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ORIGINAL RESEARCH

Analysis of Clinicopathological Characteristics of Malignancy Patients with Membranous Nephropathy and Literature Review

Guoqin Wang[1,*], Xiaoying Hu[1,*], Nan Ye[1], Xiaoyi Xu[1], Weiyi Guo[1], Lijun Sun[1], Hongrui Dong[1], Xiaoyi Zhao[2], Hong Cheng[1]

[1]Division of Nephrology, Beijing Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Division of Nephrology, Affiliated Hospital of Chifeng University, Neimenggu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hong Cheng, Division of Nephrology, Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Road, Beijing, 100029, People's Republic of China, Email drchengh@163.com

Purpose: In recent years, the incidence of malignancy patients with membranous nephropathy (MN) has gradually increased, but the clinical and pathological characteristics of these patients are still unclear. Our study aims at elucidating the clinical and pathological characteristics of malignancy patients with MN, especially the expression patterns of MN-specific antigens in both kidney and tumor tissue.

Patients and Methods: A retrospective analysis was performed to summarize the clinical and pathological data of MN patients with malignancy at Beijing Anzhen Hospital from January 1, 2012, to December 31, 2022, followed by a thorough review of relevant literature published between May 1, 2000 to May 1, 2023 and case aggregation.

Results: 19 patients in our center's MN cohort and 21 patients from literature review were diagnosed with malignancy either before or after being diagnosed with MN. Among them, 16 (40.0%) and 17 (42.5%) patients tested PLA2R-only and THSD7A-only positive in renal tissue, respectively. And 16 of 26 patients showed similar staining in tumor and kidney tissues. Compared to the idiopathic membranous nephropathy (IMN) patients at our center, patients with malignancy were older, had a lower estimated glomerular filtration rate, and had a lower rate of partial or complete response to treatment. Renal tissue from MN patients with concomitant malignancy was less frequently PLA2R-positive, more frequently THSD7A-positive, and more often glomerular IgG subclass IgG2 ($P = 0.033$) but less frequently IgG4 ($P < 0.001$).

Conclusion: The clinical and pathological characteristics of MN patients with concomitant malignancy are different from those of IMN patients. Active screening for malignancy should be performed in non-PLA2R-positive elderly MN patients with a poor therapeutic response. Staining for MN target antigens in kidney and tumor tissues may be inconsistent, and the role of MN target antigens needs to be further explored.

Keywords: malignancy, membranous nephropathy, PLA2R, THSD7A, NELL-1

Introduction

Primary membranous nephropathy (PMN) is the most common cause of idiopathic nephrotic syndrome in non-diabetic adults worldwide, accounting for 20–37% in most kidney biopsy series.[1–3] The characteristic lesions of MN are formed by the deposition of antigen antibody complexes on the outer side of the basement membrane, which leads to thickening of the glomerular capillary wall.[1] MN can be classified into primary and secondary forms, and malignancy is an important cause of secondary MN, accounting for approximately 5–20% of all MN cases.[4] The specific antigens associated with MN include PLA2R, THSD7A, NELL-1, EXT1/EXT2, SEMA3B, and PCDH7, with THSD7A and NELL-1 have been proposed as possible target antigens in malignancy-associated MN. Previous studies have indicated that the simultaneous presence of malignancy and MN can increase patient mortality rate[5] and that renal lesions can also be partially alleviated in patients with MN after anti-malignancy treatment. However, the causal relationship between

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MN and malignancy remains uncertain. Therefore, it is important to elucidate the clinical and pathological characteristics of MN patients with concomitant malignancy for early diagnosis and treatment.

Existing studies of malignancy-associated MN are mainly case reports. In order to enhance our understanding of the clinical and pathological characteristics of MN with concurrent malignancy, as well as to investigate the expression of MN-specific antigens in both tumor and kidney tissues, we conducted a retrospective analysis of the clinical and pathological data of MN patients with concomitant malignancy at our center. We also performed MN-specific antigen staining on available malignancy specimens. Additionally, we also reviewed the literature on MN with concomitant malignancy published over the past 30 years. Through this search, we screened 17 articles that reported MN antigen staining in renal tissue and tumor tissue. By combining the clinical and pathological data of cases from our center and those from the literature, we conducted a comparative analysis between MN patients with concomitant malignancy and a control group of IMN patients without malignancy at our center.

Materials and Methods

Data Source and Study Population

Patients diagnosed with renal biopsy-proven MN and comorbid malignancy detected within 5 years before and after MN diagnosis at Beijing Anzhen Hospital, Capital Medical University from January 1, 2012, to December 31, 2022, were included in the study. The control group consisted of individuals who were diagnosed with renal biopsy-proven IMN with no malignancy detected within 5 years before or after kidney biopsy and no other clear secondary cause for MN. According to the 2021 Kidney Disease Improving Global Outcomes (KDIGO) guideline definitions, complete remission (CR) of proteinuria was defined by a 24-hour urinary protein quantification <0.3 g/d, and partial remission (PR) was defined by a 24-hour urinary protein quantification of 0.3 g/d-3.5 g/d or a >50% decline from baseline.[6] The estimated glomerular filtration rate (eGFR) was calculated used the EPI formula.

