KIDNEY KOLUMNS

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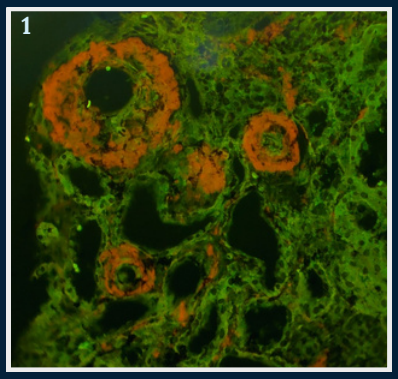
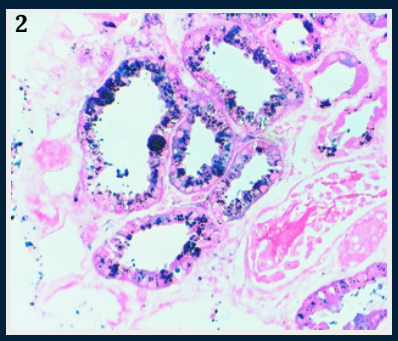
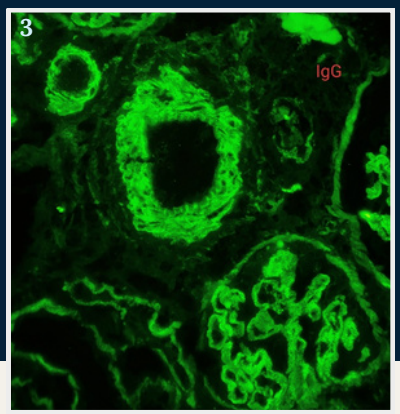
KIDNEY KOLUMNS | VOL 3 | ISSUE 2 | APRIL TO JUNE 2025







Dear Readers,

As we all also know, Operation Sindoor stands as a shining example of courage and resilience, carried out with unmatched precision by our brave defence forces. In these challenging times, when the nation grapples with uncertainty and evolving threats, their unwavering commitment offers us both safety and hope. We salute our armed forces for their selfless service and sacrifice — thank you for guarding our borders and our hearts.

We are delighted to present the latest edition of Kidney Kolumns, where our spotlight falls on Membranous Nephropathy - a diagnosis that continues to challenge and fascinate nephrologists. As our understanding of its immunological underpinnings grows with new associated antigens being identified faster than we can write about them, so do the possibilities for more targeted and effective therapies. In this issue, we explore the evolving diagnostic approaches, prognostic indicators, and therapeutic options that are shaping the modern management of this glomerular disease.

We've also played around with how the newsletter looks. Do you like what you see? Let us know. Meanwhile have fun with our crossword, quiz and stat pearls

Warm regards
Editors - in - chief

As always, we welcome your **feedback & contributions** at **education@isn-india.org**

Kidney Kolumns is the official newsletter of the Indian Society of Nephrology (ISN). Launched in 2023, it is published quarterly and serves as a vibrant platform for the nephrology community to exchange knowledge, share updates, and foster professional growth.

The newsletter currently accepts contributions by invitation only. All content is reviewed by the editorial board prior to publication. However, student contributors are encouraged to submit their work without an invitation and should contact the student editors for further guidance.

ISN GOVERNING BODY

INSIDE

Cover Images
Renal Pathology

IMAGE 1
Perivascular amyloid
Microphotograph showing congophilic amyloid deposits under fluorescent microscope (40X) seen as orangish-ore coloured deposits.

IMAGE 2 Renal hemosiderosis
Prussian blue stain- 40X- Microphotograph showing renal tubular epithelial cells with blue coloured intracytoplasmic hemosiderin granules in a case of PNH.

IMAGE 3 Lupus Flare
IgG immunofluorescence - 40X - Strong IgG positivity in all the renal compartments.

Cover Image Credits

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Kidney Kolumns

SECRETARY'S DESK

Dear friends,

Greetings from the Indian S N Secretariat!

Dr Shyam B Bansal
Honorary Secretary,
Indian SN

Welcome to another edition of *Kidney Kolumns* the mouthpiece of society and diligently carried out by our young team. This issue's theme is the latest developments in Membranous Nephropathy, a common problem for Nephrologists.

I will take this opportunity to highlight some of the essential activities done in the last quarter and update you about plans by the Indian SN:

1) Operation Sindoor

Dear Friends, you are all aware of the cowardly act of terrorists about killing innocent Indians, followed by Operation Sindoor by India, where our armed forces not only attacked the terrorist hideouts but also precisely attacked at their airbases, which brought the enemy to their knees. Our armed forces also successfully protected our citizens from attacks by the enemy. I, on behalf of the Indian SN, salute our armed forces and want to reiterate our full support to them. We are proud to have such a strong and committed army.

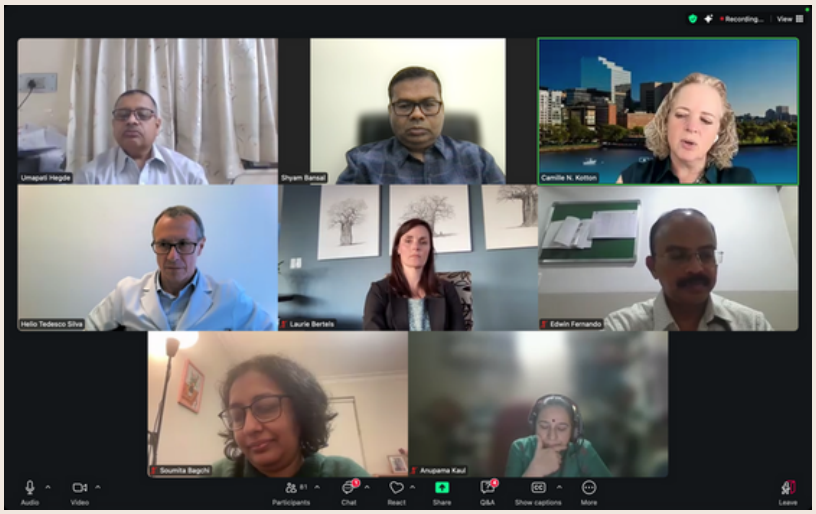
1) ISNCON 2025

As you might be getting messages, the ISNCON 2025 is planned from **18th to 21st December 2025 at SGPGI, Lucknow**. The highlight of ISNCON 2025 would be multiple **workshops on 18th December** on **Histopathology and Onconephrology**, **Critical Care Nephrology & POCUS**, **Intervention Nephrology**, **Pediatric Nephrology**, and **Transplant Immunology at SGPGI Lucknow**, along with a regular conference program. This year, we will have the maximum number of international faculty in ISNCON, including in workshops. The workshops are being planned considering the needs of our students and

early career nephrologists. The registration for the workshops is complimentary for those who have registered for the conference. One of the good things about the workshop this year is that delegates will get hands-on experience as these are being conducted in SGPGIMS itself, so to avail the benefits, register soon to get early bird discount by visiting our website, www.isn-india.org and register yourself. Please mark your calendars and stay tuned for updates.

3) Membership of Indian SN

I would request everyone to ask their colleagues and students after first year, who are not members of Indian SN yet to become member of Indian SN. Indian SN is actively collaborating with many important societies like ISN, ASN, ERA and TTS, and our members will benefit from meetings and memberships. The online membership of the Indian SN is available at **www.isn-india.org**. If you are not getting messages from the secretariat despite being a member, kindly check your spam mail or email me at **drshyambansal@isn-india.org**



4) The Educational Activities

Apart from regular journal clubs, clinical case presentation every month, Kidney Konversations and social media activities of the Indian SN, the society conducts regular webinars with international societies and experts. In the last quarter, we conducted a webinar in **collaboration with TTS on a very common problem of Post-Kidney Transplant BKV infection** on 8th May, which had both Indian and International faculty. The webinar was well attended and had a good discussion.

