Membranous Nephropathy that First Presented in Pregnancy

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Abstract

A 37-year-old woman at 17 weeks of gestation who was first noted to have proteinuria and microscopic hematuria at 13 weeks of gestation was admitted to our hospital with proteinuria that progressed to nephrotic syndrome (NS). Despite the treatment with prednisolone, including methylprednisolone pulse therapy, the NS worsened. The patient underwent an elective abortion at 21 weeks of gestation, and the NS then went into partial remission. A renal biopsy revealed membranous nephropathy (MN). There was no evidence of secondary MN. This is the first reported case of subclinical idiopathic MN that first developed in pregnancy.

Key words: membranous nephropathy, pregnancy, nephrotic syndrome

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Introduction

Nephrotic proteinuria presenting in early during pregnancy is suggestive of a primary kidney diseases, rather than preeclampsia (1). Diagnosing and treating pregnant women with active glomerular disease is often difficult. An extremely rare case of membranous nephropathy (MN) that was first noted in a pregnant woman who had not shown any urinary abnormalities on previous annual periodic examinations is presented. To the best of our knowledge, no similar cases have previously been reported in the literature.

Case Report

A 37-year-old pregnant woman was admitted to our hospital in December 2010 with nephrotic syndrome (NS). The patient’s first pregnancy involved no complications. She had been in good health and was being seen in the clinic for her second pregnancy. No urinary abnormalities had been previously detected on annual periodic examinations. The patient’s first subjective symptom was edema of the legs at 13 weeks of gestation, and a health checkup conducted at that time showed proteinuria and microscopic hematuria. At 17 weeks of gestation, she was diagnosed to have NS and was referred to our hospital for further evaluation (Fig. 1).

Her body temperature was 36.0°C, her pulse rate was 74 beats per minute, and her blood pressure was 105/64 mmHg. The findings of a physical examination were normal, except for some slight limb edema. The following laboratory results were obtained: white blood cell (WBC) count, 10,900/μL; red blood cell (RBC) count, 353×10⁴/μL; hemoglobin, 11.6 g/dL; hematocrit, 34.9%; platelet count, 20.0×10⁴/μL; total protein, 5.0 g/dL; albumin, 1.9 g/dL; blood urea nitrogen (BUN), 7.1 mg/dL; creatinine (Cr), 0.51 mg/dL; total cholesterol, 394 mg/dL; triglycerides, 145 mg/dL; C-reactive protein, 0.65 mg/dL; IgG, 606 mg/dL; IgM 146 mg/dL; IgA 157 mg/dL; and IgE 42.4 U/mL. The level of liver enzymes and blood electrolytes and the results of coagulation tests were all within the normal ranges. The tests for rheumatoid factor, antinuclear antibodies and circulating immune complex (IC-C1q) were negative. The serum complement levels were within the normal ranges. A dipstick examination of the urine revealed proteinuria (3+), with a 24-hour urine protein level of 2.26 g/day. The creatinine clearance was 232.9 mL/min.

The patient was treated with corticosteroids (prednisolone, 30 mg/day); however, the proteinuria and microhematuria persisted. She was then given methylprednisolone pulse

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therapy (500 mg/day x 3 days) followed by prednisolone at a dose of 40 mg per day. Despite the administration of this therapy, the urinary protein level increased to 5.28 g/day, and the patient’s general condition worsened. On the 24th day of admission (at 21 weeks of gestation), an elective abortion was performed (Fig. 1). The fetal growth was within the normal range during pregnancy and no evidence of malformation was detected.

A percutaneous renal biopsy was performed on the 29th day of admission. A light microscopic examination of the glomeruli showed diffuse thickening of the capillary basement membrane with focal mononuclear cell infiltration in the tubulointerstitium (Fig. 2). No features of arteritis were identified. Immunofluorescence microscopy revealed significant deposits of IgG (IgG4 >> IgG2), C3, C4 and C1q along the glomerular capillary wall (Fig. 2). Electron microscopy showed mesangial matrix expansion with cell proliferation and marked subepithelial electron-dense deposits (EDDs) (Fig. 3). A few areas of paramesangial EDDs were also observed (Fig. 3). Endothelial cell expansion was evident. There was no evidence of a tubular reticular structure. Based on these findings, a diagnosis of MN was made. Because positivity for C1q is uncommonly observed in patients with idiopathic MN, further examinations to determine the cause of MN were performed. Chest, abdominal and pelvic computed tomography, Gallium scintigraphy, mammography, colonoscopy, upper endoscopy, endometrial cytotechnology and cervical cytotechnology showed no malignancies. The levels of tumor markers such as CA125, CA19-9, carcinoembryonic antigen (CEA), and sIL-2R were within normal limits. No evidence of infections such as hepatitis B or C virus, cytomegalovirus, parvovirus or syphilis was found on
was performed because her general condition deteriorated, and wash-out lesions, indicating that the renal pathology had existed for a relatively long period before the pregnancy. Several reports have indicated that MN can exist asymptomatically (5, 6). In addition, Shiiki et al. reported that 10% of patients with MN are able to achieve a complete remission without treatment (7). This evidence suggests the possibility that idiopathic MN had been subclinically present in the current case.