This study conformed to the Declaration of Helsinki and was approved by the ethics committee of Beijing Anzhen Hospital, Capital Medical University, approval number 2023154X. Clinical and pathological data were obtained from medical records and telephone interviews.

Immunohistochemical Staining of Kidney and Tumor Tissues

Immunohistochemical staining was performed by routine procedures. The following primary antibodies were used: rabbit monoclonal anti-PLA2R1 antibody (Sigma, HPAO12657, diluted 1:800), rabbit monoclonal anti-NELL-1 antibody (Sigma, HPAO 51535, diluted 1:400), rabbit monoclonal anti-THSD7A antibody (Sigma, HPAO00923, diluted 1:3000), and rabbit polyclonal anti-EXT1/2 antibody (R & D, 8567-gt, diluted 1:800). The secondary antibodies were applied alkaline phosphatase-labeled immunohistochemical color reagent (max vision, kit-5103) or horseradish peroxidase-labeled immunohistochemical color reagent (max vision, kit-5004) with subsequent color development.

Serum Antibody Detection

The indirect enzyme-linked immunosorbent assay (ELISA) method was applied to detect serum PLA2R antibody levels. An ELISA kit of the European Union standard (Euroimmun AG, Lübeck, Germany) was used, and values > 20 IU/mL were considered positive. THSD7A and NELL-1 antibodies were detected by indirect immunofluorescence with CBA.

Literature Review

We conducted a comprehensive literature search across the MEDLINE, EMBASE, CENTRAL, CNKI and Wan Fang databases for the terms “membranous nephropathy”, “PLA2R”, “THSD7A”, “NELL-1”, “malignancy”, and their Medical Subject Heading terms covering the period from May 1, 2000, to May 1, 2023. Studies were included if they contained (1) clinical data of MN patients with concomitant malignancy and (2) results of specific MN antigen staining for both kidney and tumor tissues. The above process for the literature search, data extraction and quality assessment were performed by two authors independently.

Statistical Methods

Data were analyzed by IBM SPSS statistics v24.0 Version (IBM Corporation, Armonk, NY, USA). The Shapiro–Wilk test was applied to determine whether quantitative variables were normally distributed. Categorical variables are presented as frequencies, and continuous variables are presented as the mean ± standard deviation (SD) or median and interquartile range (IQR). Student's *t* test or the Mann–Whitney *U*-test was performed to compare data between two groups according to the distribution of variables. Odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were calculated by adjusting for possible confounders. Two-sided $P < 0.05$ was considered statistically significant.

Results

Clinical Data of MN Patients with Concomitant Malignancy at Our Center

A total of 19 MN patients with concomitant malignancy were evaluated at our center; among them, 13 (68.4%) were male, and the median age was 57.0 (45.0, 69.0) years. Malignancy occurred after the onset of renal disease in 61.1% of patients, with digestive system malignancy (36.8%) ranking as the predominant type among all malignancies, followed by urinary system malignancy (21.2%) and reproductive system malignancy (21.1%) (Table 1 and Supplementary Table S1). Of 11 patients with accessible treatment and follow-up clinical records, 6 patients received treatment with prednisolone or immunosuppressive agents. Among these patients, 8 (8/11) patients achieved either PR or CR, 1 (1/11) patient did not achieve remission, and 2 (2/11) patients died due to malignancy-related reasons (Supplementary Table S2).

Table 1 Clinical Characteristics of MN Patients with Concomitant Malignancy in Our Center

Characteristics	MN with malignancy (n=19)
Male sex, n (%)	13(68.4)
Age, yr	57.0(45.0, 69.0)
NS, n (%)	9(47.4)
Urinary protein, g/d	3.5(2.6, 8.3)
Alb, g/l	29.5(23.7, 34.0)
eGFR, mL/min/1.73^2	93.2(69.9, 112.7)
ANA, n (%)	3(20.0); n = 15
HBV, n (%)	4(21.1)
Type of cancer, n (%)	
Digestive system	7(36.8)
Urinary system	4(21.1)
Respiratory system	2(10.5)
Reproductive system	4(21.1)
Endocrine system	2(10.5)
Time of diagnosis of tumor, n (%)	
Before	5(27.8); n = 18
Same time	2(11.1); n = 18
After	11(61.1); n = 18
Renal outcome, n (%)	
CR	2(18.2); n = 11
PR	6(54.5); n = 11
Non-remission	1(9.1); n = 11
Death	2(18.2); n = 11

(*Continued*)

Table 1 (Continued).

Characteristics	MN with malignancy (n=19)
Hollow organs tumor, n (%)	10(52.6)
Parenchymal organ tumor, n (%)	9(47.4)
Glomerular antigens, n (%)	
PLA2R	13(68.4)
THSD7A	3(15.8)
PLA2R+THSD7A	1(5.3)
NELL-1	1(5.3)
EXT1/2	1(5.3)
Serum antibodies, n (%)	
Anti-PLA2R antibody	9(60.1); n = 15
Anti-THSD7A antibody	0
Anti-NELL-1 antibody	0

Abbreviations: NS, nephrotic syndrome; Alb, Albumin; eGFR, estimated glomerular filtration rate; ANA, antinuclear antibody; HBV, hepatitis B virus; CR, complete remission; PR, partial remission; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain-containing 7A; NELL-1, neural epidermal growth factor-like 1 protein; EXT1/2, exostosin1/2.

