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Late Relapses of Membranous Nephropathy: A Case Series

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Key Points

- Primary membranous nephropathy can relapse after >5 years of achieving remission.
- Late relapse can occur even 36 years after initial manifestation. It has a favorable prognosis.
- Acknowledgment of this under-recognized form of membranous nephropathy may lead to early diagnosis of relapse, avoiding unnecessary workup.

Abstract

Background Relapse of the nephrotic syndrome is co mmon among patients with primary membranous nephropathy (MN). Relapses of MN typically occur within a few years of achieving disease remission. There is limited description, to date, regarding patients with MN who have late relapse of MN, *i.e.*, after >5 years of sustained disease remission. The objective of this case series was to report the clinical course of patients with MN who experience late relapse.

Methods We analyzed the patient database of the Glomerular Kidney Disease Center at Columbia University to identify patients seen at our center who had relapse of biopsy specimen–proven MN at least 5 years after achieving sustained disease remission.

Results We identified 16 patients with late relapse of MN. The median time in sustained remission before relapse was 10.2 (range, 7–29.0) years. Ten patients (63%) were diagnosed with late relapse on the basis of laboratory monitoring alone, without clinical symptoms of the nephrotic syndrome. Fourteen patients (88%) received immunosuppression during their initial presentation and late relapse. Patients had favorable long-term renal outcomes over a median 21 (range, 12–56) year follow-up period, with 14 patients (88%) in remission at study conclusion and a median decline in eGFR per year of −0.63 (range, −6.3 to 17.5) ml/min per 1.73 m^2 per year.

Conclusions This case series highlights a previously underappreciated, and likely rare, outcome of MN, namely, late relapse. Patients who experience late relapse, and who thus have a longer time in sustained remission, may have a more favorable long-term renal outcome.

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Introduction

Primary membranous nephropathy (MN) is a common form of nephrotic syndrome in adults. Kidney outcomes in MN vary depending on risk factors, clinical features, and treatment modality. The natural history of untreated MN includes spontaneous remissions in about one third of patients, persistent proteinuria in others, and progressive kidney failure in at least 30% of patients (1).

Relapses in MN are common, and approximately a third of patients who achieve remission will relapse (2). Patients who remain in remission of proteinuria have an improved kidney survival compared with those who r elapse after remission (3). Relapse typically occurs within the first few years of achieving remission (4–8). Among patients with MN who achieve remission with calcineurin inhibitors, early relapse (within 6–18 months) is particularly common when usage of the drug is tapered and discontinued (7).

Relapses of MN after 5 years of sustained remission, or late relapses, can occur, but are considered rare events (1). The literature to date is limited with respect to the prognosis of patients with late relapses, the optimal therapy for late relapses, and the need to rebiopsy patients with late relapse. To clarify these issues, we retrospectively studied the course of patients with biopsy specimen–proven MN who had late relapses, defined as occurring at least 5 years after initial remission.

Materials and Methods

Subjects

We analyzed our database from 1999 to 2019 to identify patients with a history of biopsy specimen–proven

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MN, followed at the Glomerular Kidney Disease Center at Columbia University, who achieved either complete remission (CR) or partial remission (PR) per definitions stated below, and later relapsed with proteinuria >3.5 g/d or g protein/g creatinine >5 years after achieving sustained remission. Patients with a rise in proteinuria that was <3.5 g/d were not included in this cohort. Time of remission was ascertained by clinical documentation and/or laboratory report. For patients who did not have a precise time point where clinical documentation or laboratory values explicitly confirmed remission, and who had an extended time interval (defined as >1 one year) without laboratory testing after their initial MN presentation, we report the shortest possible interval from remission to late relapse (starting from the first laboratory report confirming remission until late relapse), the longest possible interval of remission to late relapse (starting from 1 year after initial MN presentation until late relapse), and an imputed interval using the midpoint of those two values. We excluded subjects with a shortest possible interval of <5 years. All patients were evaluated for secondary MN (*e.g.*, in the setting of autoimmune disease, culprit drugs, viral hepatitis, other infection, or malignancy), and such patients were excluded. M-type phospholipase A_2 receptor (PLA2R) status, by serum antibody assay and tissue staining, was also used as evidence against secondary MN. The histology was also reviewed for findings consistent with secondary MN (*e.g.*, mesangial deposits, segmental involvement, C1q staining), and patients with this histology were excluded. Patients were followed over time to see if any developed clinical features or serologies consistent with secondary MN. At the time of the study, the Columbia Renal Pathology Department only had PLA2R staining available; therefore, staining for more recently described MN antigens was not performed.

