CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 1-2025: A 35-Year-Old Woman with Shortness of Breath and Edema in the Legs

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N Engl J Med 2025;392:186-94.
DOI: 10.1056/NEJMcpc2402498

CME

PRESENTATION OF CASE

Dr. Annie Liu (Medicine): A 35-year-old woman was admitted to this hospital because of shortness of breath and edema in the legs.

Eight weeks before the current presentation, the patient was admitted to this hospital for induction of labor at 39 weeks' gestation because of advanced maternal age and a fetus that was small for gestational age. She had begun taking low-dose aspirin at 13 weeks' gestation to decrease the risk of preeclampsia associated with antepartum obesity. She had no history of hypertension before or during pregnancy.

On admission, the blood pressure was 141/81 mm Hg, and pitting edema in the legs was present; laboratory testing was performed to evaluate for preeclampsia. The blood albumin level was 2.1 g per deciliter (reference range, 3.3 to 5.0), and the ratio of protein to creatinine in urine was 4.1 (reference value, <0.15); other laboratory test results are shown in Table 1. The patient had no headache, vision changes, or shortness of breath. Misoprostol and oxytocin were administered for induction of labor. On the third hospital day, a healthy infant was born by an uncomplicated vaginal delivery. The patient's blood pressure after delivery was 122/88 mm Hg. She was discharged home on the fifth hospital day.

After discharge, systolic blood-pressure measurements obtained at home were less than 140 mm Hg. In the 2 weeks after discharge, the patient's weight decreased by 9 kg. Six weeks before the current presentation, headache developed. The headache was nearly constant; she noted that the pain ranged from 3 to 10 on a scale of 0 to 10 (with 10 indicating the most severe pain). The pain abated with the use of ibuprofen.

Four weeks before the current presentation, the patient noted swelling in the feet and legs, along with headache. During the next week, the swelling progressed, and the weight increased by 6 kg. Systolic blood-pressure measurements remained less than 140 mm Hg. The patient was evaluated in the antepartum unit of this hospital. The blood pressure was 121/71 mm Hg, and symmetric pitting edema in the legs was present. The patient was instructed to continue taking ibuprofen for headache and was referred to the neurology clinic of this hospital for evaluation of headache.

One week before the current presentation, the patient was evaluated in the emergency department of another hospital for increased swelling in the legs. The blood urea nitrogen level was 22 mg per deciliter (7.9 mmol per liter; reference range, 6 to 20 mg per deciliter [2.1 to 7.5 mmol per liter]), the creatinine level 0.70 mg per deciliter (62 μmol per liter; reference range, 0.50 to 1.10 mg per deciliter [44 to 97 μmol per liter]), the albumin level 1.5 g per deciliter (reference range, 3.5 to 5.2), and the total protein level 4.8 g per deciliter (reference range, 5.8 to 7.7). The blood B-type natriuretic peptide (BNP) level was normal. Other laboratory test results are shown in Table 1. Ultrasonography of the legs showed no evidence of deep venous thrombosis. Treatment with oral