Histopathology of Renal and Tumor Tissue in MN Patients with Concomitant Malignancy at Our Center

As shown in Table 2 and Supplementary Table S3, most patients had pathology typical of IMN, characterized by the presence of subepithelial deposits of metanephrine visible under light microscopy. Immunofluorescence showed strong positivity for IgG (100%) along the capillary wall, whereas only 13 (68.4%) patients were positive for C3, and IgA fluorescence was observed in 4 (21.1%) patients. Electron microscopy showed electron-dense deposits predominantly

Table 2 Pathologic Characteristics of MN Patients with Concomitant Malignancy in Our Center

Characteristics	MN with malignancy (n=19)
Immunofluorescence, n (%)	
IgG	19(100.0)
IgA	4(21.1)
IgM	5(26.3)
C3	13(68.4)
C1q	3(15.8)
IgG subclass, n (%)	
IgG1	5(26.3)
IgG2	4(21.1)
IgG3	1(5.3)
IgG4	12(63.2)
Electron Microscopy, n (%)	
Multiple electron dense deposits, n (%)	2(11.1); n = 18
Stage, n (%)	
I, I–II	5(27.8); n = 18
II, II–III	9(50.0); n = 18
III	1(5.6); n = 18
Atypical MN	3(16.7); n = 18

Abbreviations: IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C3, complement component 3; C1q, complement component 1q.

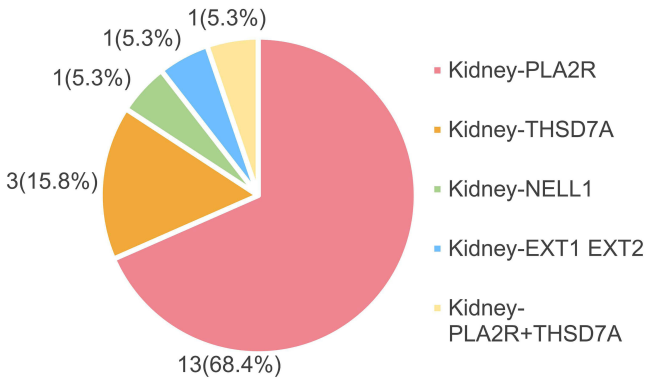

Figure 1 Pie graph depicting frequencies of antigen expression in MN patients with concomitant malignancy in our center.

located in the subepithelial and within the basement membrane, with deposits also observed in the segmental mesangial region in 11.1% of patients.

Specific MN antigen staining of renal tissues from 19 patients showed that the highest percentage was 68.4% (13/19) for PLA2R-only positivity followed by 15.8% (3/19) for THSD7A-only positivity (Table 1). In addition, there was one case each of PLA2R and THSD7A double-positive, EXT1/2-positive and NELL-1-positive staining. Serum antibodies were tested in 15 patients; 8 (80.0%) of 10 patients with renal mono-PLA2R-positive MN were positive for PLA2R antibodies, and the remaining patients were negative (Figure 1 and Supplementary Table S4).

Specific MN antigen staining of malignant tissue was performed in 5 patients whose tumor samples were available. Among them, 1 patient who exhibited positive THSD7A staining in malignant tissue also showed positive THSD7A staining in glomerular tissue. Additionally, another patient who was double positive for PLA2R and THSD7A in tumor tissue also showed PLA2R and THSD7A expression in glomerular tissue. Two patients with PLA2R-positive MN, one with a concomitant jejunal stromal tumor and the other with a concomitant urothelial tumor, were both positive for THSD7A staining in tumor tissue (Figure 2). One patient with NELL-1-positive MN showed negative staining for NELL-1, THSD7A and PLA2R in lung cancer tumor tissue.

Literature Review

We retrieved and summarized the literature on MN patients with concomitant malignancy from 1990 to the present, screening 17 articles encompassing a total of 21 patients in whom MN-specific antigen staining was performed on both renal and tumor tissues simultaneously (Figure 3).[7–23] Among these patients, 71.4% (15/21) were male, with a median age of 61.0 years (56.3, 72.8). In this cohort, malignancy was diagnosed before or simultaneously with MN in 15 patients (75.0%), with digestive system malignancy constituting the most prevalent comorbid malignancy, at 33.3%. Notably, THSD7A accounted for the highest proportion of MN antigens, at 66.7% (14/21); among these patients, 71.4% (10/14) also exhibited positive tumor THSD7A staining. Moreover, three patients (14.3%) showed NELL-1 expression in both kidney and tumor tissues, one patient (4.8%) showed PLA2R expression in both kidney and tumor tissues, and one person (4.8%) showed PLA2R and THSD7A expression in kidney tissue and THSD7A expression in tumor tissue. Of the 21 patients, 72.2% (13/18) achieved CR or PR. Within this subset, 92.3% (12/13) underwent tumor therapy, and 38.5% (5/12) received prednisolone and/or immunosuppressive agent therapy (Figure 4 and Table 3 and Supplementary Table S5).

