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Case Report

Successful Management of Complicated Membranous Nephropathy During Pregnancy. A Report on Two Cases

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Abstract

Membranous nephropathy (MN) is an uncommon, albeit serious, condition during pregnancy. It is usually associated with adverse maternal and fetal outcomes. Management of MN during pregnancy can require the use of immunosuppressive medications which may be associated with potential adverse effects for both mother and fetus. The scarcity of clear evidence-based guidelines constitutes an additional burden on the caring team. We present two cases of pregnant women without a prior diagnosis of kidney disease, who suffered from nephrotic syndrome and acute kidney injury (AKI) during pregnancy. They received a diagnosis of primary membranous nephropathy (biopsy-proven), were managed with immunosuppressive agents, achieved clinical and laboratory remission using corticosteroids and tacrolimus, and had a favorable pregnancy outcome (live babies). One baby, unfortunately though, died from neonatal sepsis after admission to neonatal intensive care unit (NICU). These cases underscore the complexity of management of glomerular diseases - particularly MN - during pregnancy. The use of dual immunosuppressive drugs was effective in achieving remission but required close patient-, and therapeutic drug level monitoring during pregnancy to avoid drug toxicity. These cases highlight the need for multidisciplinary care and further work to establish evidence-based protocols for such patients, potentially improving outcomes for both mothers and infants.

Keywords: ***Membranous nephropathy (MN), nephrotic syndrome, phospholipase A2 receptor (PLA2R) antibodies, tacrolimus (FK), pregnancy, acute kidney injury (AKI), preeclampsia.***

Introduction

The diagnosis and management of glomerular diseases during pregnancy is a complex and difficult task that requires active input from all members within the circle of care for the pregnant woman. The most difficult decision regarding continuation or termination of pregnancy is sometimes needed based on the progress or severity of a specific glomerular disease [1].

Medical literature lacks clear evidence-based guidelines for managing membranous nephropathy during pregnancy owing to the scarcity of cases reported in the literature and the non-existence of clinical trials or systematic reviews for this particular type of glomerular disease in pregnancy [2].

Here, we present two cases of membranous nephropathy that were successfully managed during pregnancy with variable maternal and fetal outcomes.

First Case

A young female patient 24-year-old G4p1+2, who had history of unexplained intrauterine fetal death (IUFD) during her first pregnancy in 2019. Her second pregnancy was uncomplicated and yielded a full-term live baby. During her 3rd pregnancy, she sustained significant bilateral leg edema in the 2nd trimester and was referred to our hospital for further management. Her clinical examination revealed a normal blood pressure (BP) at 100/65mmHg with lower extremity swelling on examination, as well as a picture suggestive of anasarca (ascites, bilateral pleural effusion). The obstetric ultrasound (USG) revealed fetal intrauterine growth retardation (IUGR). She was admitted for further investigations and management. Her blood works were positive for hypoalbuminemia (2gm/dl) and dyslipidemia. The remaining blood works were normal (namely normal renal functions, negative autoimmune profile, and negative viral markers). The urinalysis was positive for 3+ protein but the microscopic examination was negative for casts or other active urinary sediments. The 24-hour urine protein excretion was 7.44 gm/day. Unfortunately, the patient sustained another IUFD shortly after admission. A renal biopsy was performed in the postpartum period and revealed a diagnosis of primary membranous nephropathy with positive phospholipase A2 receptor antibodies (PLA2R abs) in the tissue. During the month following delivery, her clinical and laboratory abnormalities slowly resolved. She missed

her follow-up appointments with our team. The patient did not use contraceptive methods as suggested and had an unplanned conception.

She returned to our clinic in the late first trimester of the 4th pregnancy. A medical examination showed a normal BP reading at 106/70mmHg, and bilateral lower limb edema up to knees. The blood works were all within normal ranges apart from low serum albumin (3gm/dl), dyslipidemia. The 24-hour urine protein excretion was 4.5gm/day. A repeated immunological screen was again negative including extractable nuclear antigen (ENA) panel as well as an antiphospholipid antibody screen. She declined to terminate her pregnancy and hence was started on oral prednisolone 40mg daily, and oral tacrolimus (FK) 3mg twice daily, as well as aspirin. We aimed for a tacrolimus trough level around 4-6ng/ml as a therapeutic range throughout pregnancy. Eight weeks after the initiation of tacrolimus, her edema regressed significantly, her serum albumin rose to 4gm/dl, and her proteinuria improved to 1.3gm/day. At the beginning of the 3rd trimester, she sustained gestational hypertension (HTN) where her BP reading was elevated at 148/91 mmHg for which she was treated with oral nifedipine 20mg three times daily.

