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ARTICLE

Clinicopathological Features of Membranous Nephropathy Complicated by IgA Nephropathy: A Retrospective Analysis of Seven Cases

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Abstract

Aims/Background Both membranous nephropathy (MN) and immunoglobulin A nephropathy (IgAN) are immune complex-mediated glomerular diseases, but the concurrent occurrence of these two conditions in the same patient is not common, a phenomenon that is currently not supported by clinical data in terms of treatment and prognosis. This study explores the clinical and pathological characteristics, as well as the treatment outcomes, of patients affected by MN and IgAN simultaneously.

Methods The clinical data, pathological features, and diagnostic and therapeutic information of seven cases of MN complicated by IgAN, treated between December 2015 and December 2022, were retrospectively analyzed.

Results Among the seven cases, there were two male and five female patients, with an average age of 57.3 ± 9.2 years. All patients presented with clinical manifestations of proteinuria and edema upon admission, with an average 24-hour urine protein of 3716.6 ± 1519.4 mg/24 h. Phospholipase A2 receptor (PLA2R) expression was detected in all seven cases, and nephrotic syndrome was clinically diagnosed in five cases. Additionally, all seven cases showed microscopic hematuria, with intermittent gross hematuria in two cases. All seven patients included in this study underwent renal biopsy. After disease staging, the patients had MN stages I–III and IgAN stages II–III. Pathological findings revealed abnormal glomerular basement membrane (GBM) and diffuse immunoglobulin G (IgG) deposition in the subepithelial space, predominantly of the IgG4 subtype. Simultaneously, there was diffuse mesangial zone deposition of immunoglobulin A (IgA) to varying degrees, co-localization of complement component C3 and IgA, and mesangial cell proliferation. Treatment strategies included angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) in combination with steroids or immunosuppressive therapies such as tacrolimus, cyclophosphamide, and rituximab. After 2–6 months of treatment, all patients achieved complete remission with a favourable prognosis.

Conclusion MN accompanied by IgAN tends to occur more frequently in middle-aged and elderly individuals, with a relatively low incidence. The latent feature of the comorbidities manifests as a form of IgAN superimposed on the background of MN. Utilizing ACEI or ARB in combination with steroids or various immunosuppressive therapies represents a potentially effective treatment strategy.

Key words: membranous nephropathy; IgA nephropathy; anti-phospholipase A2 receptor

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Introduction

Membranous nephropathy (MN) and immunoglobulin A nephropathy (IgAN) are clinically common glomerular diseases (Rovin et al, 2021). MN is primar-

ily characterized by the formation of immune complexes through the binding of antibodies to podocyte antigens. It is characterized by diffuse deposition of immune complexes beneath the epithelial cells of the glomerular basement membrane (GBM), leading to diffuse thickening of the basement membrane, which results in a decline in glomerular filtration rate, causing significant proteinuria or varying degrees of hypoalbuminemia (Ronco et al, 2021).

MN can be classified into primary MN and secondary MN (Nieto-Gañán et al, 2022). Primary MN accounts for approximately two-thirds of all cases of MN. Antibodies against the transmembrane Phospholipase A2 receptor (PLA2R) are considered potential serum diagnostic biomarkers for MN (Nieto-Gañán et al, 2022; Pozdzik et al, 2019). IgAN refers to a type of primary glomerulonephritis characterized by the predominant deposition of immunoglobulin A (IgA) in the glomeruli. The typical pathological manifestation includes mesangial cell proliferation and mesangial matrix expansion (Gleeson et al, 2023). Clinically, it presents with recurrent episodes of gross or microscopic hematuria, often accompanied by variable degrees of proteinuria, and may result in hypertension or renal failure in severe cases (IgA nephropathy, 2023; Roberts, 2014).