Comparison of Clinical and Pathological Characteristics Between all MN Patients with Concomitant Malignancy and IMN Patients Without Malignancy

No significant difference between the baseline characteristics was observed between the 19 patients from our center and 21 patients documented in the literature (Supplementary Table S6). Therefore, the clinicopathological data of these 40 MN patients with malignancy were pooled and compared with those of 101 IMN patients without malignancy at our center. There was no notable difference between the two groups in sex, proteinuria, or the prevalence of serum PLA2R

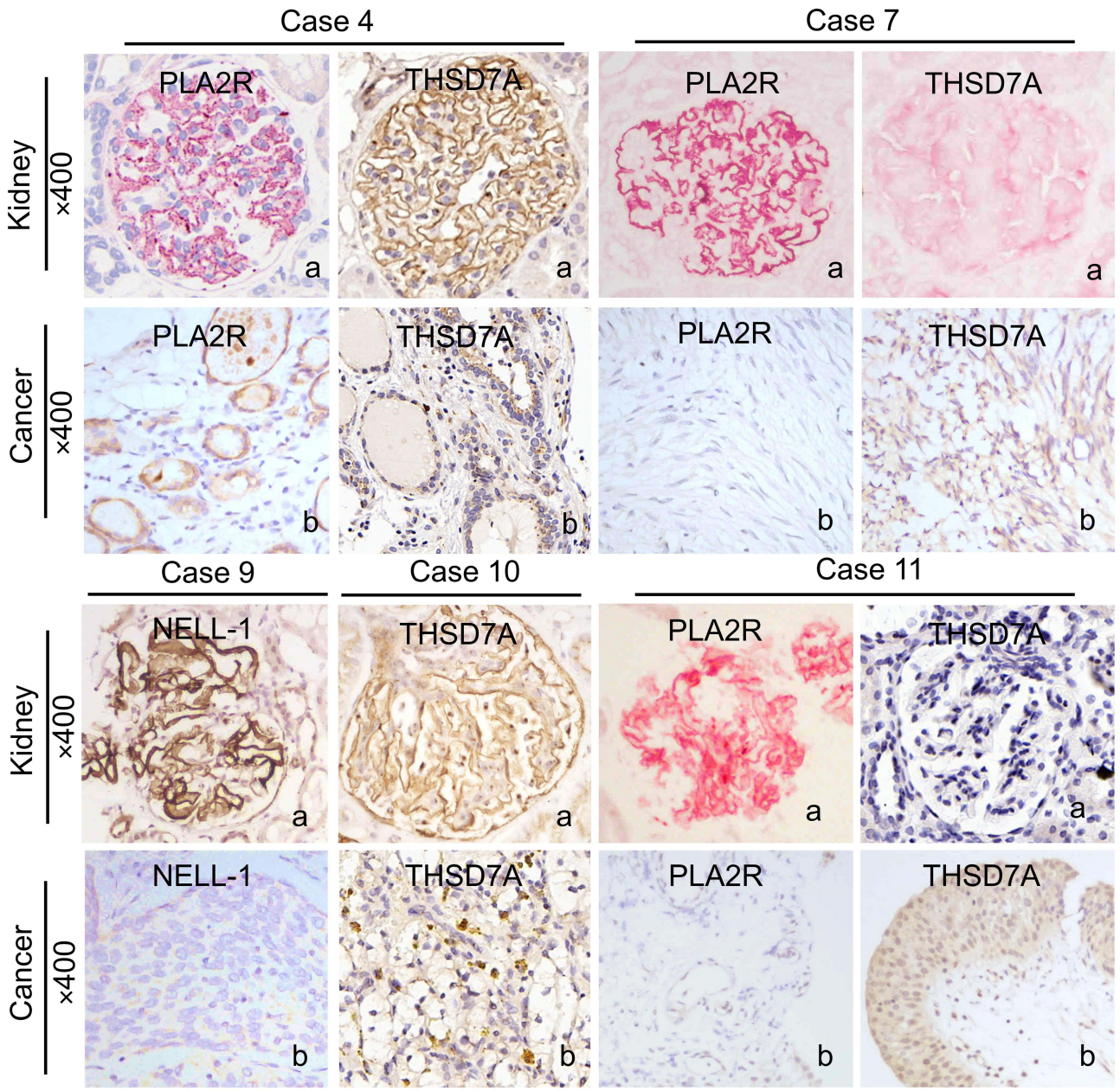

Figure 2 Representative images of antigens in five MN patients' kidney and tumor tissues. Case 4 had thyroid cancer and was double positive for PLA2R and THSD7A for both kidney and cancer. Case 7 had Jejunal Stromal Tumor, who had positive PLA2R for kidney and positive THSD7A for cancer. Case 9 had lung cancer, whose kidney was positive for NELL-1, while he had negative NELL-1 for lung. Case 10 had renal cancer and expressed positive THSD7A for kidney and cancer. Case 11 had atypical urothelioma, and had PLA2R positive MN, while his cancer expressed THSD7A. a kidney. b cancer.

antibody (Table 4). However, in contrast to patients without malignancy, MN patients with malignancy were older at the time of renal biopsy (P = 0.017), had a lower eGFR (P = 0.035) and demonstrated a lower rate of CR or PR after treatment (P < 0.001) (Table 4).