Variables

Clinical histories, physical examinations, laboratory values, and pathology were documented at the time of original diagnosis (or earliest available laboratory data) and at subsequent relapse. The following features were extracted: presence of symptoms of nephrotic syndrome, immunosuppressive therapy, and the response to immunosuppressive therapy. When available, we obtained the following laboratory values for each patient: eGFR, calculated by the Chronic Kidney Disease Epidemiology Collaboration equation in adults (9) and the Schwartz equation in children (10); and proteinuria quantification, either by spot urine protein-creatinine ratio or 24-hour urine protein amount. Serum PLA2R antibody testing was performed either by semiquantitative indirect fluorescent antibody assay or by ELISA. We recorded the treatment modalities used at original diagnosis and during subsequent relapses.

Outcomes

We used the Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Glomerulonephritis 2012 definitions for CR (urinary protein excretion <0.3 g/d or g/g creatinine) and PR (urine protein excretion <3.5 g/d or g/g creatinine, and ≥50% reduction from peak values) (11). A relapse was defined as increase in proteinuria to >3.5 g/d or g/g creatinine after a period of remission.

Statistical Analysis

We used descriptive analyses of our data and presented continuous data as median (range). Prism version 8.4.2 (GraphPad Software) was used for survival curves and the statistical significance level was set at 0.05.

This project was reviewed by Columbia University Institutional Review Boards and granted exemption on the basis that quality assurance/quality improvement activity does not meet the definition of human subjects research.

Results

Baseline Characteristics and Initial Presentation

We identified 16 patients who experienced relapse ≥5 years after their remission of MN. Of these patients, 14 were non-Hispanic White, two were of Hispanic ethnicity. Five patients were female (Table 1). The median age of first diagnosis of MN was 36.5 (range, 3–61) years; three patients (19%) were first diagnosed at or before age 18 years. The median first available eGFR was 79.7 (range, 26–110) ml/min per 1.73 m^2, and the median proteinuria at time of diagnosis was 10.5 (range, 1.5–24) g/d or g/g creatinine. A total of 14 patients (88%) received immunosuppression at the time of the original diagnosis; ten patients (63%) achieved CR, and the remainder achieved PR (Figure 1).

Late Relapse

The median time between initial MN presentation to late relapse was 17.6 (range, 8.5–36.4) years (Table 2). The median time between initial remission and late relapse was 10.2 (range, 7.0–29.0) years. Patients 1 and 8 had an extended time interval between their initial MN presentation and repeat laboratory evaluation (18 and 19 years, respectively). The shortest possible time from remission to late relapse for patients 1 and 8 was 18.9 and 14.6 years, respectively, and the time from the imputed midpoint to late relapse was 27.6 years and 24.1 years, respectively. The median proteinuria at relapse was 7.6 (range, 4.0–16.0) g/d or g/g creatinine, and the median eGFR was 68.6 (range, 26.0–110.0) ml/min per 1.73 m^2. Six patients (38%) were diagnosed with relapse on the basis of clinical grounds (*i.e.*, edema and weight gain), whereas ten patients (63%) were diagnosed by laboratory monitoring in the absence of clinical nephrotic syndrome. Eleven patients (69%) received a repeat biopsy at relapse, and all of the biopsy specimens revealed recurrence of MN. After the first relapse, four patients achieved CR, ten patients achieved PR, and two patients did not achieve remission (Figure 1). A total of 14 patients received some form of immunosuppression for their late relapse. The type of remission of initial presentation was not associated with the interval to late relapse (P=0.95, log-rank test; Figure 2).

Additional Relapses

Five patients had additional relapses (Table 3). Two of these patients (patients 4 and 6) were in CR after their late relapse, and three patients (patients 5, 7, and 12) were in PR. Additional relapses were detected in all of these patients by routine laboratory evaluation. The median time from their late relapse remission to further relapse in these patients was 4.5 (range, 1.0–14.9) years. The median eGFR was 74 (range, 66–107) ml/min per 1.73 m^2, and the median proteinuria at