Boosting Remission

THE POWER OF EXTRA RITUXIMAB IN PRIMARY MN

Dr Avichal Rajpal, Dr Arun Prabhahar, Dr Vinod Kumar

Among all glomerular diseases, primary membranous nephropathy (MN) has the best evidence-based treatment, guided by meaningful endpoints. Cyclical cyclophosphamide with corticosteroids (CYC/GC) and rituximab are both recommended as first-line therapies. CYC/GC is highly effective but raises concerns due to potential side effects. Rituximab is relatively safer but leads to remission in only about 60% of cases. Such a response rate is disappointingly low for a first-line treatment. Adding tacrolimus to rituximab has also been found ineffective. However, combining rituximab with low-dose CYC and GC has shown good results (both clinical and immunological remission).

In patients with high anti-PLA2R levels, the response rate to rituximab is particularly poor. Dahan et al reported that additional rituximab dosing after three months improved immunological remission in such patients. Evaluating the best rituximab dosing regimen is one of the recommendations of the KDIGO 2021 guidelines. Based on the findings of Dahan et al., we began administering an extra dose of rituximab between months 3 and 6. In the current manuscript, we present the analysis of our cohort of MN patients treated with three doses of rituximab.

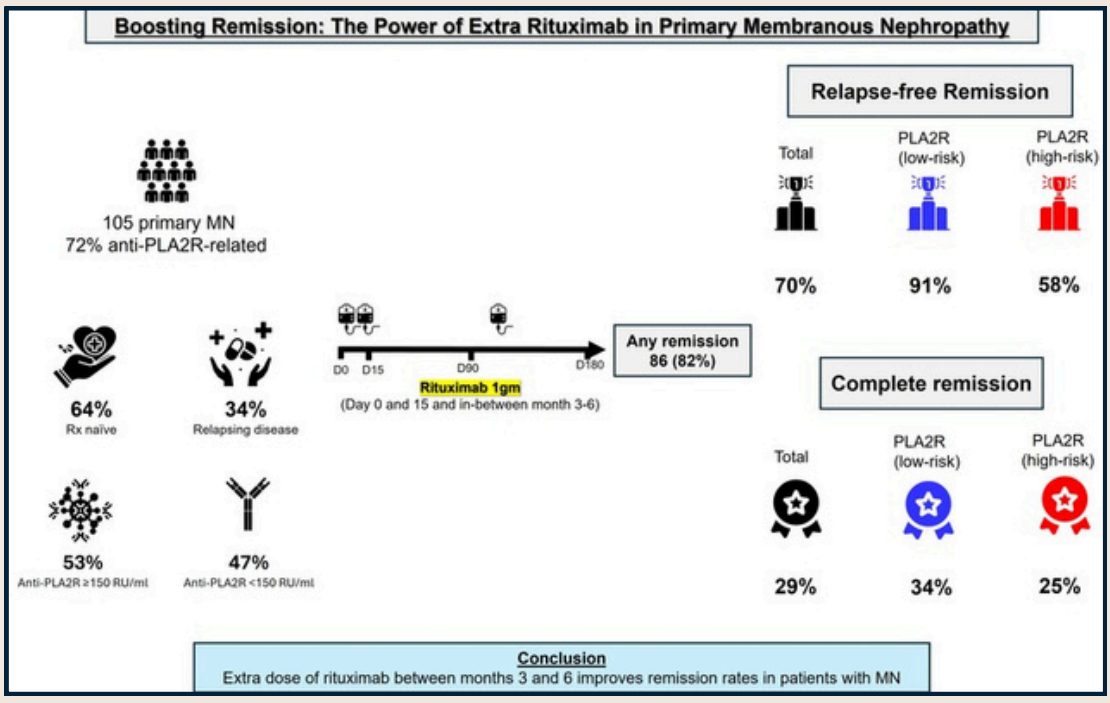
The data is from the Primary MN Registry at the Postgraduate Institute of Medical Education and Research, Chandigarh. The outcome measured was a combination of complete and partial remission. A total of 105 patients received rituximab therapy for either treatment-naïve or relapsing nephrotic syndrome due to MN. 64% of patients had treatment-naïve disease, while 34% had relapsing disease. The average age of the cohort was 45.1 years (±15.5 years), and it included 40 females and 64 males. Seventy-five patients had PLA2R-related MN, and the median anti-PLA2R level was 160.1 RU/ml (IQR, 66.2–351.4 RU/ml). Forty patients had anti-PLA2R levels greater than 150 RU/ml, which is considered high in various studies. Before starting therapy, the median proteinuria was 7.5 g/day (IQR, 5.2–10.5 g/day), with a mean serum albumin of 2.6 g/dL and mean serum creatinine of 1.0 mg/dL.

At 18 months of follow-up, 82% of patients achieved clinical remission, with

29.5% achieving complete remission and 41.9% partial remission. 19 patients (18.1%) were non-responders. During follow-up, 10.4% of patients experienced a relapse despite receiving additional rituximab doses. Patients with high PLA2R titres (>150 RU/ml) achieved lower remission rates compared to those with lower titres (<150 RU/ml) (58% vs. 91%). Remission rates tend to be lower in patients with high anti-PLA2R levels, regardless of the type of immunosuppressive therapy—our results are consistent with this observation. While direct comparisons with other studies are not appropriate, the remission rates achieved with this protocol were higher than those reported in the STARMEN and MENTOR trials, which evaluated responses beyond 12 months. Additionally, the median anti-PLA2R levels in our cohort were higher than those in the RI-CYCLO (median 63 RU/ml) and STARMEN (median 113 RU/ml) trials. The response rates were also better in patients with high anti-PLA2R levels compared to our previous study, in which most patients received only two or limited doses of rituximab.

Previous studies suggest that higher doses of rituximab lead to higher remission rates and better circulating drug levels in patients with MN. Although the results of the current study are lower than those reported by Dahan et al., we believe that adding a booster dose of rituximab between months 3 and 6 leads to better remission than giving only two doses in the first month. The median anti-PLA2R level in this study was approximately 160 RU/ml, with 54% of the patients having levels >150 RU/ml—a threshold known to respond poorly to rituximab-only therapy. This suggests that a significant number of patients who may not have responded to two doses might have responded after the booster.

Although the study has several limitations, the key ones include the study design, lack of CD19 measurement at different time points, absence of PLA2R staining on kidney biopsy, and lack of long-term follow-up. Although the response to three doses is still not ideal for a first-line therapy, until results from future trials (using AI-based approaches or newer rituximab-based combination therapies) are available, we believe that giving an extra dose of rituximab between months 3 and 6 may help improve remission rates in patients with MN receiving rituximab-only treatment.

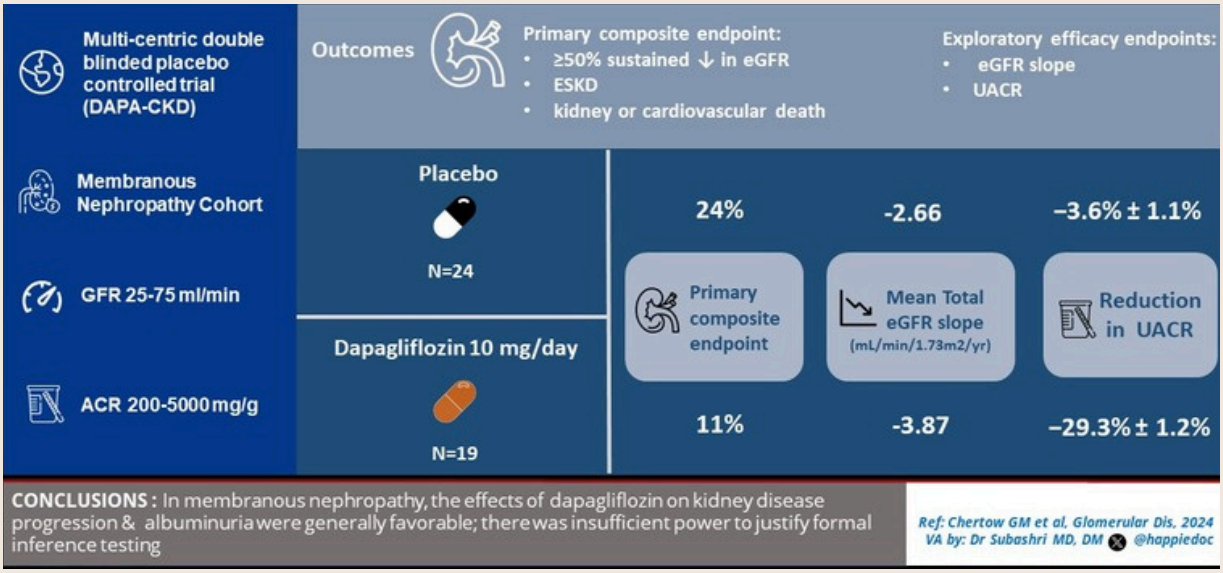


Acknowledgement

We thank Dr Raja Ramachandran for his inputs in the manuscript.

