Successful foetal outcome in a patient with primary membranous nephropathy and circulating anti-phospholipid antibodies: A case report

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Abstract

There is little information about pregnancy outcomes in patients with active membranous nephropathy (MN), especially those with circulating autoantibodies to M-type phospholipase A2 receptor (PLA2R), the major autoantigen in primary MN. Membranous glomerulonephritis (MGN) represents an immunologically mediated disease characterized by deposition of immune complexes in the glomerular subepithelial space, frequently associated with circulating M-type phospholipase A2 receptor. Nephrotic syndrome (massive proteinuria and hypoalbuminemia) at diagnosis predicts poor prognosis. Pregnancy with active MGN is high risk for foetal loss, intrauterine growth restriction, and pre-eclampsia, and may worsen maternal renal function, especially with the presence of antiphospholipid antibody syndrome (APLA).

We report a 23-year-old gravida in her first pregnancy, suffering from MGN and severe nephrotic syndrome, complicated by APLA syndrome. The patient was treated with enoxaparin, aspirin azathioprine, and Prednisone for a short time, in addition to furosemide and albumin intravenously. She was delivered at 30 weeks due to deteriorating maternal and foetal conditions.

A successful neonatal and maternal outcome was achieved in this case. The patient’s history revealed thrombocytopenia and APLA syndrome and continues to be treated chronically with enoxaparin. Kidney biopsy performed after delivery showed membranous MGN stage II-III. Herein, we present a case of successful pregnancy and foetal outcome in a young woman with APLA syndrome and MN.

Keywords: Membranous GN, Nephrotic Syndrome, Anti-Phospholipid Antibodies.
Introduction

Pregnant patients with autoimmune disease may deliver newborns with a spectrum of clinical manifestations due to the transplacental passage of circulating autoantibodies. Membranous glomerulonephritis (MGN) presents one of the most common forms of nephrotic syndrome in adults, an autoimmune disease mainly caused by autoantibodies against the recently discovered podocyte antigens, the M-type phospholipase A2 receptor 1 (PLA2R), and thrombospondin type 1 domain-containing 7A (THSD7A) [1]. MGN is histopathologically characterized by thickening glomerular basement membrane (GBM) and subepithelial deposition of immune complexes [2]. Clinical presentations of MGN include generalized oedema and body weight gain. MGN may be idiopathic, accounting for an estimated 70% to 80% of cases [2]. In approximately 20% of cases in adults, the MGN lesion is secondary to various disorders, including infection (e.g., hepatitis B), systemic disease (e.g., SLE or sarcoidosis), drugs (e.g., nonsteroidal anti-inflammatory drugs), thyroiditis, and malignancy. Deterioration in renal function and development of end-stage renal disease occurs in approximately 40% of the patients with idiopathic MGN [3]. The amount of proteinuria at time of diagnosis of MGN is an important determinant of prognosis. In women with chronic kidney disease, proteinuria >1 g/day is associated with increased risk of adverse pregnancy and neonatal outcomes, including preterm delivery, small for gestational age infants, and need for neonatal intensive care observation. Specifically, in addition to the risk described for proteinuria complicating pregnancies, pregnancy with MGN is associated with increased foetal loss and, in some instances, a progressive loss of maternal renal function [3-6].

Little literature exits about pregnancy outcomes in patients with nephrotic syndrome due to primary MN, with no data available about pregnancy in PLA2R-associated disease. Herein, we present another case what we believe to be another important case of pregnancy in a patient with PLA2R-associated MN who was treated with Enoxopan throughout the course of her pregnancy.

Case Report

A 23-year-old first pregnancy gravida with twin dichorionic-diamniotic achieved by in vitro fertilization (IVF). This woman suffered from anti-phospholipid-antibody-syndrome (APLA syndrome), was treated chronically with enoxaparin 80 mg and aspirin 100 mg, both medications taken once daily. Her sister suffered from APLA syndrome and recurrent miscarriages. At 26 weeks' gestation our patient was admitted to the high-risk unit at the Department of Obstetrics & Gynaecology in our centre (January 2017) because of intrauterine foetal death (IUFD) of one of the twins and intrauterine growth restriction of the other twin. On admission, our patient was in good general condition, without dyspnoea. Her body temperature was 36.0°C, her pulse rate was 74 beats/minute, and her blood pressure was 135/85 mmHg. The findings on physical examination were normal, except for severe pitting oedema in the lower extremities (+3) up to the height of her knees, arms, and eyelids. The following laboratory results were obtained: 24-hour urine collection for protein detected 10 grams of protein in parallel with severe serum hypoalbuminemia of 2.3 gr/dl. Additional tests showed white blood cell count 12,700/μl, 3.7 L, haemoglobin 12.3 g/dl, hematocrit, 37.3%, platelet count 166 K/μl, total protein 5.1 g/dl, Albumin 2.3 g/dl, blood urea nitrogen 12 mg/dl, serum creatinine 0.6 mg/dl, uric acid 6 mg/dl, total cholesterol 364 mg/dl, and triglycerides 185 mg/dl. Liver enzymes and blood electrolytes were within normal range. The results of coagulation tests prothrombin time and fibrinogen were normal with prolongation of PTT. Results for rheumatoid factor, antinuclear antibodies, and anti-neutrophil cytoplasmic antibodies were negative. The serum complement levels were within the normal ranges. The PLAR2 antibody was positive in titer of 1:300 measured by IIFT. A dipstick examination of the urine revealed proteinuria (4+), with a 24-hour urine protein level of 10 g/day at admission, and 800 mg/day 2 months after delivery. The urinary sediment contained 5-10 red blood cells per high-power field. A Beta-2 Glycoprotein IgM 105 high positive (N=0-20), anti-cardiolipin IgM medium positive 43 MPL U/ml (N=0-20). Anti-DNA antibody was negative, anti-Smith antibody negative, SSA and SSB antibodies
were negative. Anti-phospholipid antibody receptor was positive (Anti-PLAR2).