Table 1. Baseline characteristics at time of initial diagnosis

Patient	Sex	Age (yr)	Earliest Available eGFR (ml/min per 1.73 m^2)	Proteinuria (g/d or g/g creatinine)	Immunosuppressive Treatment	Outcome
1	M	3	79	1.5	Corticosteroids	CR
2	M	36	95	15	Corticosteroids, cyclosporine, rituximab	PR
3	M	48	96	24.0	Corticosteroids, cyclophosphamide (PO and IV)	CR
4	M	25	49	Unknown	Corticosteroids, mycophenolate mofetil	CR
5	F	27	110	12.0	Corticosteroids	CR
6	F	15	90	Unknown	Corticosteroids	CR
7	M	37	80	Unknown	None	CR
8	M	18	77	Unknown	Corticosteroids	PR
9	F	46	26	Unknown	Cyclosporine	CR
10	M	47	93	6.0	None	CR
11	M	52	28	6.2	Corticosteroids, cyclophosphamide (PO)	PR
12	F	31	38	Unknown	Corticosteroids	PR
13	M	19	97	16.9	Corticosteroids, cyclosporine	PR
14	F	44	53	Unknown	Corticosteroids, mycophenolate mofetil, cyclosporine, rituximab	PR
15	M	61	59	7.0	Corticosteroids	CR
16	M	60	81	10.5	Cyclosporine, mycophenolate mofetil, cyclophosphamide	CR

M, male; CR, complete remission; PR, partial remission; PO, by mouth; IV, intravenous; F, female.

time of further relapse was 4.1 (range, 3.6–6.8) g/d or g/g creatinine. All five of these patients went into remission after their most recent relapse after receiving further immunosuppression, with three patients achieving CR and two patients achieving PR (Figure 1).

PLA2R Status

Fifteen patients (94%) had a serum anti-PLA2R antibody assay, kidney biopsy specimen stains for PLA2R, or both (Table 4). Nine patients were positive for PLA2R antigen on kidney tissue or antibody in serum. One patient had indeterminate PLA2R in the serum and tissue, and five patients (patients 7, 8, 9, 14, and 16) had negative serum anti-PLA2R antibodies without tissue testing. Of these five patients, four were either in remission when the PLA2R antibody was checked, or achieved remission within 1 year of the antibody being checked. Patient 16 had neither repeat biopsy nor positive serum anti-PLA2R during his late relapse; however, his remission of nephrotic range proteinuria and improvement in serum albumin from 2.4 to 3.5 mg/dl after treatment with rituximab and cyclosporine were considered to be consistent with immunologically sensitive late relapse of MN.

Follow-Up

Table 5 summarizes the long-term renal outcomes over a median follow-up time of 21 (range, 12–56) years from initial MN diagnosis. At the most recent follow-up, five patients

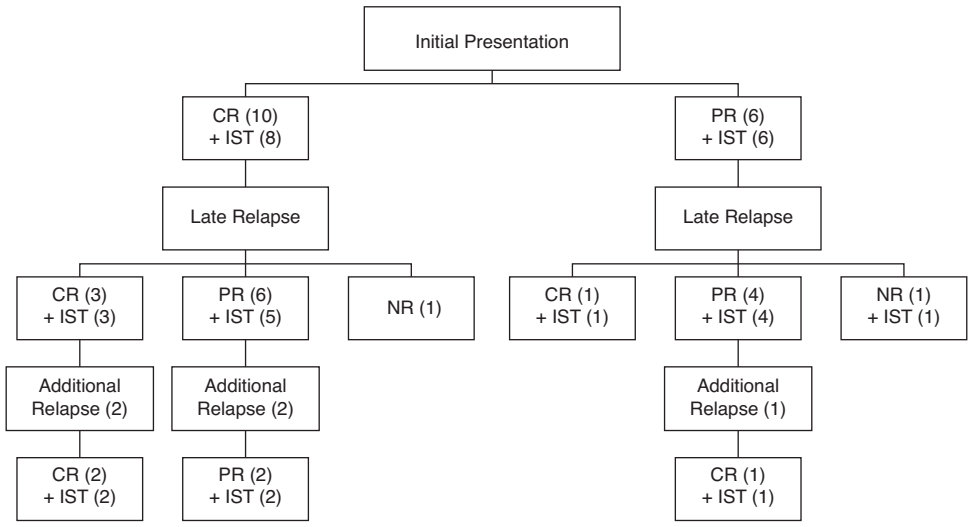

Figure 1. | Flowchart summarizing the clinical course of the 16 patients with delayed relapse of membranous nephropathy included in the study. CR, complete remission; IST, immunosuppression therapy; NR, no remission; PR, partial remission.