The Effects of Dapagliflozin

IN PATIENTS WITH MEMBRANOUS NEPHROPATHY



Dr Kartik Ganesh, *Consultant Nephrologist & Renal Transplant Physician, VPS Lakeshore Hospital & Research Centre, Kochi*

Membranous Nephropathy (MN) remains a major cause of nephrotic syndrome in adults, with various registries pegging it as one among the top three causes of nephrotic syndrome in adults. It is a disease with varying causes, phenotypes and prognosis, ranging from spontaneously remitting to progressive disease that culminates in end stage renal disease (ESRD). Despite advances in understanding its immunopathogenesis - particularly the discovery of phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) antibodies - management remains challenging. Treatment strategies for a long time were limited to conservative management with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) or immunosuppression with the modified Ponticelli regimen using steroids and cyclophosphamide. Lately, trials have

thrown rituximab and calcineurin inhibitors into the mix as fairly effective, if not comprehensive treatment options for this disease.

The DAPA CKD trial brought to the fore the benefits of dapaglifozin in slowing down progression of chronic kidney disease (CKD) and reducing albuminuria. In this trial, 4094 patients were randomized into a treatment group with Dapaglifozin 10mg and a placebo group. Chertow et al analysed a subset of patients in the DAPA CKD trial who had membranous nephropathy, 38 of whom had biopsy-proven membranous nephropathy. Out of these, 19 were randomised to the dapaglifozin group and 24 to the placebo group. Mean eGFR was 45.7 ± 12.1 mL/ min/1.73 m^2 and median UACR 1694.5mg/g.
At a median follow-up of 26.5 months, fewer patients in the DAPA group (11% vs 21%) experienced a fall in eGFR with lower annual rates of eGFR decline. Far more dramatic was the change in proteinuria (29% vs 3%).

The role of maintenance non-immunosuppressive therapies in membranous nephropathy has not been studied in depth. The use of ACEI and ARB is now considered the standard-of-care. In this scenario, dapagliflozin offers a non-specific treatment strategy to combat albuminuria and GFR loss in membranous nephropathy, as demonstrated in the subset of the DAPA CKD trial. However, a pertinent point to consider is that this trial included patients only with modest proteinuria, with concomitant ACEI/ARB administration as well. Effect on higher degrees of proteinuria has not been studied.

The application of SGLT2 inhibitors in membranous nephropathy may also have a specific action, as demonstrated in some animal models. Lv et al demonstrated that canaglifozin reverses Th1/Th2 imbalance and promotes podocyte autophagy in rats with membranous nephropathy. Whether SGLT2 inhibitors could reverse the imbalance of Th1/Th2 and suppress the humoral immune induced by B cells is unknown. However, a mendelian randomization study did not find co-localization of drug targets and membranous nephropathy.

The benefits of SGLT2 inhibitors appear to be independent of their blood glucose–lowering effects and may be mediated by natriuresis and glucose-induced osmotic diuresis, leading to a reduction in intraglomerular pressure. This suggests a mechanism that is hemodynamic and potentially anti-inflammatory or antifibrotic.

In this context, dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, has emerged as a promising agent for proteinuria reduction and nephroprotection. Current KDIGO guidelines recommend SGLT2 inhibitors as a part of standard therapy for CKD patients with albuminuria and eGFR > 20–25 mL/ min/1.73 m^2 , a category into which many MN patients fall.

In conclusion, at present, dapagliflozin represents an adjunctive therapy in the management of membranous nephropathy. Disease-modifying and disease specific data are awaited. It may be considered as part of a multimodal strategy to reduce proteinuria, preserve renal function, and improve outcomes in this complex glomerular disease.

Membranous Nephropathy

IS IT TIME TO WRITE RITUXIMAB'S OBI-TUARY?

Dr Tanuj Moses Lamech, *Assistant Professor of Nephrology, SRM Medical College Hospital & Research Centre*

Dr Edmund J Lewis, writing in the New England Journal of Medicine in 1993, declared that "For the majority of patients with idiopathic membranous nephropathy, until new treatment strategies are found, physicians are well advised to await judiciously 'the salutary operations of nature'. Fortunately, in the three decades that have followed, new treatment strategies have indeed been found, and the space for 'conservative management' of high-risk membranous nephropathy has greatly diminished.

The KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases recommends anti-CD20 therapy (specifically, rituximab) as a first-line therapeutic agent in moderate-risk and high-risk membranous nephropathy. Given that 'primary' membranous nephropathy is, quintessentially, a B-cell driven disease, it makes intuitive sense that better, deeper, and longer B-cell depletion would improve outcomes.

Obinutuzumab (a humanised, type 2, anti-CD20 monoclonal antibody) has been consistently shown to be more effective than rituximab (a chimeric, type 1, anti-CD20 monoclonal antibody) at depleting B-cells. Though there are no direct comparisons between the two molecules, recent randomised controlled trials of add-on obinutuzumab in lupus nephritis (NOBILITY, REGENCY) met their primary endpoints, whereas the older trial of add-on rituximab in similar patients with lupus nephritis (LUNAR) did not.

Furthermore, the repeated use of rituximab is plagued by the development of human anti-chimeric antibodies (HACAs), which contribute to rituximab resistance. No such events have been described with the use of obinutuzumab.

Obinutuzumab vs Rituximab in Primary Membranous Nephropathy:
Hu et al, in a recent issue of CJASN

(December 2024), report a single-centre retrospective study comparing the 12-month clinical outcomes of 63 patients with primary membranous nephropathy who were treated with either rituximab (n=42) or obinutuzumab (n=21).

All patients had proteinuria >3.5 g/day despite 6 months of RAS inhibition, and an eGFR >30 ml/min per 1.73 m^2. Over 80% of the patients in each group were classified as "high-risk", based on current KDIGO risk stratification. Propensity score matching with a 1:2 ratio was performed to attempt to adjust for known baseline confounders (age, sex, urine protein, eGFR and PLA2R antibody).

Rituximab was administered as 375 mg/m^2, weekly for four weeks, with a second course administered at 6 months if complete remission had not already occurred. Obinutuzumab was administered as 1 g, two doses, two weeks apart, without repeat dosing at 6 months.

The primary outcome, defined as a combination of partial or complete remission at 12 months, was achieved in a significantly higher number of patients in the obinutuzumab group than in the rituximab group (95% vs 67%; odds ratio 10.00; 95% confidence interval, 1.21 to 82.35; P=0.03). Furthermore, the obinutuzumab group had higher rates of complete remission at 12 months, and lower CD19 B-cell counts at 6 months. There were no concerning safety signals, and infection risks were similar in both groups.

Clinical Implications:
This study provides tangible, real-world data, supporting the superior therapeutic efficacy of obinutuzumab over rituximab in high-risk membranous nephropathy. However, the limitations of a single-centre, retrospective analysis, constrained by a sample size of only 21 patients who received obinutuzumab, must be recognised before extrapolating the results more broadly to our patients.

The study was restricted to patients who had regular follow-up data available, and of the 164 patients who received rituximab during the study period, only 42 were included in the analysis after propensity score matching. Despite similar baseline characteristics in both groups, it is unclear what factors specifically prompted the treating clinicians to choose obinutuzumab over rituximab for the 21 patients in the study. The factors that led to this choice of therapy, which may have included prevailing logistics at the time, drug availability, cost factors, hospital policy, or clinical indications, remain unknown modifiers that could potentially confound the result.

These limitations notwithstanding, it should be recognised that an appropriately powered head-to-head trial directly comparing rituximab and obinutuzumab is unlikely to materialise for at least the next few years. However, the wealth of observational data, and some indirect randomised trial data, confirms the clinical superiority of obinutuzumab over rituximab.