On the other hand, several factors, including the focal interstitial cell infiltration, mesangial expansion with cell proliferation apparent on electron microscopy and mesangial electron dense deposits with positivity for immunoglobulin and complement (C1q and C4) on immunofluorescence observed in this case in addition to the patient’s female sex and young age raised the suspicion of a diagnosis of lupus-associated MN. Histological changes on renal biopsies are detected in almost all patients with systemic lupus erythematosus (SLE), even in cases involving no clinical evidence of renal disease (8, 9), and the term ‘silent lupus nephritis (LN)’ is generally recognized to reflect a histopathological diagnosis of LN without clinical renal abnormalities (10, 11). The prevalence of silent LN type V is relatively low. Gonzalez-Crespo, et al. reported that two of their 18 cases and three of 193 cases reported in the literature involved LN type V (11). Wada et al. reported that, in their study, 25.8% of the patients with silent LN developed overt

Discussion

In the present case, a woman who had not been found to have any urinary abnormalities on annual periodic examinations developed NS during pregnancy. An elective abortion was performed because her general condition deteriorated despite steroid treatment. She was diagnosed to have MN based on the findings of a renal biopsy performed one week after the abortion. After the abortion, the NS went into partial remission, thus indicating a strong link between the pregnancy and the development of MN. In a review of 33 pregnancies in 24 women with MN, Packham et al. reported that the only predictor of a poor maternal or fetal outcome was the presence of nephrotic proteinuria during the first trimester (2). Indeed, NS is associated with the following detrimental effects on pregnancy: (i) immunosuppressive therapy for NS can cause additional maternal and fetal problems; (ii) a decreased serum albumin level is associated with low-birth-weight infants and poor fetal outcomes; and (iii) abortion may be performed considering the maternal condition if the NS does not respond to treatment.

To the best of our knowledge, evidence regarding pregnancy as a factor inducing MN has not been reported. Therefore, it is difficult to consider the renal pathology in this case as indicating de novo MN induced by pregnancy. On the other hand, the predominant deposition of the IgG4 subclass on the glomeruli was suggestive of idiopathic MN. It is well known that IgG1, IgG2, and IgG3 tend to be highly expressed in patients with lupus nephritis, whereas IgG1 and IgG4 tend to be highly expressed in patients with idiopathic MN (3, 4). In the present case electron microscopy showed a pattern of stage II-III MN with occasional washed-out lesions, indicating that the renal pathology had existed for a relatively long period before the pregnancy. Several reports have indicated that MN can exist asymptomatically (5, 6). In addition, Shiiki et al. reported that 10% of patients with MN are able to achieve a complete remission without treatment (7). This evidence suggests the possibility that idiopathic MN had been subclinically present in the current case.
LN within a follow-up period of at least 60 months (12). The renal survival rate of silent LN at 51 months is 98%, in contrast with the 60% to 86% 5-year renal survival rate observed in patients with clinical lupus nephritis (11). Although the preferred treatment for silent LN has not been clarified, in view of the superior outcomes, aggressive treatment is required only when clinical renal abnormalities manifest (11). In addition, serological abnormalities can be negative in patients with early lupus nephritis, especially in those with membranous lupus nephritis (13). Although a serological examination ruled out a diagnosis of SLE in this case, it will be important to monitor the patient’s serological status in the future. It has been reported that pregnancy-associated flares of SLE patients occur during the second trimester (42%) and in the first year after delivery (25%) (14).

MN that develops after pregnancy is often associated with gestational trophoblastic disease (GTD). GTD describes a number of gynecological tumors that originate in the trophoblast layer, including hydatidiform mole, placental site trophoblastic tumors (PSTTs), choriocarcinoma, and gestational trophoblastic neoplasm. There are several case reports documenting GTD associated with MN (15, 16) and other glomerular diseases, such as membranoproliferative glomerulonephritis (MPGN) (17, 18), focal segmental glomerulosclerosis (19), thrombotic microangiopathy (20), and pre-eclamptic glomerulopathy (21, 22). In the present case, an extensive gynecological examination revealed no GTD during pregnancy or after the abortion. In addition, no other common causes of secondary MN, including hepatitis B infection, the use of nonsteroidal anti-inflammatory drugs or malignancies other than GTD, were detected.

In conclusion, we herein reported an extremely rare case of subclinical idiopathic MN that first presented during pregnancy and was not detected during routine clinical examinations. We were unable to completely exclude the possibility of silent lupus-associated MN that might be accelerated by pregnancy and thereby become NS. The present patient therefore requires careful follow-up, particularly to monitor any future development of SLE.

The authors state that they have no Conflict of Interest (COI).

References