Table 1. Laboratory Data.*

Variable	Reference Range, Adults, This Hospital†	8 Wk before Current Presentation, This Hospital	Reference Range, Adults, Other Hospital	1 Wk before Current Presentation, Other Hospital	On Current Presentation, This Hospital
Hematocrit (%)	36.0–46.0	31.9	35.0–48.0	32.6	40.7
Hemoglobin (g/dl)	12.0–16.0	11.0	11.7–16.0	11.2	13.9
White-cell count (per μl)	4500–11,000	11,020	4000–11,000	8400	8060
Differential count (per μl)					
Neutrophils	1800–7700	—	1500–8000	2980	3550
Lymphocytes	1000–4800	—	1000–4800	4220	3460
Monocytes	200–1200	—	0–900	580	540
Eosinophils	0–900	—	0–500	590	440
Basophils	0–300	—	0–1000	40	30
Bands	0–100	—	—	—	40
Platelet count (per μl)	150,000–400,000	262,000	150,000–440,000	297,000	272,000
Sodium (mmol/liter)	135–145	134	136–145	140	137
Potassium (mmol/liter)	3.4–5.0	4.1	3.5–5.1	4.3	4.3
Chloride (mmol/liter)	98–108	104	98–107	107	104
Carbon dioxide (mmol/liter)	23–32	20	21–31	25	26
Urea nitrogen (mg/dl)	8–25	10	6–20	22	22
Creatinine (mg/dl)	0.60–1.50	0.51	0.5–1.1	0.7	0.75
Glucose (mg/dl)	70–110	101	70–99	89	84
Anion gap (mmol/liter)	3–17	10	—	—	7
Alkaline phosphatase (U/liter)	30–100	79	16–100	88	84
Alanine aminotransferase (U/liter)	7–33	17	7–30	29	28
Aspartate aminotransferase (U/liter)	9–32	22	11–30	24	32
Total bilirubin (mg/dl)	0.0–0.1	0.1	0.2–1.0	0.1	0.2
Direct bilirubin (mg/dl)	0.0–0.4	<0.2	—	—	<0.2
Total protein (g/dl)	6.0–8.3	5.1	5.8–7.7	4.8	5.3
Albumin (g/dl)	3.3–5.0	2.1	3.5–5.2	1.5	2.2
Uric acid (mg/dl)	2.2–6.6	4.2	—	—	—
International normalized ratio	0.9–1.1	—	—	—	1.1

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for uric acid to micromoles per liter, multiply by 59.48.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

furosemide was started, and the patient was discharged from the emergency department.

During the next 6 days, the weight continued to increase, swelling in the legs worsened, and dyspnea on exertion developed. The patient presented to the emergency department of this hospital for evaluation. She reported ongoing headache. The weight was 11 kg higher than her lowest weight after delivery. She had a history of obesity, with a pregravid body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 40. She also had a history of anxiety. As part of routine prenatal care, the patient had undergone testing 9 months before the current presentation, and screening tests for human immunodeficiency virus types 1 and 2, hepatitis B virus, and hepatitis C virus had been negative; blood levels of glycated hemoglobin and thyroglobulin had been normal at that time. She took furosemide, as well as ibuprofen as needed for headache. Penicillin had caused hives. The patient was married and lived with her husband. She did not drink alcohol or use illicit drugs. In the past, she had smoked tobacco occasionally, but she had quit smoking 1 year before the current presentation, in anticipation of pregnancy. There was no family history of preeclampsia.

On examination, the temporal temperature was 35.8°C, the blood pressure 142/85 mm Hg, the pulse 62 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. The BMI was 45.2. Pitting edema in the legs was present. The blood albumin level was 2.2 g per deciliter. The blood BNP level was normal. The blood thyrotropin level was 7.87 μIU per milliliter (reference range, 0.40 to 5.00), and the free thyroxine level was 0.9 ng per deciliter (12 pmol per liter; reference range, 0.9 to 1.8 ng per deciliter [12 to 23 pmol per liter]). Urinalysis was notable for 3+ protein (reference value, negative) but was otherwise normal. The ratio of protein to creatinine in urine was 5.2.

Chest radiography showed no abnormalities. Computed tomography of the chest, performed after the administration of intravenous contrast material in accordance with a pulmonary-embolism protocol, showed mild bronchial-wall thickening with scattered areas of mucous plugging. Ultrasonography of the legs was negative for deep venous thrombosis.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Jessica S. Tangren: I am aware of the final diagnosis in this case. When this 35-year-old woman was admitted for induction of labor at 39 weeks' gestation, she was found to have a urinary protein level of more than 4 g per day and hypoalbuminemia. New-onset proteinuria in pregnancy is a diagnostic challenge and has implications for both maternal and fetal health.