So, is it time to write rituximab's obituary? Certainly not. Well, not yet, anyway. In clinical practice, financial considerations, access to drugs, and physician comfort with the use of newer molecules play as much of a role in our clinical decision-making as proof of therapeutic efficacy. However, in the coming years, obinutuzumab will likely continue to challenge rituximab's place as the anti-CD20 therapy of choice for high-risk primary membranous nephropathy.

Mastermind Membranous

The Quiz Squad: Dr Vineet Behera, Dr Sree Bhusan Raju

Q1

42 year old case of chronic low back ache on recurrent NSAID use presents with nephrotic syndrome. His biopsy showed PLA2R negative membranous nephropathy. Which of the following antigens may be associated with NSAID use.

A) *Sema* 3B C) PCSK6
B) NELL-1 D) NDNF

Q2

Which antigen is associated with autoimmune diseases and was identified in secondary membranous nephropathy?

A) NELL-1 C) THSD7A
B) EXT1/EXT2 D) *Sema* 3B

Q3

50 year old, a case of acute myeloid leukemia who underwent successful haemopoetic stem cell transplant. He developed nephrotic syndrome after 1 year with biopsy showing membranous nephropathy with PLA2R and NELL antigens negative. Which of the following antigens may be associated with HSCT.

A) *Sema* 3B C) PCSK6
B) FAT 1 D) NDNF

Q4

Which antigen is commonly linked to malignancy in approximately seen in >30% cases?

A) NELL-1 C) EXT1/EXT2
B) THSD7A D) *Sema*3B

Q5

Which antigen is associated with pediatric membranous nephropathy and is less common in adults?

A) *Sema3B* C) *THSD7A*
B) *NELL-1* D) *EXT1/EXT2*

Q6

Which antigen is detected in both primary membranous nephropathy and membranous lupus nephritis?

A) *NELL-1* C) *EXT1/EXT2*
B) *THSD7A* D) *Neural cell adhesion molecule 1*

Q7

What clinical condition is associated with THS7DA positive membranous nephropathy?

A) *Malignancy* C) *Poisoning*
B) *Autoimmune disease* D) *Chronic infections*

Q8

Which antigen is strongly associated with recurrence of membranous nephropathy after kidney transplantation?

A) *PLA2R* C) *Sema3B*
B) *NELL-1* D) *EXT1*

Q9

Which technique is most appropriate for monitoring anti-PLA2R antibodies during treatment follow-up?

A) *Kidney biopsy* C) *CT scan*
B) *Serum antibody ELISA* D) *Urine protein electrophoresis*

Q10

Which antigen is associated with membranous nephropathy occurring in elderly males associated with highest chances of spontaneous remission ?

A) *PLA2R* C) *Sema 3B*
B) *Procadherin 7* D) *EXT1*

Q11

What technique was instrumental in identifying novel antigens like NELL-1 and Sema 3B in membranous nephropathy?

A) *Electron microscopy*
B) *Mass spectrometry with laser microdissection*
C) *Western blotting*
D) *Flow cytometry*

Q12

Which antigen is strongly associated with membranous nephropathy associated with syphilis?

A) *Sema 3B*
B) *FAT 1*
C) *PCSK6*
D) *NDNF*

Q13

What antigen is associated with the use of membranous nephropathy caused by regular use of fairness creams containing high levels of mercury ?

A) *Sema 3B*
B) *Nell 1*
C) *PCSK6*
D) *NDNF*

Q14

Which antigen has been identified in membranous nephropathy cases associated with demyelinating neurological disorders?

A) *Contactin 1*
B) *FAT 1*
C) *PCSK6*
D) *NDNF*

Q15

Which antigen is associated with membranous nephropathy associated with chronic infections and displays a non-IgG4 subclass pattern?

A) *PCDH7*
B) *NELL-1*
C) *NCAM1*
D) *SEMA3B*

KK Quiz
Answers @ Pg 25

Surviving The 'Survival Curves'

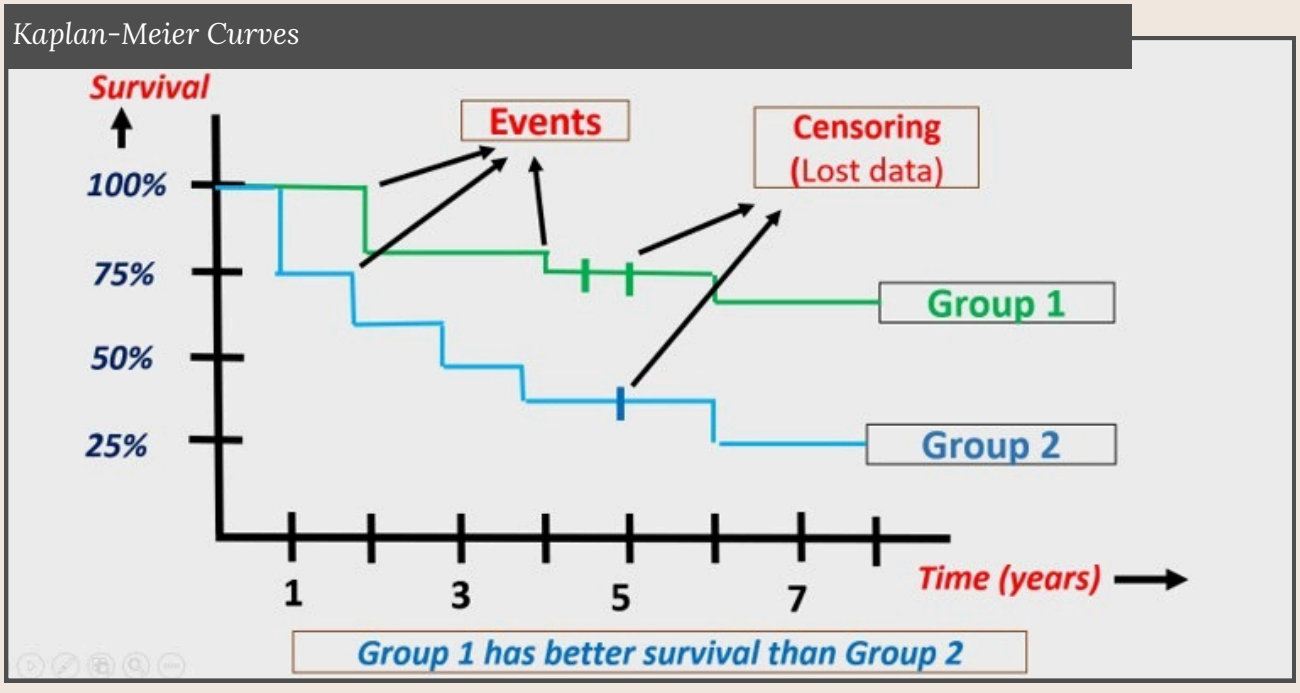
Dr Vineet Behera
Dr Aniruddha Datta

Kaplan-Meier Curves also known as the "Survival Curves" curves are a graphical method used in survival analysis to estimate the survival function, which represents the probability of a subject surviving to a given time.

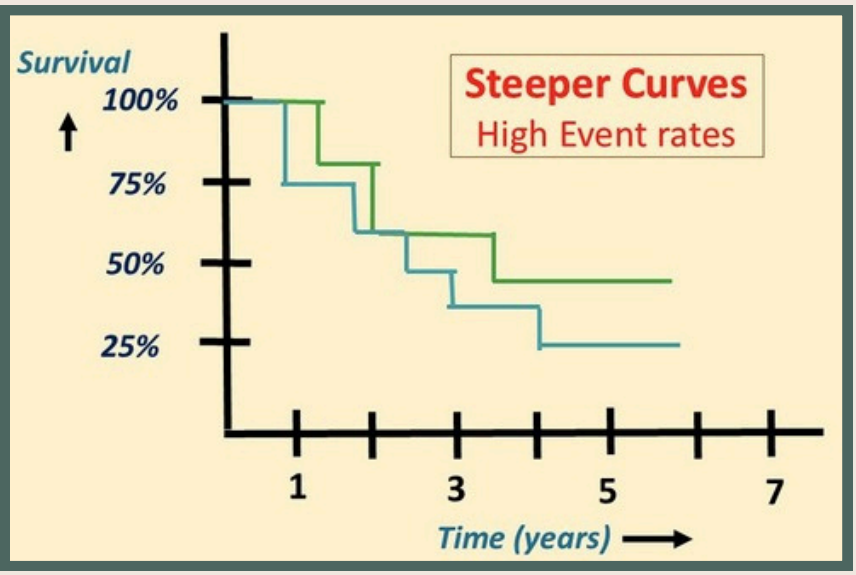
Time-to-Event Data: Kaplan-Meier Curves analyze 'time-to-event' data, meaning they track how long it takes for a specific event to occur (e.g., death, relapse, disease progression).