Several studies have reported the coexistence of MN and IgAN (MN/IgAN); however, it remains unclear whether MN/IgAN signifies a distinct pathological clinical entity or the overlap of two patterns of kidney injury. Furthermore, the treatment and prognosis of MN/IgAN are governed by multiple factors, which currently remain unclear. Therefore, we conducted a retrospective analysis of clinical, pathological, and treatment follow-up data for seven cases of MN/IgAN, aiming to provide a basis for rational diagnosis and treatment in future.

Methods

Study Design and Participants

The present study included patients who sought medical attention at Tiantai County People's Hospital and Zhejiang Provincial People's Hospital from December 2015 to December 2022. These patients were included based on the following criteria: (1) patients diagnosed with chronic kidney disease with complete case data; and (2) patients with concurrent diagnoses of MN and IgAN, confirmed with renal biopsy. Two pathologists jointly reviewed and determined the renal biopsy results. Exclusion criteria of this study were as follows: (1) patients harbouring secondary factors such as IgA vasculitis-related nephritis, chronic hepatitis B, chronic hepatitis C, autoimmune diseases, malignancies, drug-induced secondary nephropathy, *etc*.; and (2) patients without clinical and pathological data.

According to their clinical needs and condition, the included patients received medication treatment including corticosteroids, immunomodulators (such as tacrolimus, cyclophosphamide, *etc*.), angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), as well as symptomatic treatment. Follow-up was conducted through both outpatient visits and telephone interviews. The focus of the follow-up was on monitoring levels of clinical indicators and tracking the usage of therapeutic medications. Outpatient follow-up data were extracted from

the computerized medical record management system and analyzed. For telephone-based follow-up, patients or their family members were contacted to inquire about the current condition of the patients.

Data Collection

A range of data, including demographic information such as age, gender, and disease duration, were collected. Laboratory data such as urinalysis results, serum creatinine, serum albumin, blood uric acid, blood alanine aminotransferase, total cholesterol, triglycerides, blood immunoglobulins (IgG, IgA, immunoglobulin M (IgM)), 24-hour urinary protein, D-dimer, PLA2R antibodies, serum viral infection markers, antinuclear antibodies, tumour markers, and other relevant parameters were obtained after patient admission.

Biopsy Evaluation

Various techniques were employed for the histopathological examination of renal biopsy tissues. Tissue sections stained with methods such as hematoxylin and eosin (HE), periodic acid-Schiff (PAS), periodic acid-silver methenamine (PASM), and Masson stain were observed using light microscopy. Direct immunofluorescence on frozen sections was utilized to observe the location and amount of deposited immunoglobulins (IgG, IgA, IgM), complement components (C3, C1q), *etc*. Semi-quantitative assessment based on fluorescence intensity was performed. Additionally, formalin-fixed specimens were prepared for electron microscopy.

IgAN was diagnosed in accordance with the classifications defined by Lee et al (2005), while MN was diagnosed based on staging.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software (IBM Corporation, Armonk, NY, USA). For quantitative data, normality distribution was assessed using the one-sample Shapiro–Wilk test. Normally distributed data are expressed as mean ± standard deviation (SD), while skewed data are presented as medians and interquartile range (IQR).

Results

Clinical Features of Patients with MN Complicated by IgAN

A summary of clinical and laboratory data of patients with MN complicated by IgAN is presented in Table 1.

The present study included a total of seven patients, consisting of two males and five females, with an average age of 57.3 ± 9.2 years (range 48–74 years). Five of the seven patients had a history of hypertension. None of the patients had a history of diabetes or other diseases, and none reported alcohol abuse, drug use, or other unhealthy habits. All patients presented with clinical manifestations of proteinuria and edema upon admission. Specifically, five cases exhibited proteinuria indicative of nephrotic syndrome (24-hour urinary protein excretion ≥3.5 g/24 h). All seven cases also presented with microscopic hematuria, with intermittent gross hematuria in two cases (Table 1). Most patients exhibited low levels of hemoglobin

and serum albumin, but elevated blood lipid levels. All patients had significantly elevated PLA2R antibodies. However, serum immunoglobulin-related indicators, including IgA, IgG, and IgM, were within the normal range. Additionally, all cases showed normal renal function. Secondary disease markers, including hepatitis B or C virus infection markers, anti-nuclear antibodies, and tumour antigen markers, were all negative.

