



## Post Transplant Membranous Nephropathy: A 10-year Single-Centre Experience

### Abstract

Membranous nephropathy (MN) post-renal transplant can present as a recurrent or *de novo* disease, often impacting graft outcomes. We retrospectively analyzed 530 allograft biopsies over 10 years, identifying five MN cases (~1%): four *de novo* (0.8%) and one recurrent. Among the former, 75% had concurrent antibody-mediated rejection (AMR); serum anti-PLA2R and tissue PLA2R were detected in 25%. All patients received plasmapheresis and low-dose intravenous immunoglobulin, with one requiring rituximab. Two patients stabilized, one experienced graft loss, and one attained complete remission. The recurrent MN case presented 10 years post-transplant and partially responded to rituximab. AMR influenced prognosis, with a 33% graft loss rate in *de novo* MN. Individualized treatment based on etiology, particularly targeting rejection, may improve outcomes. The study highlights the need for early diagnosis and personalized management in post-transplant MN.

**Keywords:** *De novo, Membranous nephropathy, Post-transplant, Recurrent*

### Introduction

Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in non-diabetic adults. In native kidneys, 80% of cases are primary (anti-PLA2R-mediated). Secondary MN arises from malignancies, infections, or autoimmune diseases.<sup>1</sup> MN may be recurrent, *de novo*, or, rarely, donor-derived in allografts.<sup>2</sup> We retrospectively analyzed post-transplant MN from January 2015 to December 2024, focusing on incidence, characteristics, and treatment response.

### Case Series

Among 530 renal allograft biopsies over 10 years, MN was identified in 5 patients (~1%). Four had *de novo*, and one had recurrent MN [Table 1]. Of the former, two received cadaveric transplants with anti-thymocyte globulin induction, and two had live donor transplants without induction. Chronic glomerulonephritis (n=1), membranoproliferative glomerulonephritis (n=1), IgA nephropathy (n=1), and Alport syndrome (n=1) were the underlying native kidney diseases.

**Table 1: Baseline characteristics of patients with post-transplant membranous nephropathy**

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/Sex	71/M	48/F	32/M	25/M	27/F
Year of transplant	2007	2017	2018	2019	2022
Donor	Mother	Cadaver	Cadaver	Father	Father
Native kidney disease	MN	CGN	MPGN	IgAN	Alport syndrome
Induction IS	Nil	ATG	ATG	Nil	Nil
Time post-transplant to MN diagnosis (years)	10	3	3	2	2
Serum creatinine at presentation (mg/dL)	1.6	3.27	4.3	1.4	0.95
UPCR at presentation (g/g)	3.8	1.1	4.2	5	2.6
Serum albumin at presentation (g/dL)	3.0	3.7	3.3	3.0	3.5
Serum PLA2R (RU/mL)	NA	20	Negative	Negative	62
Hepatitis B or C	Negative	Negative	Negative	Negative	Negative
Concurrent antibody mediated rejection	Nil	Yes	Yes	Yes	No
Treatment given	Rituximab	PLEX + IVIG + Rituximab	PLEX + IVIG	PLEX + IVIG	Rituximab
Response to treatment	Attained partial remission	Serum creatinine - 1.6 mg/dl with no decline in proteinuria	Serum creatinine - 2.64 mg/dl with decline in proteinuria	Serum creatinine - 1.0 mg/dl with decline in proteinuria	Attained complete remission
Follow-up duration (months)	36	24	48	36	3
Serum creatinine (mg/dL) at follow-up	1.5	4.2	2.2	1.2	0.8
UPCR (g/g) at follow-up	0.5	2.86	0.7	0.6	0.2
Outcome	Functioning graft	Died	Functioning graft	Functioning graft	Functioning graft

CGN: Chronic glomerulonephritis, MPGN: Membranoproliferative glomerulonephritis, IgAN: IgA Nephropathy, IS: Immunosuppression, ATG: Antithymocyte Globulin, UPCR: Urine protein creatinine ratio, PLA2R: Phospholipase A2 receptor, NA: Not available, PLEX: Plasmapheresis, IVIG: Intravenous immunoglobulin, MN: Membranous nephropathy.

At diagnosis, the mean serum creatinine and UPCR were  $2.48 \pm 1.58$  mg/dL and  $3.23 \pm 1.73$  g/g, respectively, with a 2.5-year median onset post-transplant. Serum anti-PLA2R and tissue PLA2R were positive in 25% (1/4) of *de novo* cases. Renal histology revealed concurrent antibody-mediated rejection (AMR) in 75% (3/4) of cases [Supplementary Table S1]. All were given plasmapheresis and low-dose intravenous immunoglobulin, one also receiving rituximab. Renal function stabilized and proteinuria reduced in two patients, while one experienced progressive graft dysfunction and succumbed to infection in two years. The patient with Alport syndrome presented with sub-nephrotic proteinuria (2.6 g) and normal graft function; she received a single rituximab dose (500 mg) and achieved complete remission in three months. The recurrent MN case, PLA2R positive on biopsy, presented with nephrotic syndrome 10 years post-transplant and attained partial remission with two rituximab doses (500 mg).