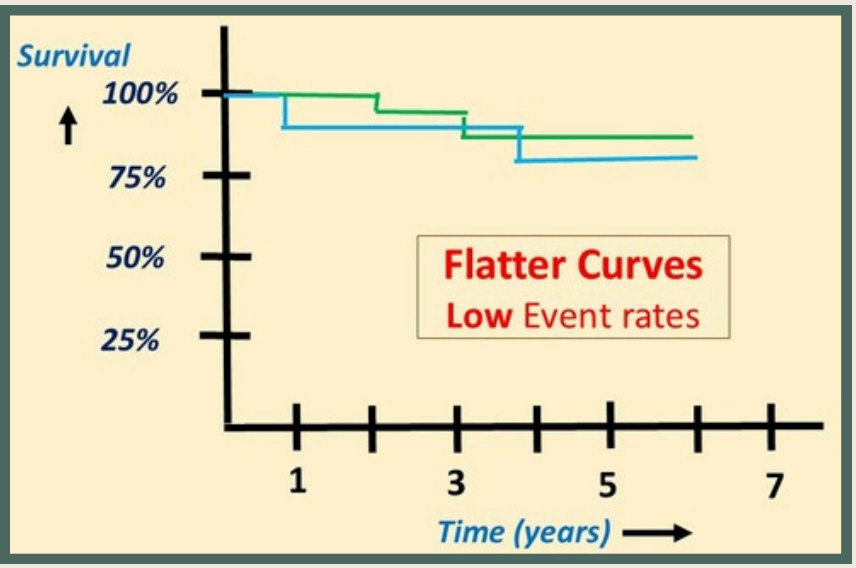
Censoring: These curves have the ability to handle censored data, where the exact time of an event is not known for all subjects like in cases of lost to follow up.

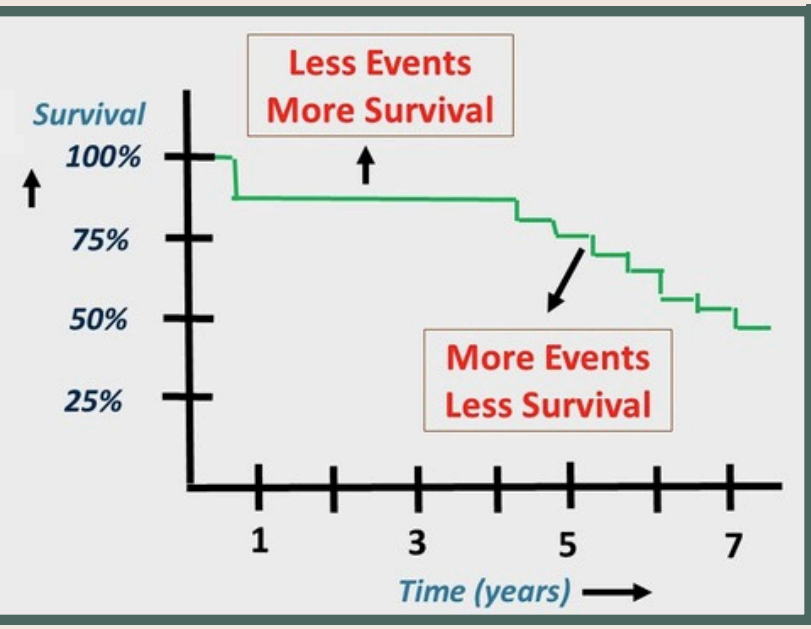
Kaplan-Meier Curves

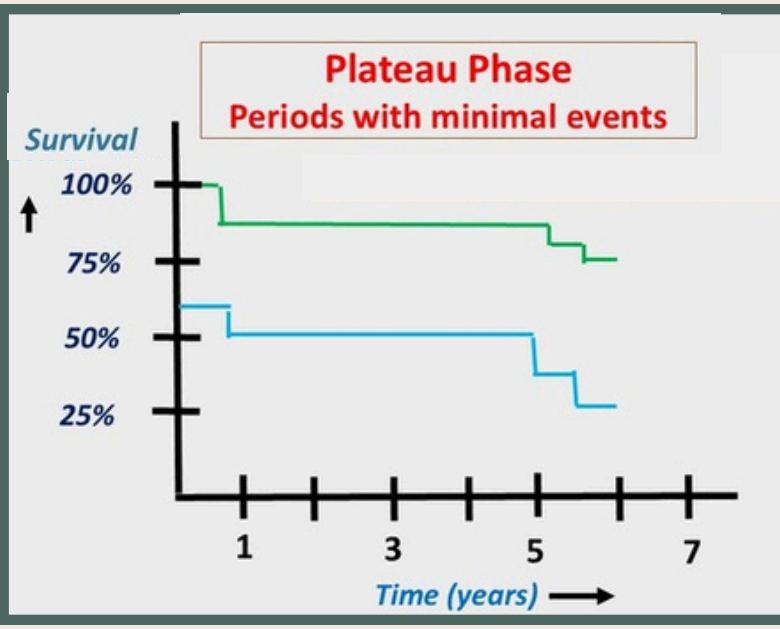


INTERPRETING KAPLAN-MEIER CURVES









WHO WERE KAPLAN & MEIER

Paul Meier

1924 - 2011

A statistician from New Jersey

Edward L Kaplan

1920 - 2006

A mathematician, from Pennsylvania

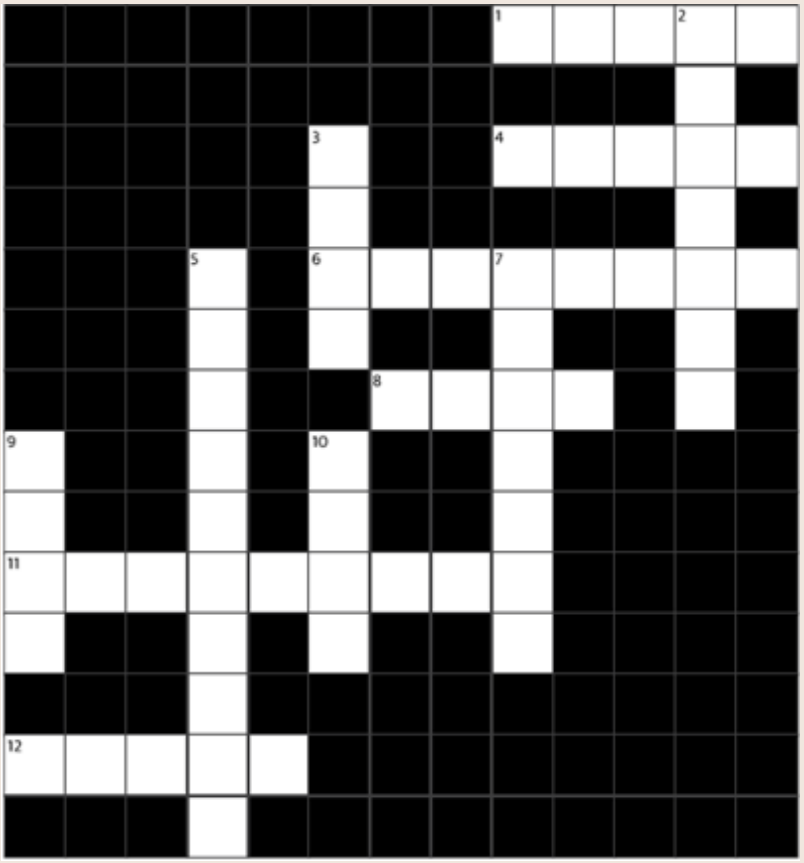
The ***Kaplan-Meier Curve*** is named after EDWARD L KAPLAN and PAUL MEIER. Both of them submitted similar manuscripts to the Journal of the American Statistical Association. The journal editor, John Tukey, convinced them to combine their work into one paper, which has been cited more than 34,000 times since its publication in 1958.