A month later, she was admitted to our hospital due to an episode of acute kidney injury (AKI) and uncontrolled HTN, BP:178/102 mmHg. A comprehensive clinical exam was done by the caring obstetrician and nephrologist to ensure absence of preeclampsia among other serious diagnosis that may require immediate termination. There was no evidence serious conditions like preeclampsia or thrombotic microangiopathy (TMA) to name a few. In the end, she was found to have a toxic FK level due to unreported episode of diarrhea prior to admission. The FK trough level was 19ng/ml, so it was put on hold. Liver enzymes were elevated too. A few days later, her BP normalized with treatment (on average was 115/78 mmHg), so did liver and renal functions. Unfortunately, due to financial deterrents, the resumption of tacrolimus was not possible. She was managed conservatively but the proteinuria relapsed to 4.8 gm/day. At 34 weeks of gestation, a planned termination was carried out with successful delivery of a term live small-for-gestational-age (SGA) who weighed 1840 grams and was admitted to neonatal intensive care unit (NICU) for observation after respiratory difficulties. The baby died of neonatal sepsis due to pneumonia 14 days following admission.

Second Case

A female patient, 31 years old, G1P0. Her pregnancy was progressing smoothly during the 1st trimester. A few weeks into the 2nd trimester and during a routine obstetric follow up, she was noted to have facial and lower extremity swelling and her urine dipstick was positive for +3 protein. She was then referred to our hospital for evaluation and management. During our encounter with the patient, a comprehensive clinical exam was positive for the swelling in the face and lower extremities, and a normal BP reading at 104/69mmHg without other significant clinical exam findings. The repeat urine dipstick was positive for +3 protein. The urine microscopic exam was negative for active sediment. Laboratory work was within normal apart from a low serum albumin (2.9gm/dl), abnormal lipid profile. The 24-hour urine protein excretion was 3.4gm/day. She had negative autoimmune profile, negative viral serology as well as negative serum PLA2R antibodies. Pelviabdominal ultrasound was unremarkable aside from viable fetus. A medical decision was made to observe patient for 2-4 weeks as possible spontaneous regression of proteinuria may occur ensue given possible differential diagnosis then. Aspirin was added to her oral iron and vitamins.

That said, after 3 weeks of follow-up, the repeat 24-hour protein excretion indicated worse proteinuria (5.2 gm/day), so she was started on a trial of corticosteroids therapy, as patient couldn't afford tacrolimus. She was started on prednisone 40mg daily and given a one month follow up appointment. Given the 24-hour urine protein excretion worsened to 7.5gm/day, a decision for termination was offered to the patient but she vehemently declined and opted to continue the pregnancy and accepted all possible risks. She was expected to have a possible MN as an underlying renal condition leading to nephrotic syndrome. We used available donations money to start patient on oral tacrolimus along with oral corticosteroids (after literature review). We aimed for a tacrolimus trough level around 4-6ng/ml as a therapeutic range throughout pregnancy. Four weeks later, she showed remarkable clinical and laboratory improvement. Her edema and puffiness subsided, so did the proteinuria. The 24-hour urine protein excretion decreased to 1.5gm/day. Her BP was trending up and patient was noted to have HTN (BP was 142/84mmHg), hence nifedipine was prescribed.

Patient missed two follow up appointment with our team as she lived away from the hospital. At 33 weeks of gestation, she presented to our ER with complaints of fatigue and was noted to have progressive hand tremors that were interfering with her day-to-day activities. She was found to have a toxic level of tacrolimus (FK trough level was 21 ng/ml). She was managed with appropriate dose reduction with subsequent clinical improvement of tremors. She was allowed to continue pregnancy until 36 weeks when a routine cardiotocography (CTG) performed then showed non-reassuring results, so that, a decision of delivery taken. She gave birth to a healthy live SGA boy (weighed 1950gm) with an Apgar score 8 at 1 minute and 9 at 5 minutes. The child is still alive until the time of reporting this case. Two weeks postpartum, she underwent a renal biopsy which revealed primary membranous nephropathy with negative PLA2R abs in biopsy. Four weeks later, she achieved complete remission with fading of proteinuria and her immunosuppressive agents were withdrawn. She was advised to use a contraceptive method and agreed.

