CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 17-2018: A 40-Year-Old Woman with Leg Swelling and Abdominal Distention and Pain

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PRESENTATION OF CASE

Dr. Molly E. Wolf (Medicine): A 40-year-old woman was evaluated at this hospital because of progressive edema of the legs, as well as abdominal distention and pain.

The patient had been in good health until approximately 10 months before this evaluation, when episodes of pain and swelling developed in the feet and ankles. Initially, the episodes occurred during the evening, after prolonged standing during the day. During subsequent months, the episodes became more frequent and began to occur earlier in the day. The swelling progressed to involve the lower legs and thighs. The patient was evaluated by her primary care physician, and compression stockings were recommended.

Five months before this evaluation, pain developed in the back and flank on the left side, and the patient was evaluated in the emergency department of another hospital. A provisional diagnosis of musculoskeletal pain was made, and benzodiazepines and muscle relaxants were prescribed.

Despite the administration of these medications, the back and flank pain persisted, and the patient was evaluated in the emergency department of a second hospital. The weight was 82 kg. The platelet count, results of kidney-function tests, and blood levels of hemoglobin, electrolytes, and glucose were normal. Tests were negative for hepatitis C virus antibody and for hepatitis B virus surface antigen and surface antibody. The blood albumin level was 1.9 g per deciliter (reference range, 4.0 to 5.0), and the white-cell count was 12,500 per cubic millimeter (reference range, 4500 to 11,000), with a normal differential count. The D-dimer level was more than 20 μg per milliliter (reference range, 0.27 to 20). An imaging study of the chest was scheduled, and nitrofurantoin was prescribed for a suspected urinary tract infection.

Dr. Midhir J. Patel: The next day, computed tomographic (CT) angiography of the chest revealed findings consistent with a calcified granuloma (measuring 3 mm in

diameter) in the right upper lobe and multiple pulmonary emboli involving the main, lobar, segmental, and subsegmental pulmonary arteries bilaterally.

Dr. Wolf: Anticoagulation with low-molecular-weight heparin was administered, and the patient was admitted to the second hospital. Over a period of 3 days, the anticoagulation regimen was transitioned to apixaban, and the back and flank pain diminished. The patient was discharged home with prescriptions for apixaban and nitrofurantoin. The pulmonary emboli were considered to be unprovoked, and evaluation by a hematologist was recommended.

While the patient was receiving anticoagulation, she had persistent leg swelling, but the back and flank pain did not recur. Evaluation by a hematologist did not reveal an underlying cause of the pulmonary embolism, and anticoagulation of indefinite duration was advised.

Four weeks before this evaluation, the swelling of the legs worsened and abdominal distention developed. Intermittent swelling of the hands occurred, as did swelling around the eyes in the morning upon awakening. The patient had a consultation with a vascular specialist, but no primary venous disease of the legs was identified.

The abdominal distention worsened, and 1 week before this evaluation, diffuse, crampy abdominal pain with nausea developed. The abdominal pain waxed and waned for several days but worsened on the day of this evaluation. The patient also had dyspnea, and she presented to the emergency department of the second hospital, where additional imaging studies were obtained.

Dr. Patel: CT of the chest, abdomen, and pelvis, performed after the administration of intravenous contrast material, revealed a nonocclusive thrombus in the right renal vein. Wall thickening of the gastric antrum and proximal small bowel, multiple enlarged mesenteric lymph nodes, mild mesenteric edema, and evidence of small-volume ascites were also noted (Fig. 1).

Dr. Wolf: On the basis of the results of these imaging studies, the patient sought evaluation in the emergency department of this hospital. She reported ongoing abdominal pain, nausea, and loose stools. She noted an unintentional weight gain of 10 kg since the leg swelling had begun 10 months previously, despite no change in appetite or food intake. She also reported increases in urinary frequency and sensation of thirst. She had no chest pain, hematuria, hemoptysis, dark stools, night sweats, fatigue, joint symptoms, or eye or ear symptoms.

The patient, who was black, had a medical history that was notable for hypothyroidism, latent tuberculosis with a previous negative chest radiograph, two spontaneous vaginal deliveries, and ectopic pregnancy. She had undergone an ovary-sparing abdominal hysterectomy for fibroid uterus and an appendectomy. Medications included levothyroxine and apixaban. There had been no adverse reactions to medications. She did not use nonsteroidal antiinflammatory drugs. The patient had grown up on a Caribbean island and had immigrated to the United States when she was 19 years of age. She worked as an assistant in a health care facility and lived with her husband and two healthy children. There was no history of alcohol, tobacco, or illicit-drug use. There was no family history of renal, thromboembolic, or autoimmune disease.