KK Crossword

Membrane Mysteries

VOL 3, ISSUE 2
APRIL to JUNE 2025

The Crossword Quad: Dr Pallavi, Dr Subashri, Dr Sandhya, Dr Ambily



Solve the crossword ONLINE

KK Crossword Answers @ Pg 25

ACROSS

1 Antigen found in patients with membranous lupus nephritis and associated with neuropsychiatric manifestations

4 The 4 ultrastructural stages of Membranous Nephropathy were described by Ehrenreich and .....

6 The trial that compared two 375 mg/m2 doses of rituximab to non-immunosuppressive anti-proteinuric treatment (NIAT), in patients who had persistent nephrotic syndrome after 6 months of NIAT

8 The scientist who described M type PLA2R antigen in idiopathic membranous nephropathy

11 Characteristic pattern of NELL1 staining in immunofluorescence

12 This is the immune trigger for Hepatitis B associated membranous nephropathy

DOWN

2 This ingredient in fairness creams can cause membranous nephropathy

3 Type of immunoglobulin most often found on IF in Primary membranous nephropathy

5 This Anti CD-20 agent which has been used in refractory membranous nephropathy has a C1q binding domain

7 RCT which compared cyclophosphamide and steroids with rituximab in MN

9 The most immunodominant epitope in PLA2R antigen

10 One of the most common malignancies associated with MN

Multitargeted Therapy

IS THIS SET TO BECOME THE NEW NORM IN HIGH RISK PRIMARY MEMBRANOUS NEPHROPATHY?

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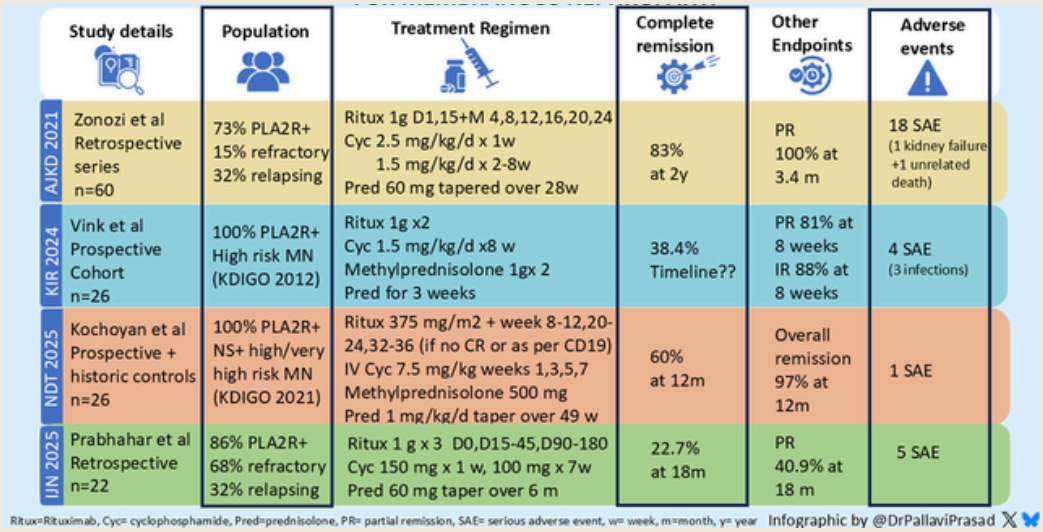
Membranous nephropathy (MN) is one of the leading causes of Nephrotic Syndrome in adults, characterized by immune-mediated damage to the glomerular filtration barrier, often driven by autoantibodies such as anti-phospholipase A2 receptor (anti-PLA2R). Traditionally, a cyclic regimen of corticosteroids and cyclophosphamide has been the cornerstone of treatment, particularly for high-risk MN. However, cyclophosphamide carries significant toxicities that has prompted the exploration of other alternatives, like rituximab and calcineurin inhibitors; rituximab is associated with a lower response rate (RI-CYCLO and Mentor Trial) and calcineurin inhibitors are associated with a high relapse rate. Recent studies have investigated combining rituximab and cyclophosphamide to leverage their complementary mechanisms, aiming to enhance efficacy while potentially mitigating individual drawbacks.

The prospective single-arm trial by Kochoyan and Dobronravov evaluated a new treatment strategy for high-risk primary membranous nephropathy (PMN) by combining low-dose rituximab, intravenous cyclophosphamide, and a rapidly tapered course of corticosteroids (RCP). In a prospective single-arm trial with historical controls, 30 high-risk PMN patients with persistent nephrotic syndrome and elevated anti-PLA2 receptor antibodies received the RCP treatment. Compared with historical control groups receiving either rituximab-based therapy (RTX) or cyclosporine plus corticosteroids, patients treated with RCP achieved significantly higher overall remission (97% vs. 60% and 50%, respectively) and complete remission (CR) rates (60% vs. 7% and 24%, respectively) by 12 months. Moreover, the time to remission was much shorter for the RCP group, with median time of 2.8 months to overall remission compared to over 7 months for the control group. The adverse events demonstrate a favorable safety profile for the RCP regimen. Despite being a combination therapy, RCP had the lowest overall AE rate (23 per 100 patient-years) and only one serious adverse event (SAE) over 56 patient-years of follow-up. The study highlights the synergistic potential of combining B-cell depletion (rituximab), cytotoxic suppression of immune activity (cyclophosphamide), and anti-inflammatory effects (steroids) to induce faster and more complete immunological remission. Furthermore, the rapid depletion of anti-PLA_2R antibodies observed in the RCP group supports the idea that early and aggressive immunological control correlates with improved clinical outcomes.

A small prospective study conducted by Coralien and Wetzels on a low-dose

combination of rituximab, cyclophosphamide, and prednisone in PLA2R-positive MN achieved rapid immunological remission in 88% and CR in 73% of patients. Similarly, a retrospective study by Zonozi assessed a combination of RCP in 60 PMN patients. All patients achieved partial remission, and 83% achieved CR by 2 years. Immunologic remission occurred rapidly, with 100% achieving anti-PLA2R negativity by 6 months. Prabhahar et al recently published a retrospective case series using combination therapy in refractory and relapsing membranous nephropathy. Out of 22 patients, 86% were Anti PLA2R+. At 18 months follow up, 22.7% achieved CR and 40.9% achieved PR. Serologic remission was seen in 100% patients with relapsing disease at 12 months.

Cyclophosphamide-based regimens, particularly when combined with corticosteroids, achieve overall remission rates ranging from 73% to 83% and CR in 35% to 60% (RI-CYCLO and Starmen trial). Rituximab monotherapy demonstrates overall remission rates around 60%, with variability based on disease severity and treatment protocol. Complete remission rates with rituximab typically range from 16% to 35% (RI-CYCLO and Mentor Trial). These findings suggest that targeting both B-cell-mediated and T-cell–dependent immune mechanisms with lower cumulative doses can achieve a goal of rapid immunological and clinical remission with fewer adverse events. In summary, this novel RCP combination therapy shows promise as an effective and safe method to induce early remission in high-risk PMN patients. Still, the point to ponder is that patients who have received high immunosuppression in the past may display poor response to RCP, as seen in this study. Amongst all patients treated with RCP, those without CR (n=10) more frequently had been pretreated with other IST (80% vs 25%, P = 0.007) than those who attained CR (n = 20). Second, a word of caution is warranted regarding infections with multitargeted immunosuppression. Third, it will be important to validate the results in larger cohorts and compare them to other therapies in randomized controlled trials. Fourthly, long term remission rates and the regimen required as “maintenance” therapy in patients treated with combination therapy is yet to be determined. While the findings are compelling, the study calls for further validation through randomized controlled trials. If confirmed, this approach could reshape the treatment landscape for high-risk PMN, offering patients a faster path to remission and potentially better long-term kidney outcomes.