Pregnancy induces remarkable changes in both systemic and renal physiology.[1] Interpretation of laboratory test results obtained during pregnancy must account for the differences in expected values in pregnant adults as compared with those in nonpregnant adults, as well as the variation in expected values according to gestational age.[2] Starting as early as 6 weeks' gestation, the low-resistance placental circulation develops, leading to a decrease in the mean arterial pressure and to increases in cardiac output and blood volume. The resulting vasodilation and increased plasma flow in the kidneys leads to an increase in the glomerular filtration rate.[3] Changes in renal tubular handling of proteins, glucose, amino acids, and electrolytes occur to maintain the optimal environment for fetal development. However, despite the increased glomerular filtration rate, proteinuria in pregnancy is abnormal. In addition, although the serum albumin level decreases throughout pregnancy, the albumin level of 2.0 mg per deciliter measured in this patient in the third trimester was abnormally low.

When this patient was admitted for induction of labor, she met criteria for nephrotic syndrome — a clinical syndrome consisting of heavy proteinuria (a urinary protein level of >3.5 g per day), hypoalbuminemia, and peripheral edema. Nephrotic syndrome results from failure of the glomerular filtration barrier, which normally prevents proteins from being filtered into the urinary space. Most causes of nephrotic syndrome target podocytes. When evaluating a patient with nephrotic syndrome in pregnancy, the first step is to distinguish between pregnancy-specific conditions (preeclampsia) and new-onset glomerular diseases (Fig. 1). The correct diagnosis is crucial because management strategies for these conditions differ substantially, especially when the fetus is remote from term.

PREECLAMPSIA

Preeclampsia is a syndrome that is unique to human pregnancy. It occurs in the second half of pregnancy and is diagnosed by means of clinical criteria, which include new-onset hypertension with proteinuria or other signs of end-organ dysfunction.[4] Patients with preeclampsia are at increased risk for rapid deterioration from