Discussion

Membranous nephropathy is a well-known, renal-limited autoimmune disorder in its primary type, with clear guidelines of management among the general population contrary to less clearly defined therapeutic approaches among pregnant women [3]. Both of our cases initially presented as a nephrotic syndrome in the absence of any previous renal illnesses which converted them to high-risk pregnancies with significantly higher adverse outcomes for both mother and fetus including preeclampsia, intrauterine growth retardation (IUGR), intrauterine fetal death (IUFD) [4].

Kidney biopsy is generally a safe procedure during pregnancy especially before 20 weeks, while after that (as long as it is performed before 32 weeks), renal biopsy should be done with caution as it comes with serious maternal and fetal risks like renal hematomas, abruptio placentae, preterm labor among others. In our cases renal biopsy was delayed until the postpartum period, as the first case presented lately after 20 weeks of gestation with anasarca and progressed rapidly to IUFD while the second case refused to do biopsy fearing from adverse fetal events that can affect her baby [5,6].

The kidney biopsy unveiled membranous nephropathy in both cases in cases. In the first case, The PLA2R abs staining was positive as seen in figure 1. Antibodies (IgG4 isotype) usually target the PLA2 receptor which is found abundantly in podocytes - its clear function has not been yet identified - initiating a cascade of glomerular injury & proteinuria, based on that, detection of PLA2R

abs either in tissue or serum is diagnostic for primary membranous GN [7].

The second case also was diagnosed with primary membranous nephropathy with negative PLA2R abs staining confirmed by electron microscopy figure 1, however, after negative screening of secondary causes, she was considered primary form as 20- 30% of primary MN cases may have negative PLAR abs [8].

