59 years). Our results confirm that IMN is slightly more common among males and middle-aged individuals. The IMN patients in Group 2 had higher levels of hematuria and proteinuria, both of which confer a poor prognosis. The most plausible reason for these changes in clinical features may be the renal pathology of IMN.

5.1. Conclusions

In conclusion, the percentage of patients with IMN among those with PGD, as well as IMN-TIL scores, increased overtime at our center, with IMN becoming the leading

cause of PGD in northeast China. However, we did not analyze the ultimate cause of this change in-depth. Moreover, advanced age, high levels of proteinuria, and serum triglyceride were the risk factors for developing IMN-TIL, reminding us that we should closely monitor changes in important clinical risk factors.

Footnotes

Authors' Contribution: Wenpeng Cui designed the manuscript; Yan Lou, Dan Gao, Qiaoyan Guo, and Ping Nie collected the data; Yan Lou and Dan Gao analyzed the data; Wenpeng Cui and Yan Lou wrote the article. Ping Luo reviewed the article.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: This study was approved by the Ethics Committee of the Second Hospital of Jilin University.

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