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Case Series

Late Relapse of Membranous Nephropathy: Case Series and Literature Review

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Introduction

Primary Membranous Nephropathy (PMN) is one of the commonest causes of adult nephrotic syndrome having peak incidence in the 4th and 5th decades [1,2]. The control of proteinuria is associated with prolonged renal and patient survival [3]. With new drugs in the basket for the treatment, more patients have controlled disease using immunosuppressive drugs or even spontaneously. There is always a chance of relapse among PMN patients. The average relapse rate ranges from 25% to 50% depending upon the type of remission, with a low relapse rate in complete remission and a high relapse rate in partial remission [4,5]. The timing is unpredictable but can occur within the first year of achieving remission and range up to 29 years [6]. Late relapse of PMN (after five years of remission) is rare [7]. The literature regarding the relapse is from the pre-PLA2R (M-type phospholipase A2 receptor) era. The duration for monitoring in case of complete remission, the need for rebiopsy in patients with late relapse and the treatment modality to be used in patients having late relapse are still confusing. The present case series examined the characteristics of PMN patients who relapse late.

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Methodology

This retrospective study was performed at a tertiary care hospital in northern India. We identified all consecutive membranous nephropathy patients who presented with relapse of proteinuria from Jan 2021 to Dec 2021 after five years of remission. The diagnosis at the time of initial presentation was made on kidney biopsy in 4 patients using light microscopy only with features of diffuse thickening of capillaries along with altered membrane texture and prominent intramembranous mottling in silver methenamine staining suggestive of membranous nephropathy. All patients were evaluated for chest X-ray, autoimmune markers, viral markers, detailed drug history, pap smear (female) for secondary causes of membranous nephropathy. In one patient, the diagnosis was made by clinical and treatment details of cyclic therapy due to a patient's misplacement of kidney biopsy reports. Tissue and Serum PLA2R antibody testing was unavailable commercially in India before 2014. Hence this test was not done at the time of initial diagnosis. Baseline characteristics at the time of diagnosis of MN were noted as age at presentation, baseline eGFR, 24-hour urine protein, renal biopsy findings, treatment given, renal outcome, duration of remission. Remission and relapse status were evaluated based on the "KDIGO Clinical practice guidelines 2021" for the management of glomerular diseases for complete and partial remission [8]. Patients relapsing after five years of complete remission were considered as having "late relapse." The diagnosis of PMN was made at relapse by nephrotic range proteinuria along with serum PLA2R positivity or renal biopsy having tissue PLA2R positivity on immunohistochemistry. Symptoms, 24-hour urine protein, eGFR, PLA2R status, treatment and its response at relapse were recorded. The institutional ethics committee of the hospital approved the research.

Results

Baseline characteristics

Five patients fulfilled the criteria of late relapse of MN. The median age at baseline was 38 (IQR 21-48) years, with 3/5(60%) male patients. The mean duration of remission was 9±2.9 years. The baseline characteristics of the study population at the time of diagnosis of PMN are described in Table 1. The median eGFR and 24-hour proteinuria were 89 (IQR 67.2-109.7) ml/min/1.73m^2 and 4.1(IQR 2.4 - 6.9) grams, respectively. None of the patients had baseline eGFR less than 60 mL/min/1.73 m^2. Renal biopsy details at the initial diagnosis were available in 4/5(80%) patients. Four patients received cyclic therapy (alternating steroid and cyclophosphamide) regimen for six months as their treatment, while one received rituximab (500

S No	Age (years)	Sex	eGFR# (ml/min/1.73m2)	24 hours proteinuria (grams)	Renal Biopsy	Duration of Remission (years)	Previous Treatment	Outcome
1	38	M	112	2.2	Yes	13	Cyclic therapy*	CR
2	62	M	NA	NA	NA	10	Cyclic therapy*	CR
3	48	F	69	2.5	Yes	9	Cyclic therapy*	CR
4	21	M	62	10.3	Yes	5	Tacrolimus / Rituximab	CR
5	18	F	109	5.8	Yes	8	Cyclic therapy*	CR

Table 1: Characteristics of the study population at initial diagnosis. CR; Complete remission, PR; Partial remission, eGFR, Estimated glomerular filtration rate.

*Cyclic therapy of cyclical steroid/cyclophosphamide regimen,

#Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration equation: eGFR = eGFRcr = 142 x min (Scr/κ,1)α x max(Scr/κ, 1)-1.200 x 0.9938Age x 1.012 [if female].

S No	Symptom at relapse	24 hours Proteinuria (grams)	eGFR# (ml/min/1.73m2)	Repeat Biopsy#	PLA2R +ve	Treatment	Follow up duration (months)	Outcome
1	Anasarca	8.4	110	Yes	+(tissue)	Rituximab	36	PR
2	Pedal edema	10	50	Yes	+(tissue)	Rituximab	13	PR
3	Anasarca	10.2	53	No	+(serum)	Cyclic therapy*	15	CR
4	Pedal edema	5.2	106	No	+(serum)	Rituximab	11	CR
5	Frothy urine	3.6	29	Yes	+(tissue)	Cyclic therapy*	13	PR

Table 2: Characteristics of the study population during late relapse. CR; Complete remission, PR; Partial remission, eGFR; Estimated glomerular filtration rate, PLA2R; Phospholipase A2 receptor.