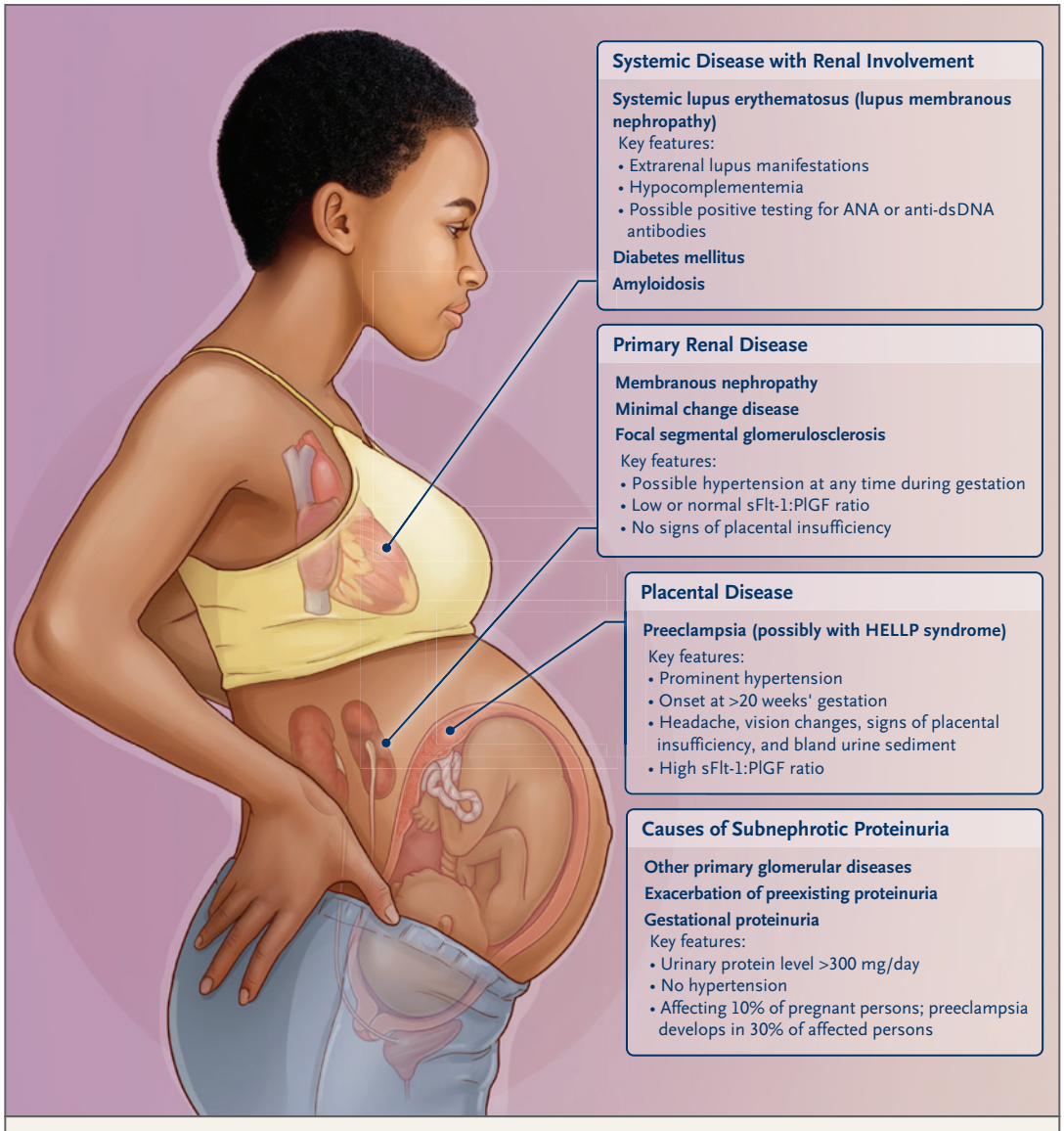

Figure 1. Proteinuria in Pregnancy.

In a pregnant person, nephrotic-range proteinuria can be caused by new-onset glomerular diseases, including renal manifestations of systemic diseases (e.g., lupus membranous nephropathy) as well as primary renal diseases (membranous nephropathy, minimal change disease, and focal segmental glomerulosclerosis). Nephrotic-range proteinuria in pregnancy can also be caused by placental disease such as preeclampsia, which may occur in the context of HELLP syndrome (characterized by hemolysis, elevated liver-enzyme levels, and low platelet counts). Subnephrotic-range proteinuria in pregnancy can result from other primary glomerular diseases: IgA nephropathy, membranoproliferative glomerulonephritis, vasculitis, thrombotic microangiopathy, acute kidney injury, and others. In addition, preexisting proteinuria can be exacerbated by gestational glomerular hyperfiltration (with an increase in the glomerular filtration rate leading to an increase in the urinary protein level), and gestational proteinuria can also develop. ANA denotes antinuclear antibodies, dsDNA double-stranded DNA, PlGF placental growth factor, and sFlt-1 soluble fms-like tyrosine kinase 1.

life-threatening obstetrical or medical complications. When preeclampsia is left untreated, it can progress to eclampsia and cause stroke, pulmonary edema, acute kidney injury, liver rupture, and seizures. The only treatment for preeclampsia is delivery of the fetus and placenta.

Preeclampsia is caused by a state of angiogenic imbalance.[5] The diseased placenta releases an excessive amount of a protein called soluble fms-like tyrosine kinase 1 (sFlt-1), a soluble vascular endothelial growth factor (VEGF) receptor. In healthy pregnant persons, proangiogenic factors such as VEGF and placental growth factor (PlGF) maintain the health of the maternal endothelium. In patients with preeclampsia, excess sFlt-1 binds to VEGF and PlGF, causing widespread endothelial dysfunction that leads to the clinical manifestations of preeclampsia. The ratio of sFlt-1 to PlGF can be directly measured in the blood of pregnant persons and has been shown to predict the onset of severe preeclampsia.[6,7] This ratio has been used as a biomarker in Europe and Canada for nearly a decade and was recently cleared by the Food and Drug Administration for use in the United States. Although it is not yet in widespread use, this biomarker can be an important tool for diagnosing preeclampsia, especially when clinical features are inconclusive and the fetus is preterm.

