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Case series of low dose rituximab for membranous nephropathy; a single centre experience

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ABSTRACT

Introduction: Rituximab is the recent treatment of choice for primary membranous nephropathy However, dose of rituximab mentioned in literature is high and not economical in middle income countries. Low dose rituximab based on CD 19 cell count can be tried as an alternative for high dose rituximab for inducing clinical remission in appropriate clinical settings.

Case Series: Four patients were administered low dose rituximab and initial CD 19 count was monitored for optimal rituximab response. Three males and one female are part of this case series. Renal biopsies showed membranous nephropathy with tissue phospholipase A2 receptor (PLA2R) positivity in two cases. Serum PLA2R was positive for the same two cases. Two patients completely remitted after one year, one male patient required additional rituximab dose based on CD19 count, one patient required single dose of rituximab for partial remission in the background of tacrolimus with steroids. One patient failed to remit on low dose rituximab protocol.

Conclusion: Low dose Rituximab can be tried as a favorable alternative for high dose Rituximab in appropriate clinical settings.

Implication for health policy/practice/research/medical education:
Low dose rituximab should be considered as a safe, effective and economical treatment strategy in primary membranous nephropathy in selected patients in appropriate clinical settings.

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Case Series

Introduction

Membranous nephropathy is a notable cause of adult nephrotic syndrome with spontaneous remission noted in 32% cases even after 14 months of diagnosis (1,2). The clinical course of membranous nephropathy follows a non-uniform and heterogenous pattern indicating that the same treatment strategies may be inappropriate for different ethnicities (3). Rituximab is a monoclonal antibody targeting B cells which was initially utilized in the management of B cell lymphoproliferative disorders . It has now become the treatment of choice for primary membranous nephropathy (4). However the dose of rituximab adopted for the treatment of idiopathic membranous nephropathy by nephrologists are those which are required to treat B cell dyscrasias (5). Low dose rituximab with a minimum dosage of 100 mg has been effective in persistent depletion of B cells (6). Rituximab is a costly molecule and is logistically difficult to afford in middle income countries like India. Our case series sheds a glimmer of light on the effective use of low dose of rituximab for management of idiopathic membranous nephropathy and its future prospects.

Case Series

Patient 1

A 19-year-old female presented with history of pedal oedema and frothy urination since two weeks in January 2021. Urine showed 3 + albumin with 3-4 RBC/high power field and her proteinuria was greater than 8 grams on presentation. Her anti-nuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (anti-dsDNA), anti-neutrophil cytoplasmic antibodies (ANCA), human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), anti-HCV (hepatitis C virus) reports were negative with normal complement levels. Rest of her baseline investigations are outlined in Table 1. Renal biopsy revealed 17 glomeruli with glomerular basement membrane showing spike formation without any

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Table 1. Baseline characteristics of the patients

Parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	19	43	52	54
Gender	Female	Male	Male	Male
Haemoglobin (g/dl)	13.6	14.8	11.6	13.4
White blood cell count (per µL)	7800	9500	7400	6900
Platelets (per µL)	345 000	222 000	308 000	244 000
Urea (mg/dL)	50	38	25	44
Creatinine (mg/dL)	1.4	1.1	1.2	1.1
Protein (g/dL)	5.1	4.9	4.7	5.2
Albumin (g/dL)	2.4	2.6	2	2.7
24 hour urine protein(mg/d)	8719	9840	9920	12200
Serum PLA2R (RU/mL)	Negative	108	Negative	121
Tissue PLA2R staining	Negative	Positive	Not done	Positive

PLA2R, Phospholipase A2 receptor.

interstitial fibrosis (Figures 1-3). Immunofluorescence showed coarse granular positivity of IgG(3+) (Figure 4) and C3(2+) on the capillary loops. Tissue phospholipase A2 receptor (PLA2R) staining on biopsy was negative and serum PLA2R was negative. In view of eGFR (estimated glomerular filtration rate) of 56 mL/min/1.73 m^2 and proteinuria greater than 8 g/d, she was administered an injection rituximab of 100 mg after informed consent along with maximum tolerated dose of angiotensin receptor blockers (telmisartan). Meanwhile, CD 19 B cell count done 24 hours post rituximab injection by flow cytometry method showed absence of CD 19 cells. Her three-monthly trend of proteinuria is described in Table 2. The patient attained clinical and biochemical remission at the end of one year.

Patient 2

A 43-year-old male presented with history of insidious onset pedal oedema for two months in May 2021. All secondary causes of membranous nephropathy were

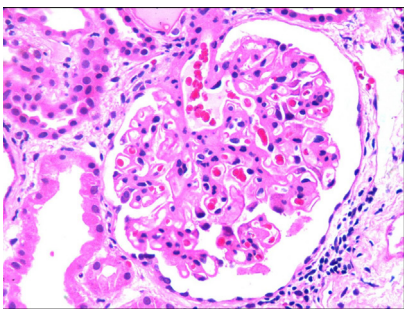

Figure 1. Haematoxylin and eosin stain showing thickened glomerular capillary loops for patient one (×400).