Table 2. Late relapse

Patient	Age at Relapse (yr)	Interval between Initial Diagnosis and Late Relapse (yr)	Interval between Initial Remission and Late Relapse (yr)	How Relapse Was Found	Proteinuria (g/d or g/g creatinine)	eGFR (ml/min per 1.73 m^2)	Biopsy at Relapse	Immunosuppressive Treatment	Outcome
1	39	36.4	27.6 (18.9–35.4)[a]	Clinical	5.0	62	Not done	Tacrolimus, rituximab	PR
2	51	15.2	9.2	Laboratory	8.5	87	MN	Rituximab	PR
3	63	8.5	7.5	Clinical	10.5	53	MN	Cyclosporine, rituximab	PR
4	55	30.7	7.0	Laboratory	7.4	52	Not done	Mycophenolate mofetil	CR
5	39	12.2	9.2	Laboratory	8.0	110	MN	Prednisone, tacrolimus, cyclosporine, mycophenolate mofetil, ACTH, rituximab	PR
6	44	30.0	29.0	Clinical	4.8	90	MN	Tacrolimus, mycophenolate mofetil	CR
7	46	10.1	9.1	Laboratory	7.8	91	MN	Cyclosporine	PR
8	51	33.6	24.1 (14.6–32.6)[a]	Clinical	9.0	77	MN	Cyclosporine, corticosteroids/ cyclophosphamide, study drug, rituximab	NR
9	54	8.6	7.6	Clinical	16.0	26	MN	Cyclosporine, corticosteroids/ cyclophosphamide, rituximab, study drug	CR
10	67	21.5	20.5	Laboratory	7.9	92	MN	None	NR
11	74	22.6	20.6	Clinical	7.2	28	Not done	Cyclophosphamide	CR
12	45	14.0	10.0	Laboratory	5.0	35	MN	Corticosteroids, cyclophosphamide, cyclosporine, mycophenolate mofetil, study drug	PR
13	32	10.3	10.3	Laboratory	4.0	60	MN	Corticosteroids, cyclosporine, azathioprine, rituximab	PR
14	56	20.3	12.3	Laboratory	5.5	51	MN	Rituximab	PR
15	88	20.1	20.1	Laboratory	4.9	79	Not done	None	PR
16	66	13.3	10.1	Laboratory	8.9	75	Not done	Cyclosporine, rituximab	PR

PR, partial remission; MN, membranous nephropathy; CR, complete remission; ACTH, adrenocorticotrophic hormone; NR, no remission.
aTime from imputed midpoint to late relapse, with shortest and longest possible time of remission in parenthesis, as described in the text.

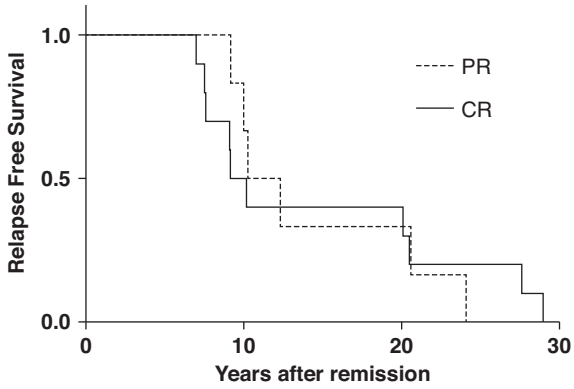

Figure 2. | There was no difference in time to late relapse between patients who achieved CR or PR after their original diagnosis (P=0.95). Time zero represents time of remission after original membranous nephropathy diagnosis, and relapse refers to late relapse of membranous nephropathy.

were in CR, nine patients were in PR, and two patients were not in remission (Figure 1). The median eGFR at the most recent follow-up was 63.3 (range, 26–102) ml/min per 1.73 m^2. The median change in eGFR per year was −0.63 (−6.3 to 17.5) ml/min per 1.73m^2 per year.