Compared with IMN patients without malignancy, the rate of PLA2R positivity in the glomeruli of MN patients with concomitant malignancy was significantly lower (40.0% vs 92.1%, P < 0.001), while the rate of THSD7A positivity was significantly higher (42.5% vs 2.0%, P < 0.001). Renal tissue IgG subclass staining showed that the rate of IgG4 positivity in MN patients with concomitant malignancy was significantly decreased compared with that in IMN patients (59.3% vs 90.1%, P < 0.001), and the rate of IgG2 positivity was significantly increased (36.0% vs 16.5%, P = 0.033) (Table 4).

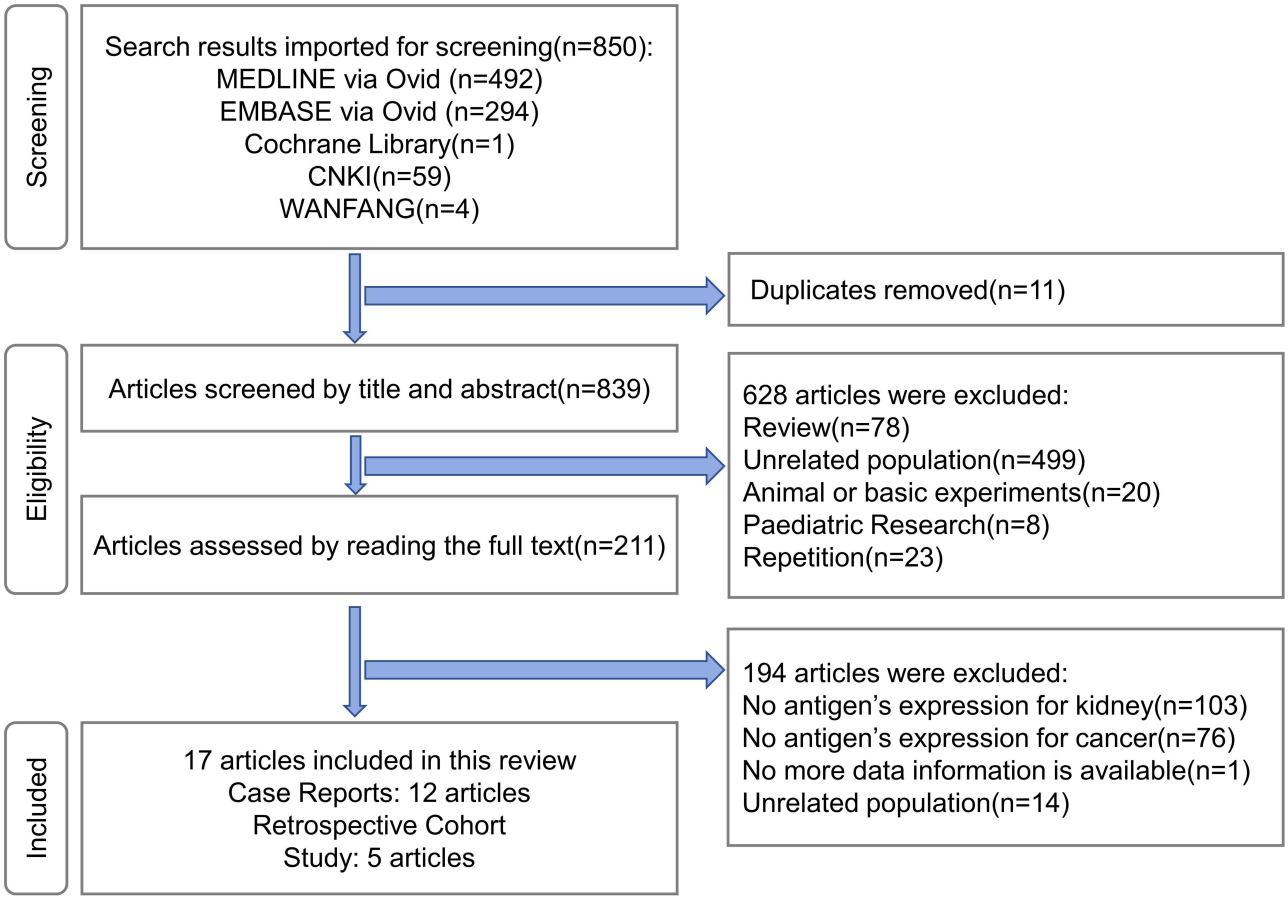

Figure 3 Screening process followed to PRISMA 2020 flow diagram.