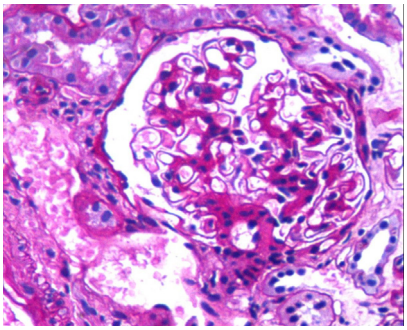

Figure 2. Periodic Schiff stain demonstrating thickened capillary walls in renal biopsy specimen of patient one (×400).

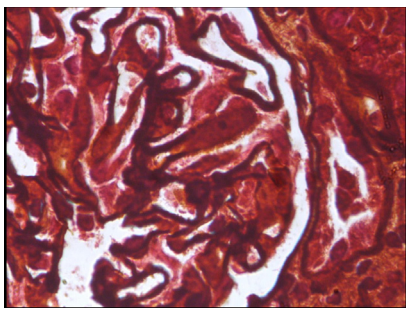

Figure 3. Silver stain demonstrating thickened glomerular capillary loops with fine spikes in biopsy specimen of patient one (×400).

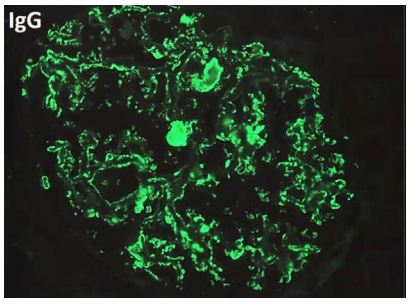

Figure 4. Coarse granular staining of IgG along capillary walls by immunofluorescence in patient 1 (×400).

Table 2. Trend of 24-hour urine protein in patients for one year after rituximab administration

Patient no.	Baseline (mg/d)	3 Months (mg/d)	6 Months (mg/d)	9 Months (mg/d)	12 Months (mg/d)
1	8719	5480	2230	440	120
2	9840	7430	2410	960	190
3	9920	6890	3190	2680	1860
4	12200	10400	7482	8460	9100

ruled out including viral causes like hepatitis B and hepatitis C. His basic investigation is tabulated in Table 1. He underwent renal biopsy which showed features of membranous nephropathy. His renal tissue showed positive PLA2R staining with raised serum PLA2R levels. After informed consent he was given an injection rituximab of 100 mg with maximum tolerated dose of telmisartan. His absolute CD 19 cell count was 2 cells/ µL after 24 hours post rituximab. On his third month follow-up, the proteinuria was 7430 mg/d. Additionally, CD19 cell count was 20 cells/ µL. Repeat rituximab dose of 100 mg was given, and then patient was followed up monthly. His three-monthly trend of 24-hour urine protein is mentioned in Table 2. He attained clinical and biochemical remission with two doses of rituximab monotherapy at the end of one year.

Patient 3

A 52-year-old diabetic for five years presented to our hospital with history of frothy urination and pedal oedema for three months. Outside he was started on tacrolimus and steroids in view of nephrotic syndrome. His baseline investigations are outlined in Table 1. He had no diabetic retinopathy and underwent renal biopsy in November 2020 which revealed six glomeruli with spike formation on the glomerular basement membrane, interstitial fibrosis and tubular atrophy of 10 % and prominent coarse granular IgG deposition along the capillary walls suggestive of membranous nephropathy. His serum PLA2R was negative along with negative workup for obvious secondary causes. He wished to continue on optimised dose of tacrolimus dose (trough level-5-8 ng/ mL) along with steroids. However due to non-reduction of proteinuria it was decided to give injection rituximab 100 mg on January 18, 2021with continuation of tacrolimus with low dose steroids. His initial CD 19 level was suppressed beyond detectable limits. He attained partial remission at the end of 6 months as described in Table 2. He again has a relapse of nephrotic syndrome with urine spot protein creatinine ratio (PCR) -5.68 as in December 2022 and is planned for another dose of rituximab.

Patient 4

A 54-year-old diabetic presented to our hospital in May 2020 with complaints of increasing pedal oedema since one month. He had no evidence of diabetic retinopathy with nephrotic syndrome. His blood and urine investigations with serum PLA2R levels are outlined in Table 1. His blood and urine workup for secondary causes of membranous nephropathy were negative. He underwent renal biopsy which revealed 16 glomeruli with spike formation of the glomerular basement membrane with granular IgG deposition along capillary walls and positive tissue PLA2R staining. He had interstitial fibrosis and tubular atrophy of 15-20 percentage on the biopsy sample. He was given an injection rituximab of 100 mg with informed consent with maximum tolerated dose of telmisartan. His CD19 level was not monitored due to financial constraints. His proteinuria trend is tabulated in Table 2. His proteinuria reduction was erratic and he was started on tacrolimus and low dose steroids as per his wish after 3 months of rituximab dose. He did not have a clinical or biochemical remission despite optimisation of tacrolimus and telmisartan dosage. He was lost to follow-up after one year.