Table 1. Summary of the clinical and laboratory data of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Mean ± SD/Median (P25, P75)
Age	49	48	61	59	74	60	50	57.3 ± 9.2
Sex	M	F	F	F	F	F	M	/
Duration (months)	19	8	8	11	57	9	9	/
Albuminuria	2+	2+	3+	4+	2+	2+	2+	/
Microscopic hematuria	2+	1+	3+	2+	2+	3+	1+	/
Swelling of the limbs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	/
Hypertension	Yes	No	Yes	No	Yes	Yes	Yes	/
Hemoglobin (g/L)	70	81	130	82	73	56	71	73 (80, 82)
Serum creatinine (μmol/L)	84.1	61	68.6	67.5	117.3	56	77	75.9 ± 20.5
Serum albumin (g/L)	28.8	27.7	29.2	20.3	23.3	25.6	40.6	27.9 ± 6.4
Serum ALT (U/L)	33	30	18	5	22	33	28	24.1 ± 10.1
TC (mmol/L)	7.64	7.75	8.5	6.93	9.1	6.5	3.94	7.2 ± 1.7
TG (mmol/L)	2.9	1.92	2.13	1.93	2.88	1.1	2.92	2.3 ± 0.7
Serum IgG (g/L)	/	8.39	6.95	6.21	7.85	9.85	/	7.9 ± 1.4
Serum IgA (g/L)	/	3.41	2.28	2.58	2.37	1.71	/	2.5 ± 0.6
Serum IgM (g/L)	/	1.02	0.64	0.79	2.05	1.62	/	1.02 (0.72, 1.84)
PLA2R (RU/mL)	58.6	61.02	121.9	30.14	42.25	32.35	/	50.43 (31.80, 76.25)
Urine RBC (/HP)	40.7	37.3	53	47.1	14.6	31	11	33.5 ± 15.8
24-h urine protein (mg/24 h)	5584	3865	3928	4646	4489	2500	1004	3716.6 ± 1519.4

Note: Serum IgG, IgA, and IgM in Case 1 and Case 7, and PLA2R in Case 7 are not available,
1+: Albuminuria (+): indicates that the 24-hour albuminuria quantification >500 mg and <1000 mg;
Microscopic hematuria (+): means that there are 10 in the field of high magnification;
2+: Albuminuria (++): Indicates that the 24-hour albuminuria quantification >1000 mg and <2000 mg;
Microscopic hematuria (++): means that there are 20 in the field of high magnification;
3+: Albuminuria (+++): Indicates albuminuria quantification >2000 mg/24 h;
Microscopic hematuria (+++): means that there are 30 in the field of high magnification;
4+: Albuminuria (++++): Indicates albuminuria quantification >3500 mg/24 h.
Abbreviations: ALT, Aspartate aminotransferase; TC, total cholesterol; TG, triglycerides; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; PLA2R, Phospholipase A2 receptor; RBC, Red blood cell; F, Female; M, Male.

Pathological Features of Patients with MN Complicated by IgAN

Pathological characteristics of these patients, based on the renal biopsy results, are detailed in Table 2. According to the staging of MN lesions, one case was in

stage I, one case in stages I–II, two cases in stage II, and three cases in stage III. Additionally, there were four cases in stage II and three cases in stage III based on the classifications set forth by Lee et al (2005) for IgAN.

Light microscopic examination revealed that no crescents were found in the renal biopsy tissues obtained from all seven patients. However, there was diffuse mesangial widening, mesangial cell proliferation and increased mesangial matrix in the mesangial area. All seven patients exhibited stiffening of the capillary loops, thickening of the basement membrane, multifocal swelling of tubular epithelial cells, focal mononuclear and lymphocytic infiltration in the interstitium, and thickening of small arterial walls. Furthermore, four of the seven patients showed glomerulosclerosis. Fig. 1A shows a representative PAS staining image and Fig. 1B a representative Masson's staining image showing immune complex deposits in the mesangial domain. Three patients exhibited diffuse thickening of the glomerular capillary basement membrane accompanied by segmental spike formation, as shown in Fig. 1C, a representative PASM staining image.