Illustrative Cases

Two patient cases are highlighted here as they are particularly illustrative of the clinical course of patients with MN who experience late relapse. Patient 1 was initially found to have hematuria and proteinuria of 1.5 g/d at 3 years of age. A kidney biopsy in 1978 confirmed MN with intense IgG and C3 granular staining on immunofluorescence, and numerous subepithelial deposits on electron microscopy. He was treated with steroids for <1 year and had clinical remission. In 1996, when he was 20 years old, a 24-hour urine test yielded 270 mg protein and a protein-creatinine ratio of 114 mg/g creatinine. For the subsequent 20 years, he had intermittent protein quantification assessments that showed a slow rise in his protein excretion, remaining subnephrotic, with a normal serum albumin. In 2015, at the age of 40, approximately 36 years after his initial disease presentation, he presented to the hospital with heartburn, abdominal pain, and bilateral edema. Subsequent laboratory testing showed 1.8 g/dl serum albumin, urine proteinuria of 10.6 g/g creatinine, and 55 RU/ml serum PLA2R antibody. He refused kidney biopsy due to anxiety. The patient was treated with tacrolimus and rituximab for his late relapse and entered a sustained PR with clearance of his PLA2R antibody. He has remained with stable renal function throughout his follow-up, with an average yearly eGFR decline of −0.34 ml/min per 1.73 m^2. Patient 2, at age 36, was found to have asymptomatic proteinuria, and a kidney biopsy was performed that confirmed MN. Indirect immunofluorescence staining for PLA2R, performed later on a pronase-digested paraffin section, was found to be positive. He was treated with prednisone and cyclosporine without remission, and then rituximab, which led to PR. He continued with regular urine dipstick assessments and presented back to the clinic 9 years later with laboratory testing showing 2.7 g/dl serum albumin and 24-hour urine protein excretion of 8.5 g, but without symptoms. The second kidney biopsy specimen revealed MN with positive tissue PLA2R, and his serum PLA2R was 21.3 RU/ml. He was treated with rituximab during his relapse and reachieved partial, sustained remission and clearance of his PLA2R antibody. Similar to patient 1, he had remained with stable renal function throughout his follow-up, with an average yearly eGFR decline of −1.1 ml/min per 1.73 m^2.

Discussion

In contrast to some systemic diseases with an active GN, maintenance therapy is not typically given for MN after remission has been achieved. Early relapses in MN are, nevertheless, still common and mostly occur within the first few years of achieving remission (Figure 3). In the recently published Membranous Nephropathy Trial of Rituximab (MENTOR) trial, for example, 53% of patients randomized to the cyclosporine arm had disease relapse within 24 months (8). In this case series, we reviewed the clinical characteristics and long-term outcomes of 16 patients evaluated at the Center for Glomerular Disease at Columbia University who experienced a late relapse of MN, *i.e.*, >5 years of sustained remission. On average, we see 3000 patients each year, including approximately 100 unique patients with MN each year.

Table 3. Additional relapses

Patient	Age at Second Relapse (yr)	Interval between Late Relapse Remission and Second Relapse (yr)	How Second Relapse Was Found	Proteinuria (g/d or g/g creatinine)	eGFR (ml/min per 1.73 m^2)	Biopsy	Treatment	Outcome
4	58	1.9	Laboratory	5.1	74	Not done	Mycophenolate mofetil, cyclosporine, rituximab	CR
5	46	4.5	Laboratory	4.1	107	Not done	Rituximab	PR
6	50	4.7	Laboratory	6.8	82	Not done	Rituximab	CR
7	49	1.0	Laboratory	3.7	72	Not done	Corticosteroids/ cyclophosphamide	PR
12	64	14.9	Laboratory	3.6	66	MN	Tacrolimus	CR

CR, complete remission; PR, partial remission; MN, membranous nephropathy.

Table 4. PLA2R tissue antigen and serum antibody

Patient	Tissue PLA2R in First Biopsy	Tissue PLA2R in Second Biopsy	Serum PLA2R Antibody (titer)	Clinical Status at Time of Serum Sampling
1	Not done	Not biopsied	Positive (55 RU/ml)	Relapse
2	Positive	Positive	Positive (21.3 RU/ml)	Relapse
3	Not done	Positive	Not checked	Serum PLA2R antibody not checked
4	Not done	Not biopsied	Positive (1:160)	Relapse
5	Not done	Positive	Negative	Remission
6	Not done	Not stained	Not checked	Serum PLA2R antibody not checked
7	Not done	Not stained	Negative	Relapse (had clinical remission same year)
8	Not done	Not stained	Negative	Relapse (did not achieve remission)
9	Not done	Not stained	Negative	Remission
10	Not done	Indeterminate	Indeterminate	Relapse
11	Not done	Not biopsied	Positive (1:20)	Relapse
12	Not done	Positive	Negative	Relapse (had clinical remission same year)
13	Not done	Positive	Not checked	Serum PLA2R antibody not checked
14	Not done	Negative	Negative	Relapse (had clinical remission same year)
15	Not done	Not biopsied	Positive (1:80)	Relapse
16	Not done	Not biopsied	Negative	Relapse (had clinical remission same year)

PLA2R, M-type phospholipase A_2 receptor.