Kidney biopsy was postponed after delivery. The most appropriate clinical diagnosis was MGN. Immediate treatment with 60 mg/day Prednisone and 150 mg/day azathioprine (Imuran) was started. Imuran was stopped a few days later because of dermal allergic reaction and Prednisone was tapered gradually. After a few weeks, the patient developed pre-eclampsia manifested by blood pressure 150/100 mmHg in addition to headache. She was re-hospitalized and treated with intravenous furosemide and albumin, in addition to enoxaparin and aspirin. Intrauterine growth restriction with utero-placental insufficiency features was diagnosed in the foetus. At 30 weeks gestation, our patient underwent an urgent caesarean section due to deteriorating biophysical profile and Doppler indices. The baby was born in good condition, 940 grams, very growth retarded. Apgar score 1st min was 8, 5th min 8, and cord pH was 7.33, within normal range. The mother was feeling good during the puerperium and discharged in good general condition a week after delivery. The neonate was admitted to the intensive care unit for observation and was discharged home at two months of age in good condition.

Two months after delivery, because of mild proteinuria, a closed renal biopsy was performed and revealed stage II-III membranous nephropathy (MGN) with tubule-reticular inclusions in the endothelial cells.

The patient continued treatment with prednisone 60 mg daily with slow tapering after 2 months in addition to 100 mg aspirin. A percutaneous renal biopsy was performed 2 months after delivery because of persistent proteinuria of 6 gr/24 hrs. Three months after delivery her glomerular filtration rate was 120 ml/min and daily protein excretion of 800 mg/24 hrs with serum albumin of 3.5 gr/dl. A light microscope examination of the glomeruli showed diffuse thickening of the capillary basement membrane (Fig. 1A) without sclerosis and normal tubule-interstitial area (Fig. 1B). On immunofluorescence there were peripheral granular depositions of IgG, IgM, Lambda, and Kappa without deposition of IgA C3 C1Q.

Electron microscopy showed diffuse GBM thickening with intramembranous and subepithelial deposits. There was evidence of a tubular reticular structure in one endothelial cell. Staining for PLA2R was not performed because of technical problem. Based on these histological findings, a diagnosis of idiopathic MGN was made. Seum levels of PLAR2 was not performed after delivery.

**Discussion**

We report a case of nephrotic syndrome due to MGN and anti-phospholipid antibodies, with successful foetal outcomes naive to any medications, although
the presence of persistent proteinuria during the pregnancy predicts poor foetal and poor maternal outcomes [7]. Literature review also highlights the point that spontaneous remission of maternal MGN with good foetal outcome rarely happens. Mechanisms underlying spontaneous remission of MGN and successful foetal outcomes without any medication are not fully understood.

Membranous glomerulonephritis, a cause of nephrotic syndrome, is histopathologically defined by the presence of immune complexes on the extracapillary side of the glomerular basement membrane [1-2]. Most often, this condition is idiopathic as in our case. Positive anti-phospholipid antibody in plasma and the presence of tubuloreticular inclusions in the endothelium on kidney biopsy, can suggest lupus erythematosus systemicus (SLE), but not enough to do diagnosis of SLE. However, it can be secondary to a wide spectrum of aetiologies, for instance infections, tumours, autoimmune diseases, or exposure to drugs or toxic agents. The presence of persistent proteinuria during the pregnancy predicts poor foetal and maternal outcomes [4-6]. Nephrotic proteinuria presenting in the first half of pregnancy is suggestive of a primary kidney disease, rather than pre-eclampsia [1]. Diagnosing and treating pregnant women with active glomerular disease is often difficult [7-9]. However, the presence of nephrotic range proteinuria with or without hypertension in the first trimester is pathological and may be associated with underlying primary or secondary renal insult (e.g., systemic lupus erythematosus), in any case ending in poor prognosis. Although some studies have shown good neonatal outcomes in patients with nephrotic syndrome, others have demonstrated foetal loss rates ranging from 24% to 35%. Most of these losses were attributed to first trimester spontaneous miscarriages [9-11].

Managing nephrotic syndrome in pregnancy is difficult. Our patient presented with significant weight gain secondary to peripheral oedema as a result of hypoalbuminemia, and was treated with furosemide and albumin intravenerously to correct this complication. The patient's intravascular fluid status, as opposed to the severity of peripheral oedema, needs to be vigorously assessed when administering loop diuretic therapy. Many patients with a low serum albumin may have gross peripheral oedema but may have diminished intravascular volume. Aggressive diuresis may worsen the intravascular depletion, causing poor placental perfusion and increasing the risk of acute renal failure [9,10].

Adequate anticoagulation in pregnant patients with nephrotic range proteinuria is important, as renal vein thrombosis has been reported more frequently in these patients [8]. Nephrotic syndrome is associated with hypercoagulability due to increased clotting factors V, VII, and VIII, fibrinogen, and 2-antiplasmin; and depletion of factors IX and XII, antithrombin III, and plasminogen. Enoxaparin is the recommended treatment in pregnancy.

Conclusion
Although the outcome of pregnancy in our case was favourable, we are hesitant to suggest that pregnancy is universally safe in nephrotic patients with immunologically active PLA2R-associated MN. In fact, we might have predicted a worse outcome to the mother and foetus. Therefore, we recommend close attention to the immunologic course of MN in the mother, frequent assessments of the mother and foetus throughout the pregnancy, and careful monitoring of the infant in the perinatal period. The patient is under follow up in our outpatient clinic, because of the suspicion of latent SLE.

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