Does this patient have nephrotic syndrome due to preeclampsia? Preeclampsia is the most common cause of nephrotic-range proteinuria in pregnancy. In addition, the patient had evidence of placental dysfunction (a fetus that was small for gestational age) and risk factors for preeclampsia (pregravid obesity and advanced maternal age). However, she had only one mildly elevated blood-pressure measurement, whereas patients with preeclampsia typically have more sustained and severe hypertension. Because this patient presented with hypertension when she was at full term (39 weeks' gestation), she was treated as though she had preeclampsia, without additional workup for nephrotic syndrome. If she had presented with hypertension, proteinuria, or swelling earlier in pregnancy and had not proceeded to immediate delivery, obtaining levels of angiogenic markers could have been diagnostically helpful; a low ratio of sFlt-1 to PlGF would have suggested that preeclampsia was not the cause of nephrotic syndrome.

This patient's course after delivery also argues against a diagnosis of preeclampsia, which would have abated rapidly. Follow-up testing for proteinuria after delivery is not part of standard care for preeclampsia because the proteinuria resolves completely by 6 weeks postpartum in most cases.[8] When proteinuria does not resolve, it is usually in the subnephrotic range and caused by residual renal damage from severe preterm preeclampsia. This patient had persistent nephrotic-range proteinuria at 8 weeks postpartum, which makes the diagnosis of preeclampsia unlikely. I will therefore review other possible causes of nephrotic syndrome in this patient.

NEW-ONSET GLOMERULAR DISEASE

The maternal immune system must adapt to allow for coexistence of the mother and the fetus, which contains "foreign" paternal antigens.[9] High estrogen levels during pregnancy inhibit cell-mediated immune responses and increase antibody production. Pregnancy can trigger a relapse or new onset of glomerular disease in which autoantibodies target the glomerular basement membrane.

Minimal Change Disease

Minimal change disease is the most common type of nephrotic syndrome in children. In adults, the condition can be associated with the use of nonsteroidal antiinflammatory drugs (NSAIDs), can be a paraneoplastic effect of cancer, or can be seen as idiopathic.[10] Minimal change disease is diagnosed by means of kidney biopsy. The term "minimal change" refers to the normal appearance of the glomerulus on light microscopy despite the diffuse effacement of epithelial-cell foot processes on electron microscopy. The underlying cause of minimal change disease is unknown, but it is thought to involve the production of a circulating glomerular permeability factor targeting the filtration barrier that leads to podocyte foot-process effacement and proteinuria. More than 40% of patients with primary minimal change disease have circulating antinephrin autoantibodies.[11,12] Nephrin is an important component of the glomerular slit diaphragm, and antinephrin autoantibodies induce podocyte dysfunction. A further understanding of the pathogenesis of minimal change disease

may allow for noninvasive diagnostic testing and more tailored therapies in the future.

Although this patient was taking NSAIDs for headache, her nephrotic-range proteinuria preceded the use of this class of medications. In addition, the gradual onset of symptoms (over a period of weeks) is not a typical feature of minimal change disease, which usually manifests rapidly (over a period of days). Her age is also atypical for this diagnosis.

Membranous Nephropathy

Membranous nephropathy is one of the most common types of primary nephrotic syndrome in adults, occurring most commonly in older White men. The condition is diagnosed by means of kidney biopsy, which shows thickening of the glomerular basement membrane with electron-dense deposits. Primary membranous nephropathy is most commonly caused by autoantibodies directed against the phospholipase A2 receptor (PLA2R) on podocytes.[13] Multiple additional antigens have recently been identified in association with membranous nephropathy, including neural epidermal growth factor–like 1 (NELL1). Many patients with NELL1-associated membranous nephropathy have underlying cancer or have a history of use of Ayurvedic medicines, which can contain high levels of mercury.[14,15] This patient's proteinuria and disease course align with primary membranous nephropathy, but her age makes the diagnosis unlikely.