Therefore, over a 20-year period, the fact that we were only able to identify 16 patients who had late relapses of MN suggests this form of MN is indeed rare, approximately 1% of our MN cohort. To our knowledge, a period of remission of 29 years before disease relapse (patient 6) and initial presentation followed by first relapse 36 years later (patient 1) are among the longest duration of sustained remission of MN before disease relapse reported in the literature (12,13).

In our case series, all 11 repeat biopsies in disease relapse revealed MN, and, given that serum anti-PLA2R antibodies can be followed to assess impending relapse or remission in cases when MN is PLA2R mediated, *i.e.*, 70%–80% of the time (14), we question the utility of repeat biopsies in patients already known to have MN with relapse of nephrosis and stable GFR. We would recommend pursuing a biopsy in patients with known history of MN if there are other clinical indications, other than relapse of nephrosis. These include unexpected decline in renal function, which might be due to transformation to crescentic GN (15) or associated acute interstitial nephritis or acute tubular necrosis. Likewise, those with long-standing diabetes and those with indications of a monoclonal disease might benefit from rebiopsy, especially if they are PLA2R negative or unknown for initial MN presentation.

The majority of patients during their late relapse were identified by routine laboratory assessments as opposed to

Table 5. Long-term renal outcome

Patient	Duration from Initial MN Diagnosis (yr)	Most Recent eGFR (ml/min per 1.73 m^2)	Age at Last eGFR (yr)	Earliest GFR Available (ml/min per 1.73 m^2)	Age at Earliest eGFR (ml/min per 1.73 m^2)	Δ eGFR per Year (ml/min per 1.73 m^2 per yr)
1	41	66	43	79	3	−0.34
2	17	76	53	95	36	−1.12
3	18	64	66	96	60	−5.33
4	37	63	62	49	52	1.40
5	21	102	48	110	40	−1.00
6	39	80	54	90	44	−1.00
7	18	73	55	80	46	−0.78
8	41	26	59	77	51	−6.38
9	12	61	58	26	56	17.50
10	21	92	68	93	66	−0.50
11	25	29	77	28	52	0.04
12	56	62	66	35	47	1.42
13	12	58	31	97	19	−3.25
14	14	55	58	53	50	0.25
15	28	63	89	59	61	0.143
16	14	43	74	81	60	−2.71

MN, membranous nephropathy; Δ, change.

clinical finding of the nephrotic syndrome, and, thus, it is necessary to follow urine protein assessments even many years after remission of MN. Moreover, it may be helpful to serially follow anti-PLA2R antibody titers, because recent work has shown that a rise in anti-PLA2R titer can predate clinical disease by a significant time interval (16,17).

Patients who have untreated, persistent nephrotic syndrome due to MN are at the highest risk of progressing to end stage kidney failure (50%–60% at 10 years) (18), whereas patients with CR or PR have much lower rates of kidney failure (with >80%–90% 10-year kidney survival) (3). Thus, patients with MN, with higher risk of persistent nephrotic syndrome, are treated with a variety of immunosuppressive agents in an attempt to induce remission. The immunosuppression regimens used for MN are evolving, with the recently published MENTOR trial reporting a 60% composite remission rate at 24 months with rituximab, which shows a lower relapse rate compared with cyclosporine (8). Of the 16 patients in this case series, 14 received some form of immunosuppression to treat their initial MN presentation; notably, six of these 14 patients received corticosteroid monotherapy. The other common immunosuppression therapy regimens used after initial presentation included calcineurin inhibitors, alternating steroid and alkylating agents, and—more infrequently—mycophenolate mofetil or rituximab. After late relapse, 14 patients received immunosuppression and, after additional relapse, all five patients received immunosuppression. The most common immunosuppression regimens used during relapse were calcineurin inhibitors and rituximab. The immunosuppression regimen used during relapse differed than the immunosuppression used during initial diagnosis for all of the patients included in the study.