Immunofluorescence analysis of the renal biopsy tissues revealed the presence of IgG, IgA, and IgM deposition in all patients. Morphological analysis of the deposits showed diffuse granular IgG deposition along the blood vessels in all patients, as shown in Fig. 1D. Subsequently, IgG subtyping was performed in six patients, with three patients testing positive for IgG1 and six patients testing positive for IgG4. All seven patients exhibited diffuse mesangial zone block-like deposition of IgA, with some patients showing dot-like segmental deposits in the mesangial area (Fig. 1E). To further study the expression, fluorescence intensity analysis was conducted, depicting IgG (+++) in seven cases; IgA (+) in one case, IgA (++) in two cases, IgA (+++) in three cases, and IgA (++++) in one case; IgM (+) in four cases, IgM (++) in one case, and IgM (+++) in two cases; C3 (+) in one case, and C3 (+++) in three cases. Additionally, all seven patients had positive PLA2R test results, characterized by fine granular globular deposits along the capillary walls (Fig. 1F). Also, hepatitis B surface antigen and hepatitis B core antibody subtyping were negative in all seven patients. Type IV collagen $\alpha 1$, $\alpha 3$, and $\alpha 5$ were consistently positive.

Simultaneously, we observed the renal biopsy tissues by means of electron microscopy and found that all seven patients exhibited significant vacuolar degeneration of glomerular capillary endothelial cells. The wall layer of the glomerular capsule was thickened, and the layer cells showed vacuolar degeneration. Additionally, there was irregular thickening of the basement membrane, swelling and vacuolar degeneration of visceral epithelial cells. Electron-dense deposits were observed in the subepithelial, intrabasement membrane, and mesangial areas, with some electron-dense material enveloped within the GBM with signs of absorption (Fig. 1G,H). Furthermore, a diffuse fusion of podocyte foot processes was observed. In the renal interstitium, no specific pathological changes were observed.

Table 2. Summary of the pathological characteristics of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Pathological stages of MN	III	I	II	II	I–II	III	III
Grade of IgAN[a]	II	II	III	III	III	II	II
Light microscopy							
Crescent	0	0	0	0	0	0	0
Proportion of glomerular sclerosis	0/12	1/11	0/10	2/20	4/33	2/21	0/10
Proportion of renal tubular atrophy	0	0	0	10%	10%	5%	0
Mesangial cell proliferation	+	+	+	+	+	+	+
Mesangial matrix hyperplasia	+	+	+	+	+	+	+
Thickening of the capillary walls	-	+	+	+	+	+	+
Spikes	+	-	-	-	-	+	+
Interstitial inflammation	+	+	+	+	+	+	+
Immunofluorescence							
IgA	++++	+++	+++	++	++	+++	+
IgM	+++	+++	+	+	++	+	+
IgG	+++	+++	+++	+++	+++	+++	+++
IgG1	+	+	-	-	-	+++	+
IgG4	+++	+	++	+	+	+++	++
C3	+++	-	-	-	+++	+++	+
PLA2R	+	++	++	++	+	+++	+
C1q	-	-	-	-	-	-	-
Electron microscopy							
Mesangial area EDD	+	+	+	+	+	+	+
Subepithelial EDD	+	+	+	+	+	+	+
Fusion of foot processes	+	+	+	+	+	+	+

Note: [a] Based on Lee et al (2005).