	Study details	Population	Treatment Regimen	Complete remission	Other Endpoints	Adverse events
AJKD 2021	Zonozi et al Retrospective series n=60	73% PLA2R+ 15% refractory 32% relapsing	Ritux 1g D1,15+M 4,8,12,16,20,24 Cyc 2.5 mg/kg/d x 1w 1.5 mg/kg/d x 2-8w Pred 60 mg tapered over 28w	83% at 2y	PR 100% at 3.4 m	18 SAE (1 kidney failure +1 unrelated death)
KIR 2024	Vink et al Prospective Cohort n=26	100% PLA2R+ High risk MN (KDIGO 2012)	Ritux 1g x2 Cyc 1.5 mg/kg/d x8 w Methylprednisolone 1gx 2 Pred for 3 weeks	38.4% Timeline??	PR 81% at 8 weeks IR 88% at 8 weeks	4 SAE (3 infections)
NDT 2025	Kochoyan et al Prospective + historic controls n=26	100% PLA2R+ NS+ high/very high risk MN (KDIGO 2021)	Ritux 375 mg/m2 + week 8-12,20-24,32-36 (if no CR or as per CD19) IV Cyc 7.5 mg/kg weeks 1,3,5,7 Methylprednisolone 500 mg Pred 1 mg/kg/d taper over 49 w	60% at 12m	Overall remission 97% at 12m	1 SAE
IJN 2025	Prabhahar et al Retrospective n=22	86% PLA2R+ 68% refractory 32% relapsing	Ritux 1 g x 3 D0,D15-45,D90-180 Cyc 150 mg x 1 w, 100 mg x 7w Pred 60 mg taper over 6 m	22.7% at 18m	PR 40.9% at 18 m	5 SAE

Ritux=Rituximab, Cyc= cyclophosphamide, Pred=prednisolone, PR= partial remission, SAE= serious adverse event, w= week, m=month, y= year Infographic by @DrPallaviPrasad

Cyclophosphamide + Rituximab combination therapy for membranous nephropathy

Renal Riddle

UNRAVELLING AN UNCOMMON FAILURE

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The nutmeg plant (Myristica fragrans Houtt) is a common flavoring agent also known for its medicinal properties. While generally safe, excessive consumption of nutmeg can elevate serum oxalate levels. Normally, the intestine absorbs 10-15% of dietary oxalate, but this can increase with high oxalate intake. Elevated oxalate levels are linked to kidney disease through crystal deposition and tubular epithelial damage, which triggers inflammation and exacerbates kidney injury. Although plant-derived products are often considered safe, their excessive use can pose risks, highlighting the importance of assessing safety limits. This report presents a case of acute renal failure following nutmeg extract consumption.

A 42-year-old male manual laborer presented with five days of vomiting, diarrhea, and abdominal discomfort, followed by edema. Two friends had similar symptoms, one with elevated creatinine. The patient admitted to consuming a locally brewed alcoholic beverage infused with nutmeg extract (10-15 seeds) and jaggery. He was hemodynamically

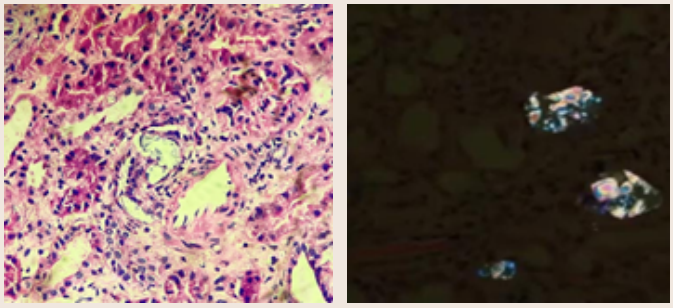

Figure 1: (a) Renal biopsy showing acute tubular injury with intraluminal colourless crystals with fractured glass appearance (LM; H and E) ; (b) Oxalate crystals seen under polarized light

stable with a BP of 150/90 mmHg. Initial investigations revealed urea at 130 and creatinine at 10.5. Urinalysis showed 1+ albumin, 2-3 RBCs, and 1-2 calcium oxalate crystals. An abdominal ultrasound showed normal-sized kidneys with increased echotexture. Fundus examination was normal. Renal biopsy revealed acute tubular injury with birefringent oxalate crystals in the tubules. The patient underwent conservative management with intravenous isotonic saline for one week, resulting in a gradual decline in creatinine levels to 2.6 and ultimately to 1.2 by discharge. There were no adverse events, and follow-up showed continued improvement.

This case highlights a potential nephrotoxic effect of nutmeg, a previously under-reported cause of AKI in humans. Oral administration of nutmeg has been previously shown to have deleterious effects

on rat kidneys in animal studies. Crystal-induced AKI occurs due to intratubular crystal precipitation, leading to tubular obstruction. Elevated plasma oxalate can result in hyperoxaluria and kidney crystal deposition, usually linked to primary (genetic) or secondary hyperoxaluria. Secondary hyperoxaluria results from exogenous factors, such as increased dietary oxalate intake. Early recognition of crystal-induced AKI requires suspicion, particularly with unexplained renal impairment and dietary exposures. In this case, nutmeg extract suggested dietary oxalate overload. Histological examination of the renal biopsy confirmed acute tubular injury with birefringent oxalate crystals.

Nutmeg contains the highest oxalate concentration (194 mg/100 g) among various fruits, much higher than bilimbi, pineapple, or tomato. This high oxalate content suggests its potential role in hyperoxaluria and crystal-induced AKI when consumed in significant quantities, highlighting the need for increased awareness among clinicians.

Crystal-induced AKI is generally reversible with early recognition and management. Treatment involves discontinuing the causative agent and providing supportive care. Healthcare professionals should routinely assess dietary habits in patients with unexplained AKI which can facilitate early diagnosis.

This case underscores the importance of integrating dietary history into the diagnostic workup of acute kidney injury, particularly in regions where traditional herbal remedies are common. Early recognition can facilitate timely intervention, potentially preventing long-term complications. Future studies are needed to establish evidence-based guidelines for plant toxin-related AKI diagnosis and management.

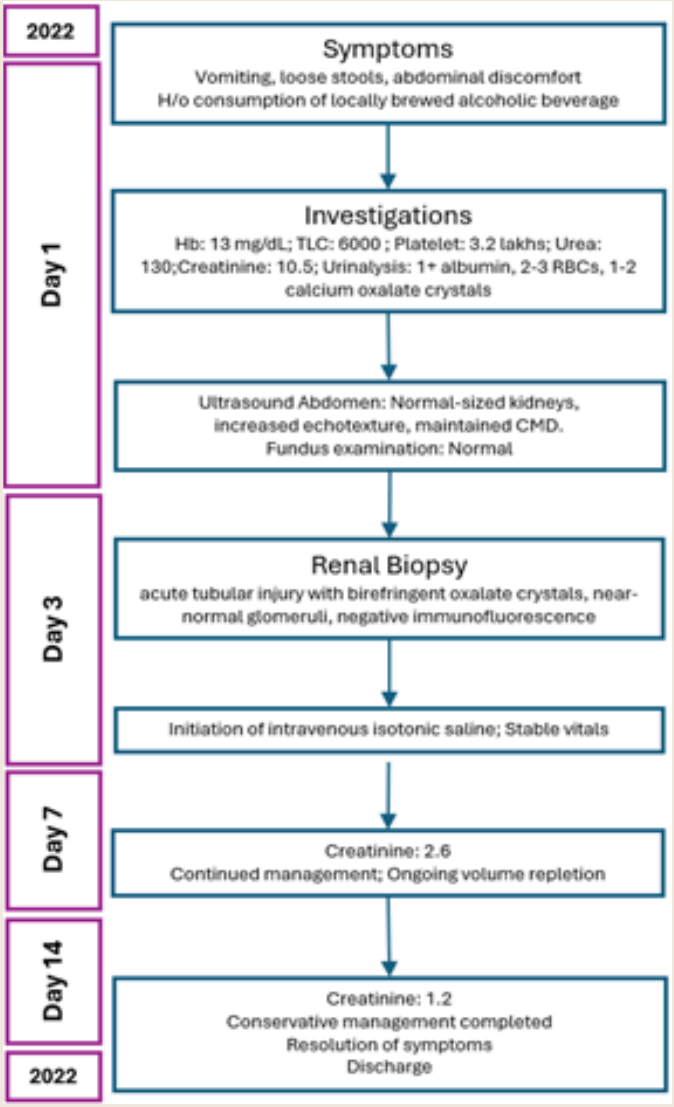

Figure 2: Case report timeline. Presented according to CARE guidelines

Behind the curtain, a story unfolds,
A new chapter begins, with a life to mold.
Years of suffering, finally laid to rest,
A fresh start awaits, with a hope for the best.