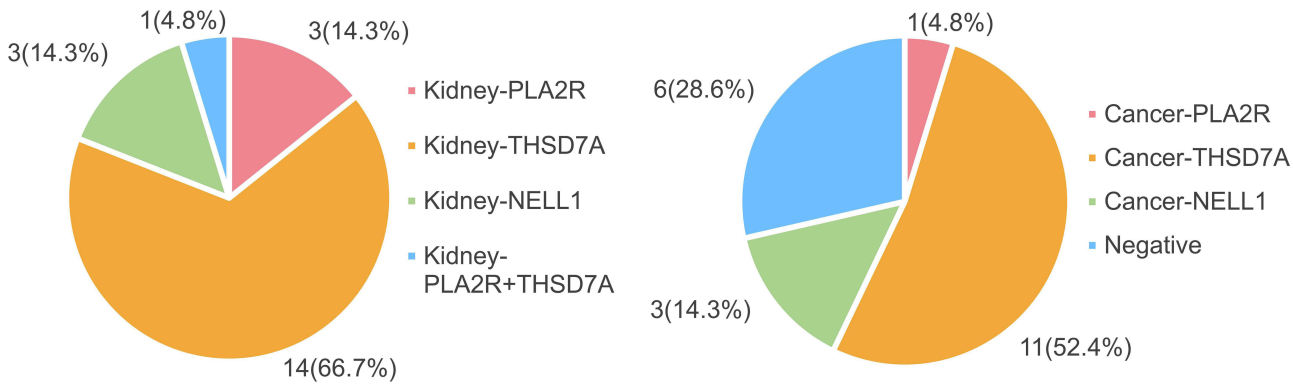

Figure 4 Pie graph depicting frequencies of antigen expression in malignancy-associated membranous nephropathy from the literature review.

Comparison of Clinical and Pathological Characteristics Between MN Patients with Concomitant Malignancy Showing Concordant Renal and Tumor Antigen Staining and IMN Patients without Malignancy

Previous studies have shown that certain patients with MN with concomitant malignancy exhibit consistent MN-specific antigen expression in both tumor and kidney tissues, suggesting a potential pathogenic connection between malignancy and MN.[10] Therefore, we compared the clinical and pathological data of patients with the same antigen expression in tumor and kidney tissues with those of IMN patients without malignancy. MN patients with concomitant malignancy

Table 3 Summary of Clinical Characteristics of MN Patients with Concomitant Malignancy Form the Literature

Characteristics	MN with malignancy (n=21)
Male sex, n(%)	15(71.4)
Age, yr	61.0(56.3,72.8)
Time of diagnosis of tumor, n (%)	
Before	7(35.0); n = 20
Same time	8(40.0); n = 20
After	3(15.0); n = 20
Relapse	2(10.0); n = 20
Type of cancer, n (%)	
Digestive system	7(33.3)
Urinary system	3(14.3)
Respiratory system	6(28.6)
Reproductive system	2(9.5)
Skin cancer	1(4.8)
Nervous system	1(4.8)
Blood system	1(4.8)
Hollow organs tumor, n (%)	8(38.1)
Parenchymal organ tumor, n (%)	13(61.9)
Glomerular antigens, n (%)	
PLA2R	3(14.3)
THSD7A	14(66.7)
PLA2R+THSD7A	1(4.8)
NELL-1	3(14.3)
Renal outcome, n (%)	
CR	6(33.3); n = 18
PR	7(38.9); n = 18
Non-remission	5(27.8); n = 18

Abbreviations: CR, complete remission; PR, partial remission; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain-containing 7A; NELL-1, neural epidermal growth factor-like 1 protein.

showing consistent antigen staining were found to be older (P = 0.025) and have worse renal function (P = 0.05). The CR/PR rate after immunosuppressive therapy was significantly lower in these patients than in malignancy-free IMN patients (P = 0.038), with lower rates of PLA2R positivity and higher rates of THSD7A positivity (P < 0.001) in renal tissue and higher rates of IgG2 positivity and lower rates of IgG4 positivity in renal tissue (P =0.001 and P =0.024, respectively) (Supplementary Table S7). In addition, we also conducted a comparison between MN patients with concomitant malignancy showing concordant and discordant antigen staining. However, those in the concordant group exhibited a significantly higher rate of THSD7A expression in tumor tissue than those in the discordant group (75.0% vs 40.0%, P = 0.04) (Supplementary Table S8).

Comparative Analysis of Clinical and Pathologic Characteristics Between THSD7A-Positive MN Patients with Concomitant Malignancy and THSD7A-Positive IMN Patients Without Malignancy

Furthermore, we also compared the clinical and pathological data between 17 THSD7A-positive MN patients with concomitant malignancy and 7 THSD7A-positive IMN patients. Compared with the latter group of patients, patients with concomitant malignancy were older at the time of renal biopsy (P = 0.028) and had lower eGFRs (P = 0.003), with lower rate of IgG4 predominant deposits (P = 0.005). No significant distinctions were observed in sex, proteinuria, or the rate of CR/PR following treatment between the two groups. In addition, the analysis revealed no significant differences in other pathological characteristics between these two groups (Supplementary Table S9).