+: Mesangial cell proliferation (+): There is mesangial cell proliferation; Mesangial matrix hyperplasia (+): There is mesangial matrix hyperplasia; Thickening of the capillary walls (+): There is thickening of the capillary wall; Spikes (+): There is spikes formation; Interstitial inflammation (+): There is interstitial inflammation; IgA (+): Mild IgA deposition; IgM (+): Mild IgM deposition; IgG1 (+): Mild IgG1 deposition; IgG4 (+): Mild IgG4 deposition; C3 (+): Mild C3 deposition; PLA2R (+): The titer is less than 1:100; Mesangial area EDD (+): There is Mesangial area EDD deposition;
Subepithelial EDD (+): There is Subepithelial EDD deposition; Fusion of foot processes (+): There is a fusion of foot processes.

-: Thickening of the capillary walls (-): There is no thickening of the capillary wall; Spikes (-): There is no spike formation; IgG1(-): There is no IgG1 deposition; C1q (-): There is no C1q deposition; C3(-): There is no C3 deposition.

++: IgA (++): Moderate IgA deposition; IgM (++): Moderate IgM deposition; IgG4(++): Moderate IgG4 deposition; PLA2R (++): The titer was between 1:100 and 1:200.

+++: IgA (+++): Severe IgA deposition; IgM (+++): Severe IgM deposition; IgG (+++): Severe IgG deposition; IgG1 (+++): Severe IgG1 deposition; IgG4 (+++): Severe IgG4 deposition; C3 (+++): Severe C3 deposition; PLA2R (+++): The titer is more than 1:200.

++++: IgA (++++): Extremely severe IgA deposition.

Abbreviations: EDD, Electron-dense deposits; IgAN, immunoglobulin A nephropathy.