*Cyclic therapy of cyclical steroid/cyclophosphamide regimen for six months

#Renal biopsy was performed in patients who were serum PLA2R negative.

mg IV weekly four doses) followed by tacrolimus 0.2 mg/kg/day for 20 months. All patients were in complete remission. The duration of remission of all these patients before a diagnosis of relapse and treatment outcome is described in (Table 1).

Characteristics at the time of late relapse

The most common presentations of relapse were lower limb swelling and anasarca. All patients had nephrotic range proteinuria with an average 24 hours proteinuria of 7.4±2.9 grams. 3/5(60%) had eGFR <60 mL/min/1.73 m^2 compared to baseline status. Repeat biopsy was done in 3/5(60%) of the patients. The reasons for repeat renal biopsy in our study were 1) serum PLA2R was not raised in two of the patients and 2) there was raised serum creatinine in one patient, so a biopsy was done to know the chronicity status whether there is any chance of reversibility or not. Three patients were given Inj. Rituximab 1 gram IV 2 doses 15 days apart and in two patients, cyclical therapy with steroid and cyclophosphamide was given. Details of treatment and response to treatment are summarized in (table 2). The average follow-up in these patients was 17 months. Complete remission was seen in 2 patients, in 3 patients, there was partial remission.

Discussion

In KDIGO guidelines, immunological monitoring is mentioned six months after therapy initiation.[8] Patient achieves remission and is symptom-free for over 3-4 years; they usually stop visiting medical professionals. After searching the literature, we could find only five studies on late relapse in membranous nephropathy (table 1). However, 4 out of 5 studies mentioned the cumulative incidence of relapse without distinguishing between early and late relapse. These studies showed that there are increased chances of relapse as time passes. There are 30-45% chances of recurrence of PMN in post-renal transplant patients also [9], but the reason for the resurgence of autoimmunity is unclear. There are case reports of relapse of PMN after inactivated SARS-CoV-2 virus vaccination [10]. In our study, five patients had a late relapse of PMN with a median time between PMN remission and a late relapse of 9 (range 5.0-13.0) years. In a Pegel Y et al. study, the median time between PMN remission and late relapse was 10.2 (range 7.0-29.0) years and comparable. The median age of first diagnosis was 36.5 (range 3-61) years in a study by Pegel Y et al., whereas, in our research, it was 38 (IQR 21-48) years and had comparable results. Repeat biopsy was done in 3/5 patients. The reasons for repeat renal biopsy in our study were 1) serum PLA2R was not raised in two patients and 2) to know the chronicity status and whether there is any chance of reversibility. Most of the Pegel Y et al. cohort patients were identified by routine laboratory assessment. In contrast, in our study, all patients were clinically symptomatic at relapse. One patient's disease progressed with eGFR declined from 109 ml/min/1.73m2 to 29 ml/min/1.73m2 during the eight years. After giving repeat immunosuppression, her eGFR was stable for 18 months of treatment and follow-up. Besides, two more patients had a decline in renal function (eGFR <60 mL/min/1.73 m^2) compared to baseline status. This indicates that the underlying disease process may lead to more rapid deterioration of renal function due to ongoing inflammation despite remission compared to natural age-related progression. During the follow-up of these patients, only two patients achieved complete remission and the rest were in partial remission in a span of

17 months of follow-up. Pegel Y et al. reported that 5 and 9 out of 16 patients achieved complete and partial remission, respectively. The limitation of the present study was a single-centered observational study with a limited number of patients. But this study highlighted the entity of late relapse of PMN with many unanswered questions which need further research: 1) duration and method of monitoring of patients with PMN in complete remission, 2) indications of rebiopsy in patients with late relapse, 3) treatment plan in late relapse- upfront immunosuppression vs. wait and watch policy. We need large prospective studies of this subset of patients (Table 3).

S.No.	Study	Average Duration of followup	Late relapse after five years
			Cumulative incidence (95%CI)
1	Jan A.J.G. van den Brand (2013) [11]	57 (32-90)	27(20-36) at 5 years 37 (26-50) at ten years
2	Durga A.K. Kanigicherla (2016) [12]	128 (80-216)	19 (11-27) at five years, 40 (25-52) at 15 years
			No of patients
3	Natalia Polanco (2010) [7]	91±61	6
4	Chadwick E. Barnes (2011) [13]	108 (60- 192)	5
5	Yonatan Peleg (2021) [6]	120 (84-468)	16

Table 3: Various Studies Having Late Relapse.

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