Overall, the patients with late relapse had a good long-term renal prognosis with stable renal function over the duration of follow-up, and this is consistent with the observation of a favorable renal prognosis associated with durable remission (3). Genetic studies have shown strong association of MN with MHC class II and *PLA2R1* risk alleles (19–21). Xie *et al.* (22) performed a genome-wide association study that elucidated two previously unreported loci, in addition to PLA2R1 and ancestry-specific HLA alleles, which explain a significant proportion of MN disease risk. The late relapse pattern of MN may represent a less severe immunologic cause, or a lower-risk genetic profile, than that seen in those with early relapse or in those who maintain a state of persistent proteinuria and ultimately progress to kidney fail ure (Figure 3). Conversely, it is also possible that patients who experience late relapse are at a higher genetic risk than those who do not relapse.

The limitations of this case series include the fact that it was a small, retrospective study and that certain pertinent clinical data were missing. Moreover, because treatments were not randomized, we cannot comment on treatment effect. The patients in this series may not entirely reflect the clinical course of patients who are newly diagnosed with MN, because current treatments are often dictated by PLA2R antibody titer trends rather than proteinuria, and rely far less on steroids and cyclophosphamide; instead, patients are more commonly treated with calcineurin inhibitors and rituximab (8). The other limitation of this study is that, in two patients in the case series (patient 1 and 8), the exact time of clinical remission was not explicitly clear from clinical documentation, and the first available laboratory reports confirming remission were many years after the initial disease presentation. We compensated for this limitation by providing a range of sustained remission times for these patients; however, we suspect the true time of sustained remission before late relapse for these two patients is closer to the higher end of the provided range. Lastly, we cannot exclude the possibility that some of the patients with late-relapse MN seen for consultation at the Center for Glomerular Diseases at Columbia University were lost to follow-up, and that, in fact, late relapse may be more common than our experience and the previous literature suggests.

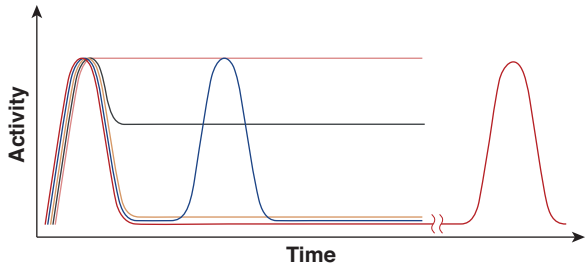

Figure 3. | **Membranous nephropathy has various natural courses.** It may remit spontaneously (black), improve with persistent proteinuria (purple), or progress to kidney failure (green). Relapse can occur after remission, and typically occurs within a few years of remission (blue). This series highlights the rare late-relapse pattern of membranous nephropathy (red) occurring >5 years after remission.

This case series highlights a previously underappreciated, and likely rare, outcome of MN, namely, late relapse. Overall, the long-term renal prognosis among the patients included in this case series were favorable, with slow eGFR decline over time. Although the majority of patients in our case series underwent several rounds of immunosuppressive therapy, it is noteworthy that 63% of the cohort achieved CR after initial disease remission, and 60% of these patients required no immunosuppressive therapy or steroid alone to attain CR. The long duration of remission in these patients, and the relative ease at which they were able to attain remission after their initial presentation, may predict a more favorable long-term kidney outcome, as we observed. It remains to be seen whether we will continue to find late relapse in the future as more patients are treated with anti-CD20–based regimens, and if they will have a similar course. Emerging genetic risk scores (22) may play a role in risk stratifying patients for the likelihood of late relapse, which could potentially help in personalizing long-term surveillance plans and retreatment strategies, but these will need to be clarified in future studies. Meanwhile, the appreciation of the favorable long-term clinical course of late relapse in MN by clinicians and patients will lead to the avoidance of unnecessary testing and early diagnosis and treatment.

Disclosures

G. B. Appel reports having consultancy agreements with Achillion, Alexion, Aurinia, Bristol Myers Squibb, E. Lilly, EMD Serono, Genentech, Genzyme-Sanofi, Mallinkrodt, Merck, Omeros, Pfizer, Regulus, Reata, and Travere Therapeutics; serving on the medical

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Author Contributions

W. Ahn was responsible for software and visualization; W. Ahn and G. B. Appel provided supervision; W. Ahn and Y. Peleg wrote the original draft and were responsible for formal analysis, investigation, validation, and methodology; and all authors conceptualized the study, were responsible for data curation, and reviewed and edited the manuscript. Each author also provided clinical management of patients, contributed important intellectual content during manuscript drafting or revision, and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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