Discussion

This case series adopts a novel approach of low dose rituximab in the management of primary membranous nephropathy. Two patients completely remitted with low dose rituximab monotherapy with one patient receiving additional rituximab dose based on CD19 B cell count. One male patient (patient three) attained partial remission with a top up dose of rituximab in the background of Tacrolimus and low dose steroids. Whether rituximab played a role in accelerating the remission process or was an incidental, additional treatment in the background of calcineurin inhibitors is a matter of further scientific introspection. Patient 4 did not clinically remit on low dose rituximab. This patient differed from other cases in terms of a higher PLA2R level with advanced degree of chronicity on renal biopsy. High dose rituximab maybe beneficial in these subset of patients for appropriate clinical outcome which needs to be justified by future randomized controlled trials in the Indian ethnic population.

The treatment of membranous nephropathy has underwent a paradigm shift after the discovery of PLA2R antibodies and the superiority of rituximab observed in the MENTOR trial(4). In the yesteryears ,the treatment of idiopathic membranous nephropathy was limited to the chlorambucil, cyclophosphamide based modified Ponticelli regimen(7) and tacrolimus

with low dose steroids (8). However, these treatments have undesirable side effects like neurological dysfunction including seizures and myoclonus, gonadal toxicity, bone marrow suppression, malignancies like acute leukaemia and infectious complications like herpes zoster (7). Tacrolimus therapy was notable for a high relapse rate after discontinuation (9). The advent of rituximab has revolutionised the management of idiopathic membranous nephropathy due to its superiority in inducing clinical and biochemical remission on the basis of landmark trials like GEMRITUX (10) and MENTOR (4).

Rituximab is a superior molecule in terms of its low risk of non-compliance, efficacy, better side effect profile, remarkable safety (11) and ease of administration. Conventionally, oncological doses of rituximab like 1 g every 2 weeks (12) or 375 mg/m^2 every week for 4 doses have been advocated for the treatment of primary membranous nephropathy. This is a major barrier since it involves infectious complications including pneumocystis carinii pneumonia, reactivation of tuberculosis and hepatitis B (13) and additional burden of higher cost, which are matters of grave concern in low- and middle-income countries.

Low dose rituximab has been tried for primary membranous nephropathy by George et al (14) and Bagchi et al (15). Serial monitoring of CD 19 cell count by flow cytometry was conducted in two patients in our case series which gives reasonable evidence regarding the degree of immunosuppression induced by rituximab. One male patient received additional dose of rituximab based on CD 19 B cell count as a part of his treatment strategy. The need to repeat rituximab injection in our cases was based on the criteria of CD 19 B cell count being greater than five cells/μL, which was similar to the algorithm proposed by Jacob George et al (14). Higher PLA2R titre with more chronicity on renal biopsy can be considered as a possible explanation for poor response to rituximab as seen in patient 4 (15).

Rituximab in lower doses can be cost-effective and 100 mg dose with serial monitoring of CD 19 B cell count is still an affordable option compared to the conventionally advocated doses of rituximab (14) in middle income countries like India. There is paucity of Indian data in terms of efficacy of low dose versus high dose rituximab in primary membranous nephropathy which may be a future research question. Indian membranous nephropathy patients may have a variable and better response to low dose rituximab compared to their Caucasian counterparts, which needs to explored in future by scientifically designed randomised control trials. This case series is an effort to induce the scientific community to explore avenues to advocate low dose rituximab as a prospective treatment regimen in idiopathic membranous nephropathy especially in middle-income countries like India.

Conclusion

Low dose rituximab can be considered as a safe, effective and affordable treatment option with serial monitoring of CD19 B cell count in primary membranous nephropathy in middle-income countries. Further large scale scientifically designed studies are needed to validate efficacy of low dose rituximab versus conventional rituximab dose for induction of clinical, serological and biochemical remission in idiopathic membranous nephropathy.

Limitations of the study

This case series did not have a prolonged follow-up of patients and did not explore the utility of high dose rituximab in patients who have failed low dose rituximab protocol.

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Authors' contribution

Conceptualization: GGM, SS.
Methodology: GGM, JV.
Validation: GGM.
Formal analysis: GGM, JV.
Investigation: GGM.
Resources: GGM.
Data curation: GGM, JV, SS.
Writing–original draft: GGM.
Writing–review and editing: GGM, JV, SS.
Visualization: GGM.
Supervision: GGM, SS.
Project administration: GGM.
Funding acquisition: GGM.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case series was conducted in SRM Medical College Hospital, Kattankulathur. Informed consent was obtained from the participants. All relevant laws pertaining to research including the tenets of the Declaration of Helsinki were followed in the conduct of this study. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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