The departed soul shines so bright,
After pulling a soul, out of the dark tonight.
Grateful to the family,for decision,so bold,
Illuminated a life, with a story to be told.

Pee, a luxury, once taken for granted,
Now a blessing, with each drop enchanted.
But fears linger, like ghosts in the night,
Infections & Rejections, a constant fight.

Bravo, the warrior, won't give up the quest,
Will fight the ghosts, and beat them to rest.
'Shifted' behind the curtain, with the struggles unseen,
Shall step out of it, healed, with a new `bean'.

BEHIND THE CURTAIN IN KTU

Dr Anshul Dudani
Nizams institute of medical sciences

Acute Pancreatitis

UNVEILING A MOMENTOUS DIAGNOSIS IN A POST-KIDNEY TRANSPLANT PATIENT

Dr Vaishali Kathuria

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A 40-year-old female, with a known case of IgA nephropathy with end-stage kidney disease, underwent a kidney transplant in 2018 with her mother as a donor and no induction. She was on triple immunosuppression with normal graft function. She presented on 16.01.2024 with a history of low-grade fever for 10-15 days associated with backache and pain in the right flank. Initial investigations revealed

Hemoglobin 7.4g/dl
WBC 4590/microliter
Serum creatinine 3.7mg/dl
Sodium 122mEq/L
Potassium 5.6mEq/L
Calcium 7.2mg/dl
Total protein 5.3mg/dl
Serum albumin 2.7mg/dl
Total bilirubin 0.4mg/dl
SGOT 61U/L
SGPT 33U/L
GGT 172U/L
ALP 450U/L
Serum amylase 1055U/L
Lipase 8529U/L

She had CMV viremia with 2520 copies/ml MMF was kept on hold.

CT scan of the abdomen revealed multiple hypointense lesions in the liver and an enlarged head and body of the pancreas. She was managed conservatively with intravenous fluid and started on injection Meropenem and Metronidazole with suspicion of liver abscess. Entamoeba histolytica serology was negative. The patient improved symptomatically; fever spikes settled.

However, because of the doubtful nature of liver lesions, an MR dynamic study of the liver was performed. MRI showed innumerable conglomerated lesions showing diffusion restriction, initial hypo enhancement and delayed patchy enhancement, replacing at least 25-30% of the liver; the largest measuring 3x4 cm in segment IV/V, suggestive of metastatic nature. Mild biliary ductal dilatation was noted.

Subsequently, we performed a trucut biopsy of liver lesions, which revealed tumour cells arranged in sheets, with pleomorphic nuclei, prominent nucleoli and a moderate amount of eosinophilic neoplasm. Focal necrosis and atypical mitosis were noted. On

immunohistochemistry, CD45, CD20, CD21, CD10, bcl6 were positive, ki67- 70%, c-myc-30% and CD3, MMU-1 and bcl2 were negative. Considering differential diagnoses of diffuse large B-cell lymphoma and double/triple hit lymphoma, PET-CT revealed FDG avid SUV max 21.2 exophytic mass arising from distal ileum, confirming the diagnosis of Post-Transplant Lymphoproliferative disorder.

She was started on R-CHOP (with 75% doxorubicin) based chemotherapy in February 2024 with valaciclovir prophylaxis and granulocyte colony-stimulating factor support. Each cycle was administered every 21 days. Tacrolimus was switched to Everolimus. Her graft function remained stable.

After three cycles of chemotherapy, PET CT was repeated, and interval resolution in size and FDG avidity of the ileal and liver lesions was shown. She was continued on modified doses of R-CHOP chemotherapy as earlier for a total of 6 cycles.

However, in June 2024, the patient presented with perforation peritonitis and developed sepsis and septic shock. She subsequently took LAMA and succumbed to complications at home.

Lymphoma accounts for 21% of all cancers in solid organ transplant recipients, in contrast to 5% of cases in immunocompetent individuals. PTLD involves the gastrointestinal tract in 20 to 30% of cases, solid allografts (10 to 15%), and central nervous system (5 to 20%).

PTLD presenting as acute pancreatitis in the absence of any malignant infiltration of the pancreas is a rare presentation. Our patient presented with acute biliary pancreatitis as the initial presentation of PTLD with primary malignancy in the intestine metastasizing to the liver.

Any suspicious lesion should be evaluated and confirmed with tissue diagnosis in the post-transplant setting.

Crossword

ACROSS

1 NCAM1: NCAM1 is an autoantigen found in membranous lupus nephritis. NCAM1 autoreactivity may indicate a subset of patients at risk for both neuropsychiatric manifestations and nephritis.

4 CHURG: Ehrenreich and Churg classification based on the appearance of electron-dense deposits:
a) Stage 1: Small, sparse, electron-dense deposits on the epithelial side of GBM
b) Stage 2: Larger deposits causing GBM thickening, along with foot process effacement
giving the characteristic “spike and dome” appearance
c) Stage 3: Stage 2 plus intramembranous coarse granular deposits with “neomembrane” formation
d) Stage 4: Irregular thickening, dissolution of deposits (holes), and sclerosis of GBM

6 GEMRITUX: In patients with persisting nephrotic syndrome following six months of non-immunosuppressive anti-proteinuric therapy (NIAT), the GEMRITUX study compared two 375 mg/m2 doses of rituximab versus NIAT. The primary endpoint was reached by more patients in the rituximab group than in the control group at 6 months, although this difference was not statistically significant. However, by 17 months, the rituximab group's rate of full or partial remission was nearly twice as high as the controls' (64.9% versus 34.2%).

8 BECK: In the seminal paper published in NEJM in 2009, Laurence H. Beck described that PLA2R is present in normal podocytes and in immune deposits in patients with idiopathic membranous nephropathy, indicating that PLA2R is a major antigen in this disease.

11 SEGMENTAL: Characteristic pattern of NELL1 staining in immunofluorescence as reported by Sethi et al. 16% of their patients with primary membranous nephropathy had granular staining with NELL1 antibody, which was similar in pattern to IgG. In these cases, there was incomplete or segmental staining with IgG, prominent IgG1, mild-to-moderate staining with C3, increased mesangial deposits, and reduced extraglomerular staining.

12 *HbeAg*: HbeAg is found to have a central role in pathogenesis of HBV related MN. The subepithelial deposits are composed of HbeAg related immune complexes.

DOWN

2 MERCURY: Presence of non permissible high concentrations of mercury in fairness creams has been associated with NELL-1 Membranous nephropathy in series from India.

3 *IgG4*: IgG4 is the predominant subtype in idiopathic MN and recurrent MN, while IgG1, IgG2, and IgG3 subtypes are more common in secondary MN and de novo disease in the allograft.

5 OFATUMUMAB: This is a fully humanised anti CD 20 antibody which has been used in refractory MN. Its effect on B cell depletion may be more pronounced and prolonged due to stronger complement dependent cytotoxicity and presence of a C1q binding domain.

7 RICYCLO: Pilot trial with n=74 found no signal of more benefit or less harm associated with rituximab versus a cyclical corticosteroid-cyclophosphamide regimen in MN. Although % of patients achieving complete remission was higher in cyclophosphamide arm, the result was not statistically significant.

9 CysR: PLA2R1 is a membrane receptor with a large extracellular region which includes a cysteine-rich domain (CysR), a fibronectin type II domain and 8 different C-type lectin domains (CTLD1-8). The CysR domain is the most immunodominant with almost all patients with primary MN showing antibodies to CysR.

10 LUNG: MN may be associated with solid organ tumors, most commonly lung and breast, but also colon, prostrate and hematological malignancies may precede MN or may be diagnosed at a later point in time. NELL-1 and THSD7A may be found in malignancy associated MN.

Quiz

Q1(C), Q2(B), Q3(B), Q4(A), Q5(A)

Q6(D), Q7(A), Q8(A), Q9(B), Q10(B)

Q11(B), Q12(D), Q13(B), Q14(A), Q15(D)