Glomerular Endotheliosis in a Pregnant Woman with Severe Gestational Proteinuria

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Abstract

Preeclampsia is the most common hypertensive disorder to occur during pregnancy. A healthy 38-year-old primipara presented with pretibial edema at 33 weeks of gestation followed by the development of proteinuria at 36 weeks of gestation. She had no past medical history of hypertension and was normotensive during gestation. Her proteinuria persisted after delivery, and she was also hypoalbuminemic. A renal biopsy revealed a remodeling of the glomerular basement membrane (GBM) with double contours. Some of the glomerular segments showed endothelial swelling. Immunoperoxidase staining for C4b-binding protein was positive and Protein S was weakly detected in the GBM. Electron microscopy revealed an expansion of the subendothelial zone as well as mesangial cell interposition. This case suggests that glomerular endotheliosis may therefore sometimes be present despite the absence of hypertension.

Key words: glomerular endotheliosis, preeclampsia, gestational hypertension, Protein S/C4bp complex

Introduction

Preeclampsia is the most common hypertensive disorder to occur during pregnancy, affecting 3% to 8% of all pregnancies (1). Preeclampsia refers to a syndrome that is characterized by the new onset of hypertension and proteinuria at or beyond 20 weeks of gestation in a previously normotensive woman, followed by the disappearance of the proteinuria within 12 weeks of delivery (2).

In 2002, the American College of Obstetrics and Gynecology published updated clinical criteria for the diagnosis of hypertensive disorders of pregnancy (2). This guideline classified hypertensive disorders as follows: preeclampsia, severe preeclampsia, chronic hypertension in pregnancy, gestational hypertension and chronic hypertension with superimposed preeclampsia. Accordingly, the Japan Society of Obstetrics and Gynecology changed the commonly used term “toxemia of pregnancy” to “pregnancy-induced hypertension: PIH” in 2005 (3). The main pathophysiology of PIH is thought to be hypertension due to vascular endothelial dysfunction. The concept of PIH emphasizes hypertension, while proteinuria (“gestational proteinuria”) is mentioned solely as an additional symptom. Gestational proteinuria is defined as the new onset of proteinuria without hypertension at or beyond 20 weeks gestation, followed by the disappearance of such proteinuria within 12 weeks of delivery. Gestational proteinuria is not included in the classification of PIH.

Many physiologic changes occur during pregnancy with the emergence of the placenta being the most dramatic change. The placenta is thought to secrete various vasoactive substances. Recent studies have suggested that placental dysfunction can cause hypertensive disorders and renal diseases (4). In preeclamptic women, glomerular endotheliosis is a characteristic lesion found in the renal biopsy specimens. Glomerular endotheliosis comprises endothelial cell swelling, the obliteration of the endothelial fenestrae and the encroachment of the capillary space area (5).

We herein report the findings of a case involving a normotensive pregnant woman who presented with nephrotic syndrome following delivery. Glomerular endotheliosis was
confirmed through a renal biopsy.

**Case Report**

A healthy 38-year-old primipara presented with pretibial edema at 33 weeks of gestation followed by the development of proteinuria at 36 weeks of gestation. She had no past medical history of hypertension and her blood pressure had been normal during gestation (systolic: 90-110 mmHg, diastolic: 70-80 mmHg). She delivered a 2,476-g male infant vaginally at 38 weeks of gestation. She was re-admitted to the Department of Obstetrics at our hospital on postpartum day 6 due to worsening pretibial edema. Thrombophlebitis was suspected.

The following measurements were noted during the physical examination: a body weight of 53 kg, a height of 160 cm, and a body mass index of 20.7. Her blood pressure was 120/77 mmHg, her pulse rate was 81 beats/min and her body temperature was normal. The physical examination was unremarkable except for the presence of pretibial edema.

The laboratory findings were as follows: white blood cell count, 7,200/μL; red blood cell count, 3.32×10^6/μL; hemoglobin, 11.4 g/dL; hematocrit, 33.8%; platelet count, 29.3×10^9/μL; total protein, 4.1 g/dL; total albumin, 2.1 g/dL; creatinine, 0.5 mg/dL; blood urea nitrogen, 16 mg/dL and uric acid, 2.9 mg/dL. The liver enzymes and the electrolyte levels were within normal limits. The protein S activity was 94% of normal (normal range 65-140%). The urinalysis results were as follows: pH, 7.0; specific gravity, 1.010; protein, (3+); occult blood, (3+); 100< erythrocytes/high power field (HPF) and 1-4 leukocytes/HPF. The hematuria was likely caused by the presence of lochia in the sample as dysmorphic red blood cells were not present. The 24-hour urinary protein excretion was 5.07 g/day. The proteinuria selectivity index could not be calculated because of the contamination with lochia. Thrombophlebitis was not detected by ultrasound.