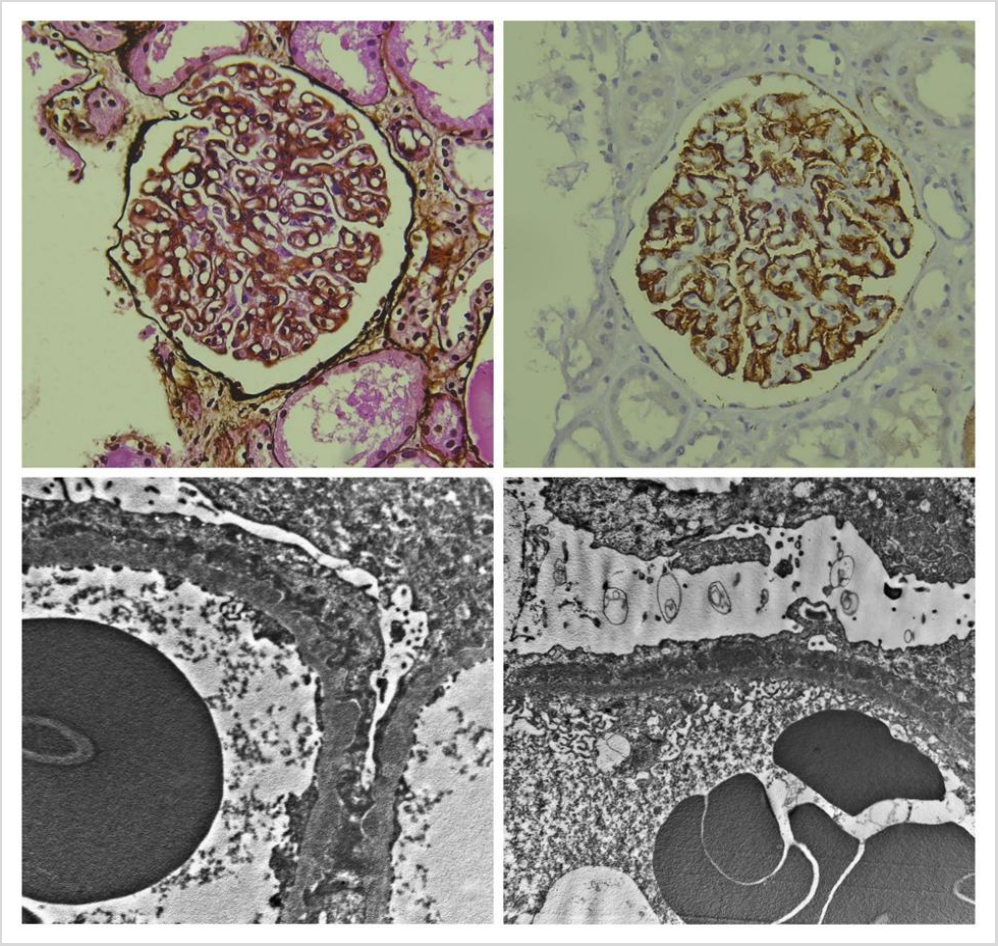

Figure 1: A&B from case I(A)light microscope(L/M)silver-prominent thickening of capillary basement membrane.
(B) immune histochemistry (IHC): segmental granular basement membrane deposits of PLA2R abs.
(C&D) from case II Electron microscope E/M.; revealed diffuse thickening of glomerular capillary basement membranes, with frequent subepithelial deposits of immune complex type, some of which are resolved. The overlying podocytes showed widespread foot process effacement while the mesangial area and endothelium were normal.

While conservative care or steroids are the cornerstones of management among most reported similar cases [9,10], in the second case, the surge of proteinuria after initiating oral steroids indicated failure and it was clear that another immunosuppressant agent is needed. Hence, we considered tacrolimus and added it to the oral steroids, there are few precedents for this route of management as far we know [11,12]. A remarkable improvement was noted over the next weeks with the fading of edema & proteinuria, as illustrated in figure 2.

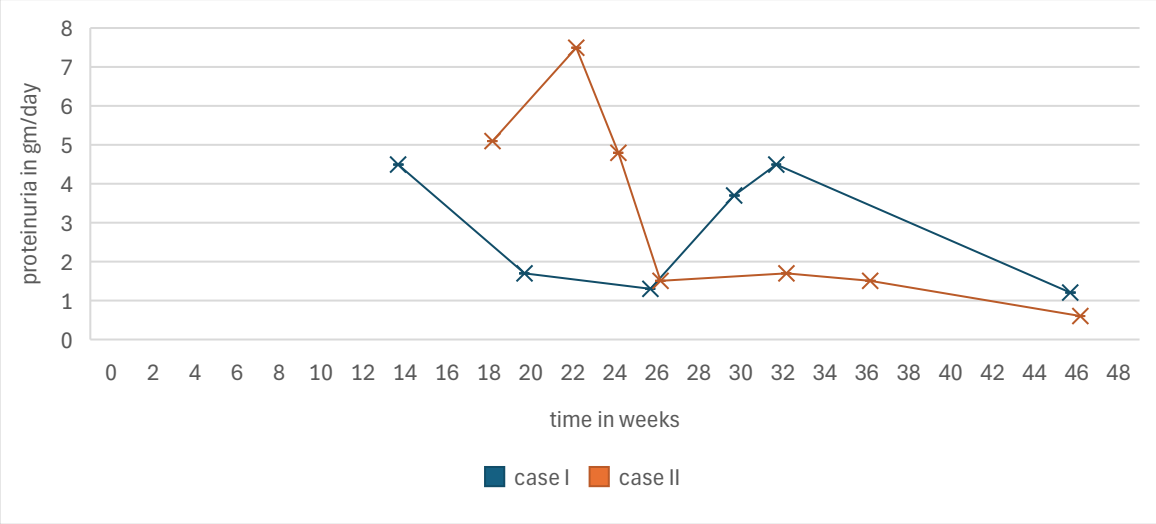

Figure 2: level of proteinuria during pregnancy and postpartum period

We observed high variability of FK trough level upon monitoring as in figure 3. Both patients had an episode of CNI toxicity. This finding was inconsistent with a literature categorizing pregnant ladies as fast FK metabolizers whose, concentration/dose (C/D) ratio -a marker of individual FK metabolism rate- may decline by around 0.7 [13]. C/D ratio is measured by dividing dose by blood level, fast metabolizers <1.05 and slow metabolizers >1.05 [14].