Table 4 Comparison of Clinical and Pathologic Characteristics Between All MN Patients with Concomitant Malignancy and IMN Patients

Characteristics	MN with malignancy (n=40)	IMN (n=101)	*P*-value
Male sex, n (%)	29(72.5)	58(57.4)	0.10
Age, yr	58.0±14.4	51.5±14.3	0.017
Urinary protein, g/d	5.5(2.9, 10.2)	5.1(3.9, 7.2)	0.80
Alb, g/l	28.0(19.0, 30.7)	25.5(20.8, 29.3)	0.73
eGFR, mL/min/1.73^2	82.2±30.2	95.8±21.3	0.035
Type of cancer, n (%)	-	-	-
Digestive system	14(35.0)	-	-
Urinary system	8(20.0)	-	-
Respiratory system	7(17.5)	-	-
Else	11(27.5)	-	-
Presence of PLA2R antibodies, n (%)	10(50.0); n = 20	56(55.5); n = 101	0.66
Complete or partial remission, n (%)	20(71.4); n = 28	97(96.0); n = 101	<0.001
Presence of glomerular IgG, n (%)			1
IgG1, n (%)	10(38.5); n = 26	26(28.6); n = 101	0.34
IgG2, n (%)	9(36.0); n = 25	15(16.5); n = 101	0.033
IgG3, n (%)	2(8.0); n = 25	20(22.0); n = 101	0.11
IgG4, n (%)	16(59.3); n = 27	82(90.1); n = 101	<0.001
Presence of glomerular IgA, n (%)	7(26.9); n = 26	19(18.8); n = 101	0.36
Presence of glomerular IgM, n (%)	6(24.0); n = 25	11(10.9); n = 101	0.09
Presence of glomerular C3, n (%)	19(73.1); n = 26	79(78.2); n = 101	0.58
Presence of glomerular C1q, n (%)	4(17.4); n = 23	5(5.0); n = 101	0.11
Presence of glomerular PLA2R, n (%)	16(40.0)	93(92.1)	<0.001
Presence of glomerular THSD7A, n (%)	17(42.5)	2(2.0)	<0.001
Presence of glomerular NELL-1, n (%)	4(10.0)	4(26.7)	0.32

Abbreviations: Alb, Albumin; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain-containing 7A; NELL-1, neural epidermal growth factor-like 1 protein; C3, complement component 3; C1q, complement component 1q; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.

Discussion

The association between MN and malignancy was first proposed as early as 1966,[24] and in recent years, the prevalence of MN with concomitant malignancy has gradually increased. Both Previous studies as well as our own research have demonstrated that patients who have both MN and malignancy tend to be older and have compromised renal function compared to those without malignancy. There is no significant difference in sex ratio, which may be related to the higher incidence of both MN and malignancy in middle-aged and older patients.[24,25] In terms of IgG subclass staining, IMN is considered predominantly IgG4-positive,[26] while the presence of other IgG subclasses suggests possible secondary factors.[27] In our study, renal tissue from MN patients with concomitant malignancy revealed a significantly elevated rate of IgG2 positivity but a lower rate of IgG4 positivity than those without malignancy, consistent with previous studies.[25,28–30] Over the past decade, research on the specific antigens of MN has advanced rapidly, with an increasing number of diseases being proven to be related to MN-specific antigens. However, to date, most studies on MN patients with concurrent malignancies have primarily focused on retrospective reviews of clinical and renal pathological characteristics. A comprehensive review summarizing the expression of MN-specific antigens in both the kidneys and tumors is yet to be conducted. These findings could potentially facilitate prompt further exploration into potential secondary factors in these patients, including malignancy. The causal relationship between MN and malignancy should be further explored.

In recent years, the discovery of MN-specific antigens has advanced the understanding of the pathogenesis of MN. Regarding the pathogenesis of MN with concomitant malignancy, some researchers have proposed that the pathogenesis of MN with malignancy may be related to the secretion of PLA2R protein.[31] Tumor cells may activate the immune system by secreting the PLA2R protein, thereby contributing to the development of MN. A study reported that only 16 of

302 (5.3%) patients with MN and concomitant malignancy were PLA2R antibody-positive.[32] Professor Zhao's team discovered that in renal tissues of malignancy-associated MN patients positive for PLA2R, IgG3 subclass of IgG was predominantly positive, while primary MN patients positive for PLA2R showed mainly positive IgG4. The absence of PLA2R and IgG4 in renal tissue is considered indicative of malignancy-associated MN.[25,33] However, in our study, 16 of 40 (40.0%) MN patients with concomitant malignancy were PLA2R-positive in renal tissue. Interestingly, IgG4 was the main IgG subclass in the renal tissue of patients with positive for PLA2R. Additionally, in 5 (12.5%) patients with PLA2R-positive MN who underwent tumor tissue antigen staining, and only 1 (20.0%) was PLA2R-positive. Therefore, the relationship between PLA2R and malignancy-associated MN needs further clarification.