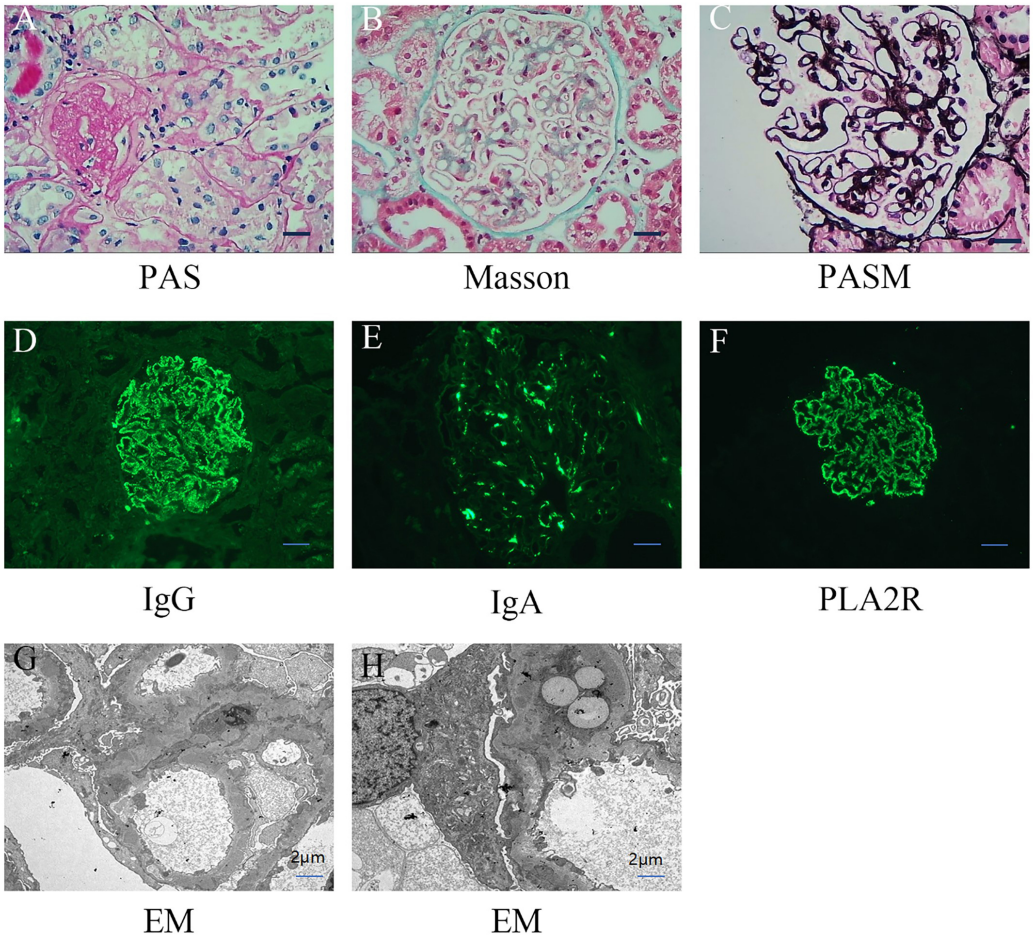

Fig. 1. Representative staining images depicting the clinicopathological characteristics of a case with membranous nephropathy (MN) complicated by immunoglobulin A nephropathy (IgAN). (A) Periodic acid-Schiff (PAS) staining showing glomerulosclerosis. (B) Masson staining showing eosinophilic deposits on subepithelial of glomerular. (C) Periodic acid-silver methenamine (PASM) staining shows thickening of the glomerular basement membrane (GBM) and formation of papillae-like structures. (D) Distribution of IgG in granular form along the capillary wall, as detected by immunofluorescence. (E) Segmental distribution of IgA in the mesangial region, as detected by immunofluorescence. (F) Distribution of PLA2R in granular form along the capillary wall, as detected by immunofluorescence. (G) The presence of mesangial electron-dense deposits in the GBM and irregular thickening of GBM, as detected by means of electron microscopy. (H) Presence of electron-dense deposits in the mesangium, as detected by electron microscopy. Scale bars: The scale length of (A–C): 50 μm. The scale length of (D–F): 100 μm. Magnifications: The magnification of (G): 5000×. The magnification of (H): 5000×.

Follow-up and Treatment Outcomes for Patients with MN Complicated by IgAN

Finally, we conducted a comprehensive assessment of the clinical test results of the seven patients. Our results showed that their renal function was within the normal range, and glomerulus, mesangial area, renal tubules, and renal interstitial lesions were mild. Of the seven patients, two cases received symptomatic supportive treatment, mainly with angiotensin II receptor antagonists; three were treated with steroids and immunosuppressive drugs; and the remaining two were treated

Table 3. Summary of treatment modality and response to therapy.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
ACEI/ARB	√	√	√	√	√	√	√
Hormone	√	√			√	√	
Tacrolimus		√			√		
CTX	√					√	
RTX			√	√			
Response to therapy	CR	CR	CR	CR	CR	CR	PR

Notes: The drugs encompassed in the category of ARBs include losartan potassium tablets (approval number: J20180006, Merck Sharp, Kenilworth, NJ, USA), irbesartan tablets (approval number: H20000513, Jiangsu Hengrui Pharmaceutical Co., Ltd., Lianyungang, China). The drug encompassed in the category of hormone is prednisone tablets (approval number: H33021207, Zhejiang Xianju Pharmaceutical Co., Ltd., Taizhou, China). Tacrolimus used by the patients in this study was acquired from Astellas (approval number: J20150102, Tokyo, Japan). CTX used by the patients in this study was manufactured by Baxter Oncology GmbH (approval number: HJ20160467, Halle, Germany). RTX utilized by the patients in this study was manufactured by Innovent Biologics, Inc. (approval number: S20200022, Suzhou, China). '√' indicates the use of current medications.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CTX, cyclophosphamide; RTX, rituximab; CR, complete remission; PR, partial remission.

mainly with rituximab. After two to six months of treatment, six patients achieved complete remission while one patient achieved partial remission. The specific details of the treatment regimens and response outcomes for each patient are provided in Table 3.

Discussion

In the present study, the clinical information, pathological features, pharmacological treatments, and prognosis of seven MN/IgAN patients were investigated to enhance our understanding of the clinical and pathological features in patients with MN/IgAN, which is instrumental to strengthening precise diagnosis and treatment in clinical practice.