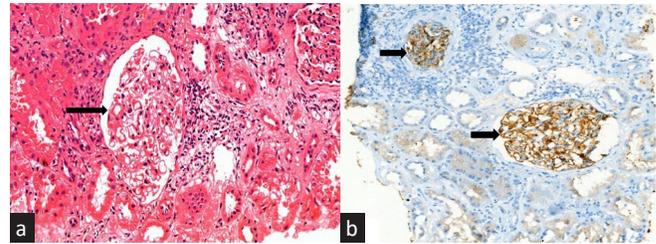
## Discussion

Four of 530 patients (0.8%) had *de novo* MN. Similarly, Aline-Fardin *et al.* reported an 18% (11/614) incidence over 17 years,<sup>3</sup> while a Paris multicentre study reported 1.9% (19/1,000 biopsies).<sup>4</sup> A recent Indian study analyzing post-transplant glomerulonephritis over 50 years reported no MN cases.<sup>5</sup>

MN's recurrence rate in renal allografts varies between 10% and 50%,<sup>6,7</sup> reflecting differences in clinical versus histological recurrence and for-cause vs. protocol biopsy use. Recurrence typically manifests within 1–3 years post-transplant,<sup>8</sup> though our patient developed it 10 years post-transplant. This delayed onset may be attributed to reduced immunosuppression over time or an infection triggering auto-antibody resurgence.

Pathogenesis likely involves triggers like viral infection, urinary tract obstruction, ischemia, or rejection, exposed cryptic podocyte antigen, and in situ antigen-antibody complex formation, leading to a membranous glomerular injury pattern.<sup>51</sup> AMR's histological features may coincide with or precede *de novo* MN.<sup>52</sup> All *de novo* MN cases (except the Alport syndrome case) were rejection-associated and PLA2R-negative. The literature on tissue PLA2R staining in *de novo* MN remains inconsistent. Larsen *et al.* reported almost always negative PLA2R staining, suggesting a distinct pathogenic mechanism in this form.<sup>53</sup> In contrast, de Sousa MV *et al.* found PLA2R-positivity in 75% of their cases.<sup>54</sup>

A patient with autosomal recessive Alport syndrome, carrying a homozygous missense mutation in the *COL4A4* gene, developed tissue and serum PLA2R-positive *de novo* MN [Figure 1] two years post-transplant and responded well to rituximab. Similarly, Prasad *et al.* reported a 10-year-old with Alport syndrome who developed *de novo* MN five years post-transplant.<sup>55</sup> We propose that alloimmune injury



**Figure 1:** (a) Light microscopy reveals diffuse thickening of the glomerular basement membrane (black arrow) (H&E stain, 400x magnification). (b) Immunohistochemistry for PLA2R demonstrates diffuse granular positivity along the glomerular basement membrane (black arrows) (400x magnification). PLA2R: Phospholipase A2 receptor.

to the normal type IV collagen of transplanted kidney exposed cryptic PLA2R antigens on podocytes, triggering anti-PLA2R antibody formation and *de novo* MN.

*De novo* MN prognosis varies, primarily depending on the presence or absence of underlying rejection. A large French cohort found no significant impact of *de novo* MN on graft function,<sup>4</sup> whereas Truong *et al.* reported allograft loss in 42% of cases, with a median time of three years post-diagnosis.<sup>52</sup> Treatment focuses on managing rejection, as seen in our series that observed a 33% graft loss rate.

Higher pre-transplant proteinuria and anti-PLA2R positivity increases recurrent MN risk. Grupper *et al.* found similar death-censored graft survival in MN and ADPKD patients, although 45% of recurrent MN cases experienced graft loss.<sup>7</sup> Early rituximab therapy (>1 g/day proteinuria) may improve outcomes. Our recurrent MN patient achieved partial remission with rituximab, maintaining good graft function.

In summary, post-transplant MN had diverse etiologies, including recurrence, rejection-associated MN, and *de novo* PLA2R-positive MN. Individualized treatment based on the underlying cause, with a focus on achieving proteinuric remission, may improve graft outcomes.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent.

**Conflicts of interest:** There are no conflicts of interest.

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**How to cite this article:** Gaggar P, Nair RR, Thakur AP, Raju SB. Post Transplant Membranous Nephropathy: A 10-year Single-Centre Experience. *Indian J Nephrol.* doi: 10.25259/IJN\_150\_2025

**Received:** 10-03-2025; **Accepted:** 01-04-2025;  
**Online First:** 08-05-2025; **Published:** \*\*\*

**DOI:** 10.25259/IJN\_150\_2025

**Supplementary available at:** [https://dx.doi.org/10.25259/IJN\\_150\\_2025](https://dx.doi.org/10.25259/IJN_150_2025)