Although the pretibial edema disappeared spontaneously on postpartum day 13, she was referred to our department due to persistent proteinuria and hypoalbuminemia. The clinical course is shown in Fig. 1. A renal biopsy was performed on postpartum day 17. The renal biopsy specimen revealed 24 glomeruli. Some of these glomeruli exhibited endotheliosis, which is a condition of narrowed lumen that develops when segmental areas are affected by endothelial swelling (Fig. 2a). The glomerular basement membrane showed double contours and remodeling, a condition that is often called the “string of beads” effect (Fig. 2b). There were few abnormal findings in the tubules and in the interstitial tissue. The immunofluorescence for C4 (Fig. 3a) was slight and segmental, and C4d (Fig. 3b) was strongly identified in glomerular capillary walls, although C3 (Fig. 3c) and C1q were negative. The stainings for IgG and IgA were negative but IgM was weakly detected. The immunoperoxidase staining for C4b binding protein (C4bp) (Binding Site, Birmingham, UK) (Fig. 3d) was positive for samples of the glomerular capillary walls. Protein S (DAKO, Glostrup, Germany) was also weakly detected (Fig. 3e). Electron microscopy revealed glomerular endothelial swelling and the expansion of the subendothelial zone (Fig. 4a). Mesangial cell interposition was also observed (Fig. 4b). These findings were consistent with the recovery process of preeclampsia. On postpartum day 18, the proteinuria disappeared spontaneously. On postpartum day 20, her serum total protein increased to 6.1 g/dL and her albumin increased to 3.2 g/dL, respectively. Her blood pressure at this time was 89/57 mmHg.
Figure 2. a: The glomerulus exhibited endotheliosis, which is segmental endothelial swelling that results in luminal narrowing (Hematoxylin and Eosin staining). b: The double contour and the remodeling of the glomerular basement membranes, often called a “string of beads” effect (periodic acid Schiff stain).

Figure 3. a: Immunofluorescence for C4c was slightly and segmentally identified in the glomerular capillary walls. b: C4d was strongly identified in the glomerular capillary walls. c: C3c was negative. d: Immunoperoxidase staining for C4b binding protein (C4bp) was identified in glomerular capillary walls. e: Protein S was weakly detected.
Figure 4.  a: Glomerular endothelial swelling and expansion (indicated by the arrow) and the expansion of the subendothelial zone (indicated by the arrow head) were detected.  b: Mesangial cell interposition was observed (indicated by the arrow).

Discussion

At present, hypertension is considered to be a necessary component in the definition of preeclampsia. However, placent al dysfunction that is triggered by poorly understood mechanisms, such as genetic, immunologic and environmental factors, plays an early and primary role in the development of preeclampsia. The diseased placenta, in turn, secretes a factor(s) into the maternal circulation, causing systemic endothelial cell dysfunction (4). All of the clinical features of preeclampsia can be explained as clinical responses to generalized endothelial dysfunction, and hypertension is only one of these clinical symptoms. Therefore, careful attention should be paid to the other clinical symptoms of preeclampsia such as the gestational proteinuria seen in this case.

In this case, the pathologic findings of preeclampsia were detected in the absence of hypertension. C4d, C4bp and Protein S were detected in the glomerular capillary wall whereas C1q and C3c were not detected. Joyama et al. reported that C4bp plays an important role in the inactivation of the complement complex and also functions as a Protein S carrier protein (6). The protein S/C4bp complex is important not only for the control of complement activation, but also for the coagulation cascade on the damaged endothelial cell surface. Kasuno et al. reported an autopsy case of Protein S deficiency and suggested that Protein S could act as an inhibitory factor for glomerular complement activation (7). When glomerular endothelial cell dysfunction occurs, the carbohydrate surface of the glomeruli is exposed. Therefore, the lectin pathway can be activated when mannose-binding lectin binds to the carbohydrate surface. At the same time, the protein S/C4bp complex inhibits the complement activation (6).

In this case, a renal biopsy was performed and an accurate diagnosis was obtained. Murakami et al. performed postpartum renal biopsies in 86 women with severe hypertension, severe proteinuria or both during pregnancy. Of the 12 women with gestational proteinuria without hypertension, 10 had underlying renal disease (8). Our case is consistent with the findings of another 2 cases. Stettler et al. examined 14 women with gestational proteinuria. Of the 5 women who were monitored for 10 years, 2 had renal insufficiency (9). Moreover, recent reports indicate that gestational proteinuria progresses to PIH at a high frequency (10, 11). Morikawa et al. considered the statement of ‘the outcome of women with isolated proteinuria is favorable’ to be incorrect and misleading from a prospective viewpoint (11). The most remarkable and worrisome fact is that the development of preeclampsia is a marker for an increased risk of end-stage renal disease (12, 13). The necessity and the safety of performing a renal biopsy during pregnancy have been widely debated. Strict indications for a renal biopsy have been recommended, such as sudden renal failure or a diagnosis of nephrotic syndrome prior to the final two months of pregnancy (14). Therefore, we propose that severe proteinuria with no hypertension during pregnancy is an indication for at least a postpartum renal biopsy, in order that future pregnancies and their prognoses can be well managed.

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

References


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