MN is a rare glomerular disease, with an estimated annual incidence of 10–20 cases per million individuals in North America and 2–17 cases per million individuals in Europe (Couser, 2017; McGrogan et al, 2011; Ronco et al, 2021). The typical clinical manifestations include nephrotic syndrome, often characterized by significant proteinuria, hypoalbuminemia and edema. Almost 100% of MN patients exhibit detectable anti-PLA2R antibodies. The pathological features observed in MN are attributed to the accumulation of immunoglobulins, complement components, and PLA2R1 on the glomerular capillary wall (Couser, 2017; Ronco et al, 2021). In our research cohort, we observed that patients with MN/IgAN exhibited typical features of MN. These patients presented with the onset of edema, proteinuria,

and hypoalbuminemia. Among them, five cases (71.4%) were clinically diagnosed with nephrotic syndrome, and all exhibited 100% positive for PLA2R. Pathologically, these patients displayed abnormalities in the GBM with a predominant IgG4 subtype, characterized by diffuse granular deposits of IgG in the subepithelial space of the GBM.

IgAN is a common cause of severe renal failure in young individuals and presents with various clinical manifestations. These manifestations range from gross hematuria following upper respiratory tract infections to incidental microscopic hematuria, hypertension, and proteinuria. Pathologically, IgAN is characterized by the presence of IgA-dominant immune deposits within the glomeruli (Floege et al, 2021; Rajasekaran et al, 2021; Roberts, 2014). In this study, patients with MN/IgAN exhibited clinical and pathological features characteristic of both MN and IgAN. Clinically, patients also presented with recurrent episodes of gross or microscopic hematuria. Pathologically, in addition to the diffuse mesangial segmental deposits of IgA within the glomeruli, there were co-localized deposits of complement component C3 and IgA, along with features such as mesangial cell proliferation and mesangial matrix expansion. Furthermore, electron microscopy results confirmed the presence of electron-dense deposits in regions such as the GBM and mesangial area.

MN and IgAN are both glomerular diseases mediated by the deposition of immune complexes and fall under the category of autoimmune diseases. Despite sharing the characteristic of immune complex deposition in the glomeruli, the pathogenic mechanisms of these two diseases are distinct. The coexistence of MN and IgAN within the same case is relatively rare (Stokes and Alpers, 1998). In recent years, there has been a growing number of retrospective studies on MN/IgAN (Alghamdi, 2023; Chen et al, 2018; Hu et al, 2016; Ma et al, 2006; Saleem et al, 2021). It has been reported patients with MN/IgAN exhibited clinical characteristics similar to those of patients with MN (Chen et al, 2018).

He et al (2022) found that compared to those with IgAN, patients with MN/IgAN have higher 24-hour proteinuria excretion but lower levels of serum albumin and creatinine, less microscopic hematuria (95 erythrocytes/μL) and less gross hematuria. Aligning with other reported clinical data, our study demonstrated similar trends. Patients in this study exhibited higher levels of proteinuria, with 24-hour urinary protein reaching 3716.6 ± 1519.4 mg/24 h, lower blood creatinine levels, and lower albumin levels. However, in our study, 71.4% of MN/IgAN patients presented with nephrotic syndrome, and all patients had microscopic hematuria. Furthermore, both serum PLA2R and renal tissue PLA2R antigens were positive, with a positivity rate similar to that observed in the MN group. These findings suggest primary MN superimposed on IgAN. In a large-scale retrospective study, it was observed that in terms of pathological features, patients with MN/IgAN had much weaker mesangial IgA deposition, with an intensity of IgA graded as 2+, compared to most IgAN patients who typically exhibited 3+. Additionally, MN/IgAN patients showed fewer crescents. In comparison to MN, the intensity of IgG and C3 deposition along the GBM in MN/IgAN patients was weaker, with IgG intensity graded as 2+ and 3+, and C3 intensity predominantly as 1+ and 2+ (He et al, 2022). In the

MN/IgAN patients of this study, the IgA intensity was mainly graded as 2+ and 3+, and no crescents were observed. The C3 intensity was predominantly graded as 3+, while IgG intensity was uniformly as 3+. In comparison to other research data, the pathological severity in MN/IgAN patients in this study appeared to be higher and more aligned with symptoms characteristic of MN.