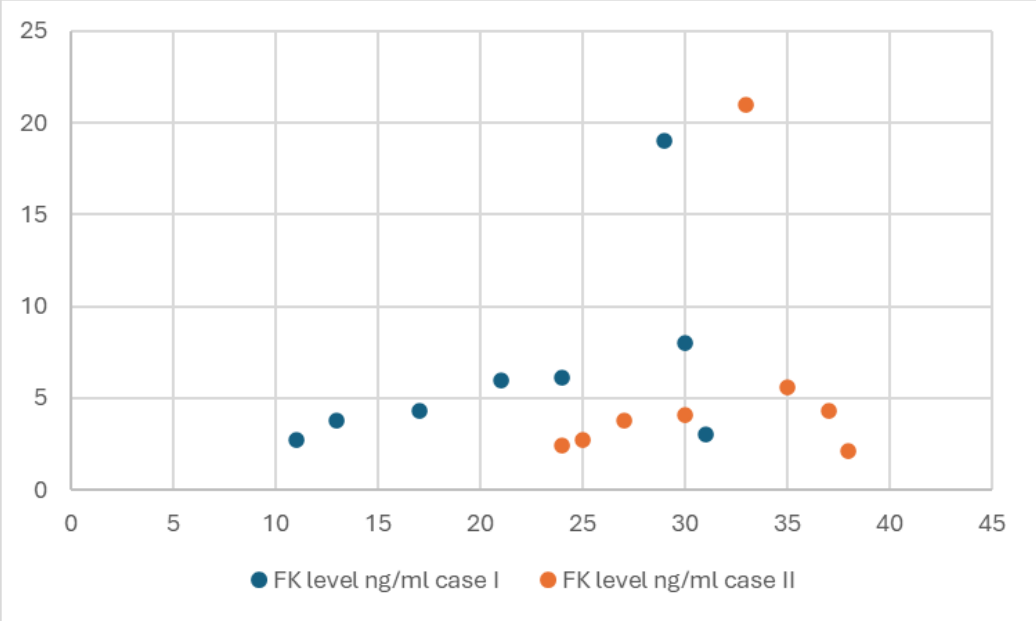

Figure 3: FK trough level throughout pregnancy case 1 and II.

Throughout the course of pregnancy, serum creatinine level remained within normal limits for both cases, except during episodes of CNI toxicity, there was elevation of creatinine to 1.98mg/dl in case 1 and to 1.51mg/dl in case 2. This AKI was temporary, and serum creatinine normalized after managing FK toxicity.

Upon the discontinuation of treatment in the first case, proteinuria relapsed rapidly, and pregnancy ended in premature birth, in contrast in the second case, the condition kept sustained remission till full-term delivery. Both babies were IUGR and delivered small for gestational age, indicating poor pregnancy outcomes with membranous nephropathy [15,16].

Conclusion

In this report, we aim to highlight some important information to the medical community and physicians looking after pregnant women with membranous nephropathy. First, we report the possible successful management of membranous nephropathy-driven nephrotic syndrome during pregnancy using oral corticosteroids and tacrolimus with good fetal and maternal outcomes. Second, we shade additional light on the under reported frequency of membranous nephropathy during pregnancy. Third, we emphasize that tacrolimus trough levels should be frequently monitored during pregnancy in order to detect any variations in its therapeutic trough level and preempt any toxicity. Finally, and perhaps one of the most important reminders to the physicians in the circle of care of pregnant women with renal diseases, that integrated management between nephrologists and obstetricians is crucial in decision making regarding those types of patients. We hope this paper adds some important value to the literature about membranous nephropathy during pregnancy and, along with other reported cases, may help nephrologists and obstetricians create evidence-based guidelines for the management of this particular glomerular diseases during pregnancy.

Declaration

Ethical approval and consent for participation

This research work is approved by our institutional review board.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

Availability of supporting Data

The medical data that supports our conclusion and diagnosis in this case will be made available upon request.

Competing Interests

I declare that I have no competing interests.

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