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Rituximab Rescue in Pregnancy: Triumph over Membranous Nephropathy

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Abstract:

Membranous nephropathy is a disease of middle age however 18.5% case are reported in younger age group. We present here a female patient with MN that resulted in complete remission 5 years later after few relapses. She then presented with relapse and pregnancy. She was treated with tacrolimus and later Rituximab was prescribed weekly doses in the 13th,14th 16th and 17th week of pregnancy with modified lower dose. She responded with improving proteinuria and successfully delivered a healthy baby although prematurely at 34 weeks. She was in complete remission 1 year after her
We here demonstrate the safety and efficacy of rituximab lower modified dose administration in our patient during pregnancy for the management of MN. Further reports and case series may help improve the protocols for use of Rituximab during pregnancy.

Keywords: Membranous Nephropathy, pregnancy, nephrotic syndrome, rituximab, calcineurin inhibitors, Anti PLA2R antibody.

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Introduction

Initially thought to be a disease of middle-aged to older adults with a mean age of onset around 50-60 years.[1] Primary Membranous Nephropathy (PMN) has been shown to account for 18.5% of renal biopsies in adolescents with idiopathic nephrotic syndrome.[2] Rituximab remains the mainstay of treatment in PMN due to improved rates of clinical remission, reduction in proteinuria and favorable adverse effect profile.[3] Data is scarce on the use of rituximab in pregnancy for nephrotic syndrome with few cases reported for minimal change disease(MCD), focal segmental glomerulosclerosis(FSGS), and only one case reported for PMN.[4,5]

Rituximab is a monoclonal IgG1 antibody directed against CD-20 antigens found on B lymphocytes. It was initially approved for the treatment of non-Hodgkin lymphoma.[7] Since then it has been approved for other hematological malignancies, auto immune conditions including Rheumatoid Arthritis (RA), Granulomatosis with Polyangitis (GPA), Microscopic Polyangitis (MP) and Pemphigus Vulgaris (PV). It's also used off-label for several neurological disorders including multiple sclerosis (MS), Myasthenia Gravis (MG), Neuromyelitis Optica Spectrum Disorder (NMOSD) and autoimmune encephalitis. Rituximab was assigned FDA Pregnancy Category C prior to the discontinuation of the

categorical system in 2015. However favorable neonatal outcomes have been reported with use of rituximab in pregnancy.[8,9]

Case

An 18-year-old South Asian female developed nephrotic syndrome. Subsequent renal biopsy showed thickened glomerular basement membrane on light microscopy Periodic Acid Schiff (PAS) stain, with spikes on silver stain. Immunofluorescence showed IgG and C3 deposits while IgA, IgM and C1q were negative. This led to a diagnosis of Membranous Nephropathy (MN). As IgG4 staining was not introduced in the country at that time, and rest of the findings were typical for MN, patient was presumed to have Primary Membranous Nephropathy (PMN).

She was treated with oral Prednisolone (60mg/day) along with Tacrolimus (0.05mg/kg/day). Prednisolone was successfully tapered off however attempting to taper tacrolimus, albeit prematurely, resulted in relapse twice. Her first presentation to us was at the age of 20. At that time, she was normotensive with pitting edema to her mid-shins. Urine routine examination showed 3+ proteinuria with no active sediment. She had a urine protein to creatinine Ratio (UPCR) of 5.8g/g, albumin of 2.47g/dl, LDL of 150 mg/dl and creatinine 0.5mg/dl. Phospholipase A2 Receptor Antibodies (anti-PLA2R) could not be checked due to unavailability of the assays at our setup at that time. Further workup was ordered to exclude secondary causes of MN. Hepatitis serology (for Hepatitis B and C) were negative. Complement levels were ordered that were normal. Erythrocyte Sedimentation Rate (ESR) was elevated at 35mm/hr. Her tacrolimus trough levels were suboptimal and her dose was optimized at 2mg twice a day. Ramipril 2.5mg twice a day was continued for proteinuria, furosemide 40 mg once a day for her pitting edema and rosuvastatin 20 mg at night for primary prevention of cardiovascular disease. She achieved partial clinical remission the following year with UPCR of 0.56g/g. After that, at the age of 21, she got married and wished to conceive. Ramipril was switched to Diltiazem. She was advised to wait till further reduction in proteinuria.

She miscarried twice during this time, at the age of 22 and 24. At 25 years of age, she achieved complete clinical remission (UPCR of 0.06g/g).

At her next presentation to us, she was in her 5th week of gestation with UPCR of 4.8g. Given that her proteinuria had increased before the 20th week mark and her blood pressure was normal, the increase was attributed to relapse of her primary disease. Tacrolimus trough levels were confirmed to be optimal. Based on available evidence of Rituximab in pregnancy, potential risks and benefits were discussed with the patient and she subsequently opted for it. She was offered a low dose regime of Rituximab 100mg/week for 4 weeks which was administered at weeks 13, 14 16 and 17. Tacrolimus was continued at the same dose of 2mg twice a day. Her UPCR, albumin and LDL were followed closely throughout her pregnancy.

At 34 weeks of gestation, due to low Amniotic Fluid Index (AFI), labour was induced and a baby boy was born. He required admission in the nursery for a week due to prematurity. Post discharge, he remained stable. He is currently 2.5 years old, healthy and developing normally.
The mother was started on Valsartan 80mg once a day post-delivery and Diltiazem was discontinued. She achieved complete remission (UPCR 0.17g/g) 1-year post Rituximab administration and is in remission to date almost 7 years since diagnosis and 2½ year after the pregnancy.

Discussion

Our patient had a relapse of PMN during 5th week of gestation despite being on adequate doses of tacrolimus. Rituximab was therefore deemed to be appropriate choice of immunosuppression. As very little IgG is known to cross the placenta to the fetus in the first trimester, with levels steadily rising in the second and peaking in late third trimester, it may be prudent to administer it during earlier weeks of gestation to avoid neonatal B lymphocyte depletion and subsequent risk of neonatal infections.

By the time our patient agreed to rituximab therapy, she was already in her late first trimester. A low dose regime was therefore preferred to the conventional regime of 1g dose given 2 weeks apart. This approach is supported by the recent meta-analysis that concludes that effective remission can be achieved with a low dose regime thereby avoiding potential risk of infections, hefty costs and cumulative exposure to immunosuppressive medication.[10] Our patient showed gradual reduction in proteinuria, improved albumin and LDL levels post rituximab administration. This resulted in a live, albeit premature delivery. However, the neonate did not warrant intensive care throughout his admission. Post discharge he remained healthy, achieved all developmental milestones on time and no increased occurrence of infections were noted. Long term follow-up to date has been uneventful. Our patient achieved complete remission one-year post rituximab administration. Since then, she is continued on tacrolimus, requiring no additional dose of rituximab to date.

There is no consensus regarding the use of rituximab in pregnancy with global guidelines varying from region to region. American College of Rheumatology (ACR) 2020 guidelines conditionally permit the use of rituximab in pregnancy in case of organ or life-threatening disease.[11] European Alliance of Associations for Rheumatology (EULAR) 2025 guidelines permit the use of rituximab if no other pregnancy appropriate alternatives are available. [12] Australian guidelines suggest avoidance during pregnancy.

Conclusion: In conclusion, a case-centric, individualized approach is warranted for each patient in the use of Rituximab during pregnancy till a wider consensus is available based on the upcoming literature.

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