Lupus Membranous Nephropathy

Although primary membranous nephropathy is unlikely in this patient, another variant remains a possibility: lupus membranous nephropathy, also known as class V lupus nephritis. Systemic lupus erythematosus is known to occur in women of reproductive age, and a flare or new onset of disease can develop during pregnancy. Although testing for PLA2R autoantibodies is often positive in patients with primary membranous nephropathy, such testing is negative in patients with lupus membranous nephropathy.[16] This condition accounts for approximately 10% of cases of lupus nephritis. On rare occasion, affected patients present without other clinical or serologic manifestations of lupus, such that they have normal complement levels and have negative testing for anti–double-stranded DNA antibodies. Although lupus membranous nephropathy is a possibility in this patient, the absence of extrarenal manifestations of lupus makes the diagnosis unlikely overall.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is one of the most common lesions underlying idiopathic nephrotic syndrome in adults. FSGS is characterized by segmental or focal areas of mesangial collapse and sclerosis on light microscopy. Primary FSGS is distinct from secondary FSGS, which is a pathological pattern seen after nephron loss.[17] Patients with primary FSGS typically present with acute-onset nephrotic syndrome and diffuse podocyte foot-process effacement. This patient's age and disease course are consistent with new-onset primary FSGS. A kidney biopsy was the next step to confirm the diagnosis.

DR. JESSICA S. TANGREN'S DIAGNOSIS

Primary focal segmental glomerulosclerosis.

PATHOLOGICAL DISCUSSION

Dr. Veronica E. Klepeis: The portion of the kidney-biopsy specimen submitted for light microscopy consisted of two cores of cortex with 24 glomeruli, 4 of which showed changes consistent with FSGS (Fig. 2A). One of the glomeruli with FSGS contained collapsing features: there was a proliferation of extracapsular epithelial cells (pseudocrescent) surrounding areas of scarring and collapse with associated protein reabsorption droplets and without evidence of necrosis, fibrin, inflammation, or breaks in the glomerular basement membrane (Fig. 2B). Glomeruli also showed reactive podocytes and some endothelial-cell swelling. No pathologically significant increase in mesangial or intracapillary cellularity was detected.

Periodic acid–Schiff staining, which highlights basement membranes, showed focal and segmental duplication of the glomerular basement membrane (Fig. 2A). This feature is suggestive of chronic endothelial-cell injury, which can be associated with several causes, including ischemia, thrombotic microangiopathy, and

membranoproliferative glomerulonephritis. In the clinical context of recent pregnancy, this finding suggests the possibility of chronic thrombotic microangiopathy related to preeclampsia. However, there was no evidence of acute thrombotic microangiopathy (e.g., fibrin thrombi or fragmented red cells) in the kidney-biopsy specimen.

There was no pathologically significant interstitial inflammation. Proximal tubular epithelial cells showed features of heavy proteinuria, including cytoplasmic vacuolization and prominent protein reabsorption droplets (Fig. 2C). In the background, minimal-to-mild arteriosclerosis and arteriolar hyalinosis were present, with only minimal chronic parenchymal changes overall. Immunofluorescence studies performed on frozen tissue were negative for IgA, IgG, IgM, C3, C1q, fibrin, kappa, and lambda, which ruled out immune complex–deposition diseases associated with nephrotic syndrome, such as membranous nephropathy and lupus nephritis.

Electron microscopy of two glomeruli revealed diffuse and global podocyte foot-process effacement involving essentially the entire capil-