On examination, the temperature was 36.8°C, the pulse 76 beats per minute, the blood pressure 131/70 mm Hg, the respiratory rate 20 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The weight was 88.5 kg, the height 173 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 29.7. There was 2+ edema of the lower and upper legs. The jugular venous pressure was 8 cm of water. There was no periorbital or hand edema. The abdomen was distended and mildly, diffusely tender, with well-healed surgical scars. The remainder of the examination was normal.

Blood levels of globulin, phosphorus, magnesium, lipase, lactic acid, bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase were normal, as were the prothrombin time and partial-thromboplastin time. Urinalysis was negative for glucose, bilirubin, ketones, nitrite, and leukocyte esterase. Tests were negative for anti–double-stranded DNA, rheumatoid factor antibody, human immunodeficiency virus (HIV) antibody, antitreponemal antibody, and hepatitis C virus antibody, as well as for hepatitis B virus surface antibody, surface antigen, and core antibody. The serum protein electrophoresis pattern was normal, except for a

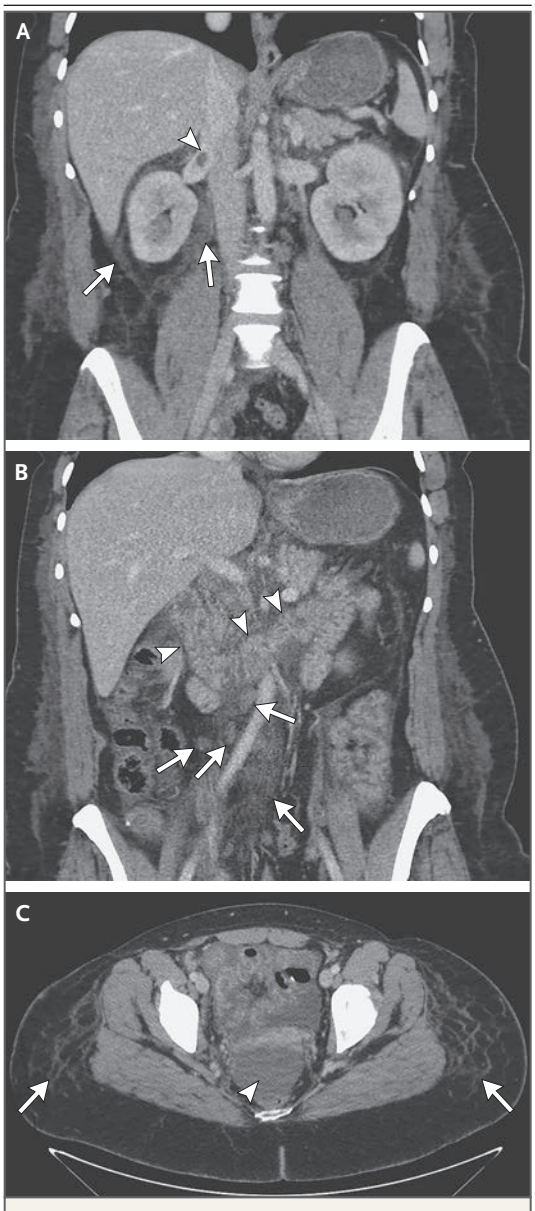

Figure 1. CT Scan of the Abdomen and Pelvis.

A contrast-enhanced CT scan was obtained at the second hospital. A coronal reconstruction image (Panel A) shows a filling defect in the right renal vein near the confluence with the inferior vena cava, a finding consistent with a nonocclusive thrombus (arrowhead), as well as mild perinephric fat stranding on the right side, a finding suggestive of edema (arrows). An image obtained on a different coronal plane (Panel B) shows wall thickening of the proximal small bowel and mild surrounding edema (arrowheads), as well as multiple enlarged mesenteric lymph nodes and mesenteric edema extending into the lower abdomen (arrows). An axial image (Panel C) shows findings consistent with small-volume ascites in the pelvis (arrowhead) and mild, symmetric soft-tissue edema bilaterally (arrows).

diffuse decrease in gamma globulin. Other laboratory test results are shown in Table 1. An electrocardiogram was normal, and ultrasonography of the kidneys revealed normal kidney size and echotexture.

Diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Charles A. Morris: This 40-year-old woman presented with progressively worsening peripheral edema and venous thrombosis. An examination was notable for the absence of hypertension and the presence of anasarca, and she had a normal blood creatinine level with marked hypoalbuminemia. Although the degree of urinary protein loss was not formally quantified, the features of her clinical presentation and the results of urinalysis strongly suggest that she had nephrotic-range proteinuria. There are several ways to approach the differential diagnosis in this case, and either the proteinuria or the thrombophilia could be a point of departure. However, I think the most judicious pathway forward is to consider the two findings in parallel, which should increase the chance of arriving at the correct diagnosis.