Previous studies have reported rates of THSD7A positivity in malignancy-associated MN of 10%-30%.[14] A German study conducted by Hoxha et al found that out of 25 patients were positive for THSD7A antibodies, 7 had malignancy. Furthermore, one patient showed THSD7A expression in kidney tissue and gallbladder tumor tissue and dendritic cells from the infiltrated lymph node germination center. This patient achieved MN remission after tumor resection. The above findings support a possible link between THSD7A expression in tumors and the development of MN.[10] However, Liu Zhihong's team in China found[21] that among the 36 patients with malignancy-associated MN, only 2 had THSD7A-positive MN, and 1 patient was double-positive for PLA2R and THSD7A. Furthermore, in a report from China revealed that 12 patients had THSD7A-positive MN. Throughout the 23±13 months of follow-up, none of these 12 patients in this study were found to have any tumor. In our center, the proportion of THSD7A positive was 15.8% (3/19), which is much lower than that of patients summarized in the literature (66.7%, 14/21). These results indicate potential variations in the prevalence of THSD7A antigen among MN patients with tumors in different cohorts. Among the 36 patients in Liu Zhihong's study, 9 patients had MN antigen cancer tissue staining results. Among them, 5 (56%) show positive expression of THSD7A, and 1 patient showed positive for THSD7A expression in both the renal and tumor tissues. This indicates that there may be inconsistencies in the staining of MN antigens in renal and tumor tissues.In this study, glomerular THSD7A staining was also positive in 17 (42.5%) of 40 MN patients with concomitant malignancy, including 12 (30.0%) patients whose tumor tissues were also positive for THSD7A.

Matsui's team in Japan reported that the renal tissue of one patient initially tested negative for THSD7A at the time of the first renal biopsy, but tested positive for THSD7A during a repeated renal biopsy conducted 1 year later due to the relapse of renal disease. Subsequently, this patient was diagnosed with bladder cancer, and the tumor tissue staining also showed THSD7A positivity.[8] In our cohort, one patient (case 11) was positive for serum PLA2R antibody and renal tissue PLA2R, and was diagnosed with a urothelial tumor two years after the diagnosis of MN. However, the tumor tissue staining was negative for PLA2R and positive for THSD7A. The patient's urinary protein levels decreased by 50% after surgical removal of the tumor but remained >3.5 g/d. Unfortunately, a repeat renal biopsy was not performed during the follow-up of this patient, so it is not possible to determine if there were any changes in the expression of renal MN-specific antigens. Studies have shown that THSD7A is expressed in different solid tumors, including prostate, breast, kidney, and colorectal cancer.[34] It is believed that THSD7A may serve as a potential tumor antigen, involved in the formation of tumor blood vessels[22] and is associated with tumor progression and a poor prognosis.[35] According to the available evidence, it is speculated that THSD7A may be a target antigen for tumors and that circulating antibodies are produced to recognize THSD7A on renal podocytes and initiate the occurrence of MN. Alternatively, exposure of the target antigen THSD7A on MN podocytes can activate the immune system to produce circulating antibodies that promote tumorigenesis. These studies strongly suggest that a close relationship between THSD7A and tumorigenesis, and the in-depth mechanism of interaction is worth further exploration.

Previous investigations have demonstrated that remission of MN can be observed following effective antitumor treatment in patients with MN with concomitant malignancy.[8,10,15,16,18,19,21] Our study supports these findings. Specifically, in case 4, case 8, case 10, and case 14, patients who did not receive immunosuppressive therapy, achieved PR/CR of MN after surgical removal of the tumor or chemotherapy. Similar observations have been made in literature reviews, indicating a possible association between tumors and MN. In addition, in our study, 5 (45.5%) patients whose tumors preceded or codeveloped with MN achieved CR/PR. Among the 6 patients who developed tumor after MN, 3

(27.3%) achieved CR/PR, 1 did not achieve remission, and 2 died. Patients with tumors occurring after MN appear to have a poorer prognosis, but further exploration is needed due to the small sample size.

While our study provides valuable insights, there are certain limitations that should be acknowledged. Firstly, because of the retrospective nature of our cohort studies, some patients did not undergo comprehensive malignancy screenings at the time of MN diagnosis, resulting in delayed diagnosis. This lack of timely screening impedes us from determining the accurate temporal relationship between malignancy and MN occurrence. Second, our study is constrained by a limited sample size of MN patients with concomitant malignancy. The limited availability of tumor tissues and kidney tissues obtained simultaneously poses a significant challenge in understanding the underlying mechanisms. Future research should aim to expand the cohort size and carefully monitor MN patients at a higher risk of developing tumors. Additionally, the application of genomic and proteomic tools can aid in unraveling the pathogenic mechanisms involved in the complex relationship between MN and malignancy.

Conclusion

In conclusion, patients with MN exhibited a diverse spectrum of malignancy types, highlighting the importance of regular malignancy screening and follow-up monitoring for these patients. MN patients with concomitant malignancy were older at the time of MN diagnosis, had lower eGFRs and were less likely to achieve remission. The rate of THSD7A positivity was high, and an elevated proportion of IgG2 and a diminished proportion of IgG4 within the renal IgG subclasses was observed. Despite this, 40% of MN patients with concomitant malignancy were positive for PLA2R. Based on these findings, it is crucial to actively perform malignancy screening for MN patients who present with the above characteristics. Further research should delve into the pathogenic mechanisms underlying MN with concomitant malignancy to provide improved insights for the diagnosis and management of this complex disease.

Data Sharing Statement

All data generated during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

Statement of Ethics

This study conformed to the Declaration of Helsinki and was approved by the ethics committee of Beijing Anzhen Hospital, Capital Medical University, approval number 2023154X. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

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Disclosure

The authors report no conflicts of interest in this work.

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