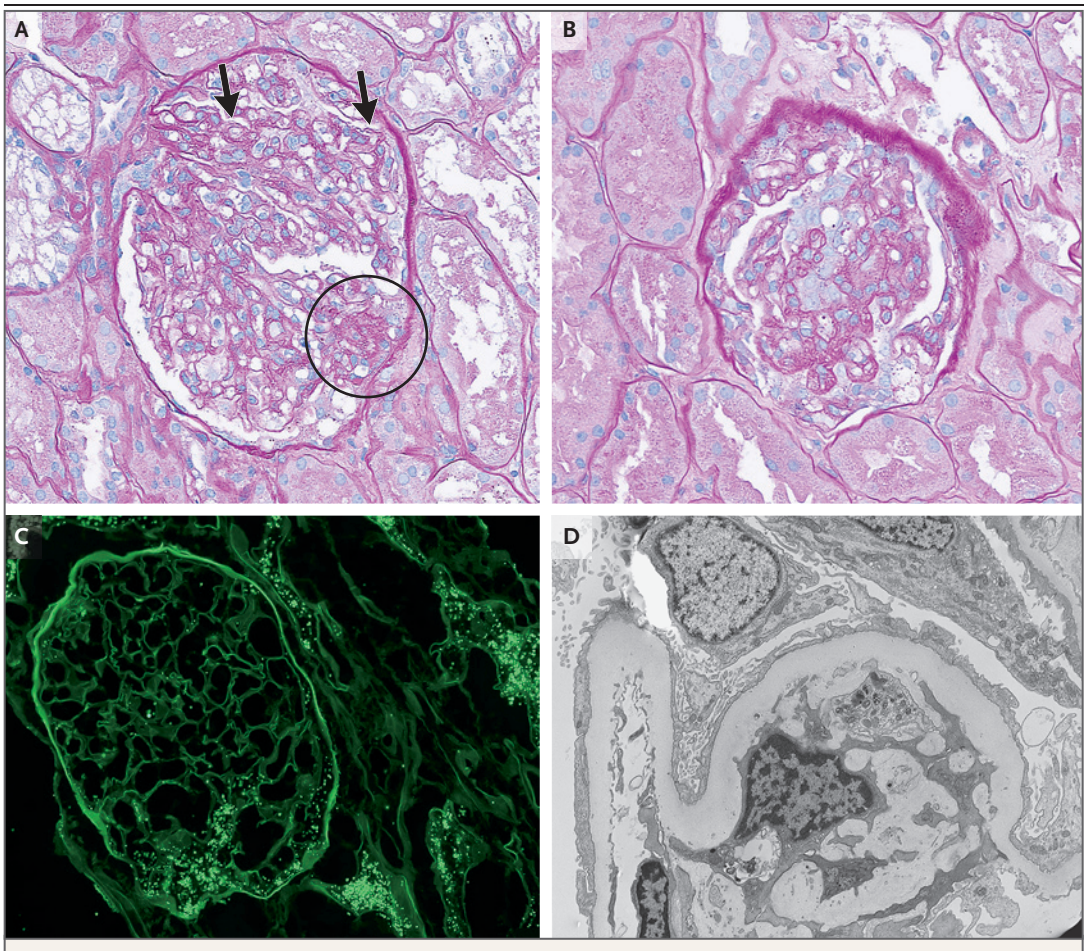

Figure 2. Kidney-Biopsy Specimen.

On periodic acid–Schiff staining, one glomerulus shows segmental scarring with adhesion to the Bowman capsule (Panel A, circle). Segmental duplication of the glomerular basement membrane is also present (Panel A, arrows). Another glomerulus shows an epithelial-cell proliferation (pseudocrescent) around areas of scarring, a feature of collapsing glomerulopathy (Panel B). An immunofluorescence study shows prominent glomerular epithelial-cell reabsorption droplets and numerous tubular epithelial-cell reabsorption droplets with staining for albumin, findings consistent with heavy proteinuria (Panel C). A representative capillary loop from electron microscopy shows extensive podocyte foot-process effacement and segmental duplication of the glomerular basement membrane (Panel D).

lary surface (Fig. 2D). In addition, occasional segmental duplication of the glomerular basement membrane was present, which is consistent with findings seen on light microscopy. Scant electron densities and hyaline deposition in areas of scarring were also present.