HYPERCOAGULABLE STATES

This patient had pulmonary thromboembolism, which was confirmed on imaging studies, and subsequent evidence of a renal-vein thrombosis. It is possible that the renal-vein thrombosis had been present earlier in her disease course and was only appreciated on the cross-sectional imaging studies that were performed later in the course. However, the acute abdominal pain suggests a second thrombotic episode, which, in the context of systemic anticoagulation, points toward a hypercoagulable state rather than an unprovoked thromboembolic event. A hypercoagulable state is usually categorized according to whether it has an inherited or an acquired cause, but in a proportion of patients with venous thromboembolism, multiple causes and risk factors can be identified.[1] In this patient, the young age and recurrent events would raise the possibility of an inherited disorder,[2] but she had no known family history of thrombophilia and an evaluation for underlying causes of venous thromboembolism was reportedly negative. On the basis of the features of this patient's presentation and the absence of a known inherited disorder, it is

likely that she had an acquired prothrombotic state.

ACQUIRED PROTHROMBOTIC STATES

Numerous risk factors have been implicated as causal factors in acquired thrombophilias. Underlying cancers (including genitourinary, gastrointestinal, pulmonary, and breast adenocarcinomas) and myeloproliferative disorders are well-described risk factors, but this patient did not have evidence of an occult neoplasm.[3,4] Administration of exogenous estrogen increases the risk of venous thromboembolism, but this patient did not have a history of use of exogenous estrogen.[5] The postoperative state and immobilization independent of surgery are each associated with an elevated risk of venous thromboembolism[6]; it is plausible that this patient's marked weight gain and leg symptoms impeded her functional status, and this may have been a risk factor for the initial venous thromboembolism, assuming that the thrombosis had originated in the veins of the leg.

The antiphospholipid syndrome is an important acquired cause of thrombophilia and warrants consideration in this case, given the suspected recurrent thrombotic episode. The antiphospholipid syndrome can be associated with arterial and venous thrombotic events and has been associated with renal-vein thrombosis.[7] However, this patient had no history of obstetrical complications, thrombosis in an arterial distribution, evidence of underlying systemic lupus erythematosus (which is often associated with the antiphospholipid syndrome), or a positive antibody test for the antiphospholipid syndrome (it is reasonable to think this test may have been included in her previous hematologic evaluation, which was negative).

Could the anatomical location of the thrombus provide a clue to the cause of this patient's underlying disorder? A thrombus in the splanchnic circulation would prompt consideration of a myeloproliferative disorder associated with a Janus kinase 2 (*JAK2*) mutation or paroxysmal nocturnal hemoglobinuria.[8,9] This patient had renal-vein thrombosis, which has been described among patients with the nephrotic syndrome.[10] The nephrotic syndrome is most likely the major risk factor for this patient and would unify her clinical presentation, laboratory findings, and renal-vein involvement.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Evaluation, This Hospital
Blood		
Hemoglobin (g/dl)	12.0–16.0	12.4
Hematocrit (%)	36.0–46.0	37.5
White-cell count (per mm^3)	4500–11,000	5920
Platelet count (per mm^3)	150,000–400,000	295,000
Sodium (mmol/liter)	135–145	138
Potassium (mmol/liter)	3.4–5.0	3.9
Chloride (mmol/liter)	98–108	102
Carbon dioxide (mmol/liter)	23–32	30
Urea nitrogen (mg/dl)	8–25	14
Creatinine (mg/dl)	0.60–1.50	0.95
Glucose (mg/dl)	70–110	86
Calcium (mg/dl)	8.5–10.5	7.0
Total protein (g/dl)	6.0–8.3	4.3
Albumin (g/dl)	3.3–5.0	1.4
Glycated hemoglobin (%)	4.3–6.4	5.2
Thyrotropin (μIU/ml)	0.4–5.0	8.8
Free thyroxine (ng/dl)	0.9–1.8	0.7
Antinuclear antibodies	Negative at 1:40 and 1:160	Positive at 1:40, with a speckled pattern; negative at 1:80
Urine		
Clarity	Clear	Slightly cloudy
Blood	Negative	1+
pH	5.0–9.0	5.0
Specific gravity	1.010–1.035	1.025
Protein	Negative	3+

* 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 calcium to millimoles per liter, multiply by 0.250. To convert the values for free thyroxine to picomoles per liter, multiply by 12.87.

† 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.

