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Membranous Nephropathy In Pregnancy

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Abstract

Proteinuria before twenty weeks of gestation should always be evaluated as it can be due to underlying glomerular diseases. We present a case of membranous nephropathy during pregnancy diagnosed by kidney biopsy and negative PLA2r aantibodies. Therapy was initiated with prednisolone 60mg per day. Calcineurin Inhibitor was also later started. Termination of Pregnancy when worsening of proteinuria was observed on followup. Patient achieved partial remission after two weeks and complete remission after one and half month of termination of pregnancy.

Key Words: Pregnancy, membranous nephropathy, nephrotic syndrome, proteinuria, remission.

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Introduction:

During pregnancy there is steady increase in renal blood flow and hence, glomerular filtration rate (GFR). These physiological changes reach their zenith during the second trimester to almost 50% increase in estimated GFR and 70% increase in renal blood flow in the second trimester and can potentially unmask renal disease.[1] Proteinuria before twenty weeks of gestation should always be evaluated as it can be due to underlying glomerular diseases. Feto-maternal complications can occur due to the glomerular disease in pregnancy. However, pre-eclampsia, is one of most important causes of nephrotic range proteinuria in pregnancy after 20 weeks of gestation. [2]

Case Report:

A 30-year-old female was referred to the Department of Nephrology for evaluation of generalized body swelling for last 2 weeks. At the time of referral, she had gestational amenorrhea of 10+ weeks, confirmed on ultrasound. Swelling was initially noticed on feet with progression to legs, accompanied by periorbital puffiness. Swelling was not associated with cold intolerance,palpitations , paroxysomal nocturnal dyspnea shortness of breath, orthopnea or steatorrhea. There was frothy urine but no complaints of hematuria, sore throat, skin rash or raised blood pressures within last 2-4 weeks prior to swelling. She denied any musculoskeletal symptoms, (joint pain , swelling or joint stiffness), skin rashes, oral ulcers or hair loss. There was no prior history of exposure to NSAIDs or herbal products or excessive skin whitening cream use. Her previous obstetric history was significant for 5 pregnancies with one abortion.

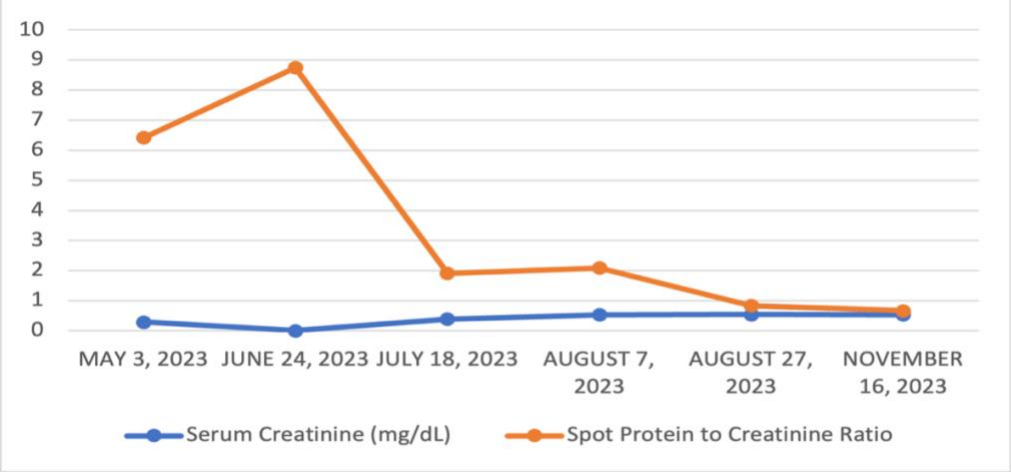
At initial visit her blood pressure was 120/70 mmHg, pulse 88 beats per minute, respiratory rate of 20 breaths per minute and was afebrile. She had symmetrical edema on lower limbs up to mid calves and sacrum. Juglar venous pressure was raised. Rest of her physical examination was unremarkable.

Her hemoglobin was 8.8 g/dL, MCV 68 and MCHC 24 suggesting with microcytic hypochromic picture. Spot urine for protein to creatinine ratio was 6.13 mg/mg. Compliment levels C3 was 96 (<85) and C4 was 24 (<20) were normal. ANA by IF was <1:80. ENA panel was negative. Antiphospholipase A2 Receptor antibody IgG was negative (9 RU/mL). Hepatitis Serology for B and C was also negative. Ultrasound of kidneys showed right kidney of 12.9 cm and left kidney of 13.1 cm with normal echogenicity.