In summary, the kidney biopsy revealed evidence of FSGS, with one glomerulus showing features of collapsing glomerulopathy. Given the diffuse podocyte foot-process effacement, a diagnosis of primary FSGS was favored. Although the duplication of the glomerular basement membrane suggested a component of chronic thrombotic microangiopathy that was possibly related to preeclampsia, the care team thought that the patient's overall clinical course was not consistent with preeclampsia.

PATHOLOGICAL DIAGNOSIS

Postpartum nephrotic syndrome due to focal segmental glomerulosclerosis.

DISCUSSION OF MANAGEMENT

Dr. Anushya Jeyabalan: It is important to note that FSGS is a histopathological pattern of injury observed on kidney biopsy, rather than a specific disease entity. There are four general categories: primary FSGS (presumed to be related to permeability factor), secondary FSGS, genetic FSGS, and FSGS of undetermined cause.[18] In this patient, given the course of nephrotic syndrome, the diffuse and global podocyte foot-process effacement seen on biopsy, and the absence of a clear inciting cause of secondary FSGS (e.g., drugs or viral infection), a diagnosis of primary FSGS was made.

The treatment of patients with primary FSGS who present with nephrotic syndrome is centered on immunosuppression, with high-dose glucocorticoids used as the first line of therapy.[18] In all patients with any form of FSGS, proteinuria reduction with renin–angiotensin–aldosterone system blockade, blood-pressure control, and dietary salt restriction is also important.

The goal of treatment is remission of proteinuria. Complete remission is defined by a urinary protein level of less than 0.3 g per day (300 mg per day), a stable serum creatinine level, and a serum albumin level of more than 3.5 g per deciliter. Patients who are in partial or complete remission have a much lower risk of progression to end-stage kidney disease than patients with persistent nephrotic syndrome.[19]

This patient received high-dose prednisone therapy daily for 2 weeks followed by a tapering prednisone course, along with prophylactic trimethoprim–sulfamethoxazole, omeprazole, and calcium with vitamin D supplementation. After 4 weeks of prednisone therapy, she was in partial remission; her urinary protein level had decreased from 6.2 g per day to 2.7 g per day, and her serum albumin level had increased from 2.4 g per deciliter to 3.3 g per deciliter.

Approximately 8 weeks into the tapering prednisone course, the patient had a relapse of nephrotic syndrome, with an increase in leg edema, a weight gain of 7 kg, and a urinary protein level of 4.3 g per day. She also reported numerous side effects of prednisone therapy, including insomnia, anxiety, and fatigue, in addition to weight gain.

More than 50% of patients with FSGS who are in partial remission can have a relapse of disease.[19] Because this patient's relapse occurred while she was receiving a tapering prednisone course, she was considered to have glucocorticoid-dependent disease. Given that side effects had developed, resuming high-dose prednisone therapy was not ideal for her. There is a lack of consensus regarding the next best line of treatment for patients with glucocorticoid-dependent FSGS. Rituximab, an anti-CD20 monoclonal antibody, has been shown to have efficacy in the treatment of patients with glucocorticoid-dependent FSGS.[20-22] Other options include calcineurin inhibitors, mycophenolate mofetil, and cyclophosphamide.[18]

After we discussed the treatment options with the patient, we elected to add a short course of low-dose oral cyclophosphamide therapy (administered for 2 months) and two doses of rituximab (separated by 2 weeks) followed by rituximab infusions every 4 months, with the goal of continuous B-cell depletion. The patient also received high-dose prednisone therapy again for 1 week followed by a tapering prednisone course over a period of 6 months with close monitoring for side effects. Approximately 6 weeks into this treatment course, she was again in partial remission. The urinary protein level had decreased to 1.4 g

per day, the serum albumin level had normalized, and the leg edema had resolved.

At the patient's most recent follow-up visit, she had completed 2 years of rituximab therapy and had not received additional glucocorticoid therapy. She remained in partial remission, with a urinary protein level of 1.2 g per day and normal kidney function.

FINAL DIAGNOSIS

Postpartum nephrotic syndrome due to focal segmental glomerulosclerosis.

This case was presented at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Eugene Rhee for review of the case history.

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