At present, there is no definitive cure for IgAN, and the main clinical treatment goals are to reduce proteinuria and prevent a decline in glomerular filtration rate. The primary treatment is the use of ACEIs or ARBs and the administration of fish oil to maintain or control blood pressure at appropriate levels (Barbour et al, 2019; Hassler, 2020; Noor et al, 2023). While spontaneous remission can occur in one-third of patients with MN, persistent high-level proteinuria, declining kidney function, or complications such as thrombosis often lead to a state where immunosuppression is required for treatment. Common strategies include the use of corticosteroids, alkylating agents, calcineurin inhibitors, such as cyclosporine and tacrolimus, and monoclonal antibodies like rituximab, utilizing a multi-targeted approach in immunosuppressive therapy (Idrees and Beck, 2021).

After treating MN/IgAN patients with renin-angiotensin-aldosterone system blockers, corticosteroids, and calcineurin inhibitors, it was found that 80% of them achieved successful remission (Khorsan et al, 2019; Saleem et al, 2021). Additionally, in a retrospective cohort of 137 patients, 73.47% of MN/IgAN patients were treated with an ACEI or ARB, and 26.53% of MN/IgAN patients were treated with glucocorticoids (He et al, 2022). The renal pathologies of patients in this study were categorized into MN stages I–III and IgAN stages II–III, based on the presentation of their complications, with a low proportion of interstitial fibrosis and tubular atrophy and the absence of severe damage such as crescents. Treatment strategies entailed a combination of ACEI or ARB with corticosteroids or various immunosuppressive therapies (tacrolimus, cyclophosphamide and rituximab). After two to six months of treatment, six of the seven patients achieved complete remission with a favourable prognosis.

However, there are several limitations of this study. Firstly, it is a retrospective study with a small-sized sample recruited from southern China, which may not be representative of a more diverse, broader population. Secondly, the present study only examined and analyzed clinical data such as pathological diagnosis, auxiliary examination information, and treatment follow-up, without exploring the pathogenic mechanisms of MN/IgAN.

Conclusion

In summary, the most common features of the combined entity of MN/IgAN, which is considered rare in the clinical scene, are massive proteinuria and stable renal function. In most cases, the etiology contributing to this strange combination of immune complex-mediated glomerular diseases is unknown. It is worth noting that the coexistence of these two pathological conditions does not lead to particularly adverse clinical outcomes.

The clinical and pathological features manifested by all seven cases in this study highly resemble to the typical hallmarks in MN, suggesting that MN/IgAN is a presentation of primary MN overlapped with secondary IgAN. The use of ACEI or ARB in combination with steroids, tacrolimus, cyclophosphamide, and rituximab, among other immunosuppressive agents, is an effective therapeutic strategy for managing this comorbidity.

Key Points

- The coexistence of immunoglobulin A nephropathy (IgAN) and membranous nephropathy (MN) in the same patient is rare. Few studies have reported the clinical and pathological features of patients with combined IgAN and MN (IgAN-MN).
- In this study, the clinical and pathological characteristics of MN-IgAN have higher similarities to those of MN.
- The most common clinical features of MN-IgAN are massive proteinuria and stable renal function.
- Combining an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker with steroids, tacrolimus, cyclophosphamide and rituximab, and other immunosuppressants, is an effective therapeutic strategy to manage MN-IgAN.

Availability of Data and Materials

All data analyzed during this study are included in this manuscript.

Author Contributions

BLX and QHB designed the study and performed data analysis. WS and QXH analyzed the data. WS and BLX drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study protocol was approved by the medical ethics committee of Tiantai County People's Hospital (Tiantai Hospital Lunshen 2023 Research No. 001). This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and all patients signed informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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