She was advised renal biopsy. Concurrent iron deficiency anemia was corrected with ferric carboxymaltose 500mg two infusions 1 week apart. Renal Biopsy was done which showed 17 glomeruli on Hematoxylin and eosin, glomeruli had thick membranes on Periodic acid-Schiff and Spikes were visible on John-Methamine Silver Stain. Interstitium was normal, tubules were closely packed and vessels showed no evidence of vasculitis or thickening. Immunofluorescence was also done showing deposition of IgG 2+, C3 1+. There was non-significant mesangial trapping of IgM and C1q. Thus, a diagnosis of AntiPLA2R negative membranous Nephropathy was established.

Considering the presence of high-grade proteinuria and the propensity of nephrotic syndrome (especially membranous nephropathy) to cause thrombotic complications magnified by presence of gestation a decision to treat with steroids was made. Counselling of the patient and the family was done for possible maternal and fetal complications associated with high dose steroid therapy. Complications of nephrotic syndrome were also discussed. Therapy was initiated with prednisolone 60mg per day. On follow up after 1 month her urinary protein to creatinine ratio increased from 6.13 to 8.75. At this time calcineurin inhibitor was also started. Worsening of proteinuria and need for multiple immunosuppressive medications, coupled with the fact that patient and her husband felt that their family was already complete family requested for termination of pregnancy. Termination of pregnancy on medical grounds was therefore done after a shared decision by family, obstetric department and nephrology department. Post termination, patient had a partial remission after two weeks. Patient achieved complete remission after one and half month of immunosuppression therapy. She was continued on Prednisolone, Tacrolimus, irbesartan with further plan to taper off prednisolone and ultimately tacrolimus over 6 months time.

Figure 1: Serum creatinine and spot urine for protein and creatine ratio over time in a pregnant patient diagnosed with Membranous GN, Termination of pregnancy was done on 5th of July 2023.



Discussion:

Membranous nephropathy is one of the most common causes of nephrotic syndrome in adults. It's the third most common cause in biopsy proven non diabetic causes of nephrotic syndrome. About 75 to 80% of the cases are primary which is caused by circulating autoantibodies against podocyte antigens. Antiphospholipase A2 Receptor, Thrombospondin type 1 domain containing 7A, Semaphorin 3B, Neural epidermal Growth factor like 1, protocadherin 7 are some of the known important antigens for primary membranous Nephropathy.[3] Antiphospholipase A2 Receptor is the most common and accounts for about 70% of the cases. 20-25% of the cases are secondary and have different causes like autoimmune disorders (Lupus Nephritis, Mixed connective tissue disorder), infections (Hepatitis B and C, syphilis) and drugs (NSAIDs, Gold).[4]

Urine complete usually shows Proteinuria whereas microscopic hematuria is present in about 30-40% of the cases but RBC casts are rare. 10 to 20% of the cases have hypertension while less than 10 of the cases have kidney impairment. Spot urine for protein and creatinine or 24-hour urine for protein and creatinine is done to quantify proteinuria. About 70-80% have nephrotic syndrome.[4] Primary membranous nephropathy does not cause systemic activation of complement pathway hence complement levels (C3 AND C4) are usually normal as were in our patient. ANA levels and chest X-ray are done to rule out secondary cause such as lupus nephritis and sarcoidosis. Antiphospholipase A2 Receptor Antibody IgG is done to establish primary membranous nephropathy which was also negative in our patient. Gynecological work up was also done to rule out gestation trophoblastic disease which has been reported to be linked with membranous nephropathy. Our patient's renal biopsy showed typical spikes on JMS and thickened membranes on PAS which were in line with the diagnosis of membranous Nephropathy. Electron microscope and AntiPLA2R Antibody Staining was not available in our center.[5,6] In Pregnancy both primary and secondary membranous nephropathy have been reported these are mainly case reports.[7,8]

Depending upon the risk stratification, the armamentarium against membranous nephropathy includes angiotensin receptor blockers, sodium-glucose cotransporter 2 inhibitors, calcineurin inhibitors (Tacrolimus and Cyclosporin), Cyclophosphamide, Mycophenolate Mofetil and Rituximab. In membranous nephropathy, Prednisolone and calcineurin inhibitors are the only safe immunosuppressive medications in pregnanc.[9,10] ACE inhibitors and angiotensin receptor blockers are teratogenic and as yet, there is no experience with using SGLT 2 inhibitors during pregnancy. In our case, as per our literature search, we planned to start prednisolone 60mg/day for 6 weeks.[11-13] However, at follow up after one month (patient was still carrying her pregnancy) her proteinuria has increased, hence, we added tacrolimus (2mg twice daily). After the termination of pregnancy irbesartan was also added for proteinuria. On this regimen patient achieved complete remission in two months.

In conclusion, we hereby, reported case of membranous nephropathy which initially did not respond to immunosuppressive medication but just two weeks after termination of pregnancy patient started responding to medication. Our patient's situation may be similar to previously reported cases of membranous nephropathy during pregnancy with resolution on delivery or termination of pregnancy.[13] At present, patient is under close follow up.

Conflict of Interest: None Declared

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