NEPHROTIC SYNDROME

It is possible for a patient with the nephrotic syndrome to have a normal blood albumin level. However, it is unlikely that this patient, who had a blood albumin level of 1.4 g per deciliter, would have had a urinary protein loss of less than 3.5 g per day, assuming that the protein

loss was not extrarenal. Therefore, I will assume that this patient had marked proteinuria, which was almost certainly in the nephrotic range (>3.5 g per day), since she had severe hypoalbuminemia, edema, and 3+ proteinuria on urinary dipstick testing. The differential diagnosis for the nephrotic syndrome can focus either on the underlying lesion identified on histopathological examination or on whether the patient has a systemic or a primary renal disorder. In this case, there was little evidence of a systemic process such as diabetes (i.e., there were normal blood glucose and glycated hemoglobin levels) or systemic lupus erythematosus (i.e., there was a weakly positive antinuclear-antibody titer and a negative test for anti–double-stranded DNA). HIV may cause a secondary or collapsing focal segmental glomerulosclerosis; however, a test for HIV was reportedly negative. In the absence of an underlying systemic disorder, I will consider the typical clinical features of the most common renal disorders, which account for approximately 70% of cases of the nephrotic syndrome.

MINIMAL CHANGE DISEASE

Minimal change disease is the most common cause of the nephrotic syndrome in pediatric populations and also occurs in adults.[11] It can be either primary or due to medication use (e.g., the use of beta-lactam antibiotics, bisphosphonates, or sulfasalazine), an underlying disorder (e.g., Hodgkin's disease), or an infection (e.g., syphilis, tuberculosis, or a tickborne disease, such as ehrlichiosis or borreliosis).[12,13] In this case, testing for syphilis was negative. The patient had some evidence of systemic lymphadenopathy, but the appearance on imaging studies was more consistent with small, reactive lymph nodes in the mesentery than with the lymphomatous involvement that is characteristic of Hodgkin's disease. Her history of latent tuberculosis, although intriguing, is most likely irrelevant, since her presentation is not consistent with active tuberculosis. Of note, the patient did not have the typical clinical features of minimal change disease, including a rapidly progressive presentation with the development of edema and proteinuria over a period of weeks; instead, she had a more protracted course over a period of 10 months.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Nearly 30% of cases of the nephrotic syndrome in the United States are due to focal segmental glomerulosclerosis. The prevalence of this lesion is rising among black patients who present with the nephrotic syndrome and end-stage renal disease.[14] Secondary focal segmental glomerulosclerosis can be caused by HIV infection, obesity, and reflux nephropathy, conditions that are not consistent with this patient's presentation. Primary focal segmental glomerulosclerosis would be a consideration in any patient with the nephrotic syndrome of unknown cause, particularly in the presence of hypertension, hematuria, and a decreased glomerular filtration rate. It is intriguing that this patient was considered to have a urinary tract infection on presentation to the second hospital; although the results of the urinalysis performed at that time are not available, there is the possibility of a misinterpretation of the cellular urinary sediment. Nevertheless, the normal blood pressure and blood creatinine level make focal segmental glomerulosclerosis unlikely.

OTHER RENAL DISORDERS

Patients with membranoproliferative glomerulonephritis and other causes of glomerulonephritis (e.g., postinfectious glomerulonephritis and IgA nephropathy) may present with the nephrotic syndrome, although they typically have active urinary sediment with red cells, casts, and occasional pyuria, findings that reflect an underlying glomerular inflammatory process. In this case, the reported history of a urinary tract infection and 1+ blood on urinalysis suggests the possibility of a nephritic lesion. However, there is no other evidence to support this possibility, such as an appropriate clinical history, the presence of renal insufficiency, or laboratory test results suggestive of the most common causes. Amyloidosis has been recognized as a cause of the nephrotic syndrome in approximately 15% of cases in adults. Both AL amyloidosis (in which monoclonal light chains lead to the accumulation of amyloid fibrils)[15] and AA amyloidosis have been reported. In AA amyloidosis, the deposition of amyloid fibrils may lead to both infectious and autoimmune systemic inflammatory states, with rheumatoid arthritis being the most common.[16]

MEMBRANOUS NEPHROPATHY

In the United States, nearly one third of cases of the nephrotic syndrome can be ascribed to membranous nephropathy. In 25% of cases of membranous nephropathy, the disease is due to an underlying cause such as medication use or a systemic disorder (e.g., hepatitis B virus or hepatitis C virus infection, syphilis, thyroiditis, or cancer).[17,18] The remaining cases are considered to be primary and of an unknown cause. Primary and secondary membranous nephropathy are indistinguishable on clinical grounds; they are both characterized by a gradual progression to the nephrotic syndrome over a period of months, often with preserved renal function and normal blood pressure. Some patients may have microscopic hematuria.

Differentiating primary and secondary membranous nephropathy has historically been possible only on histopathological grounds. Primary membranous nephropathy is characterized by the presence of IgG4-predominant subepithelial deposits. The M-type phospholipase A_2 receptor (PLA_2R), which is a transmembrane receptor that is expressed in podocytes, has been identified as a major antigen in approximately 70% of cases of primary (idiopathic) membranous nephropathy.[19] The presence of this receptor is highly specific for primary membranous nephropathy because it is absent in patients with secondary cases and in those with other causes of the nephrotic syndrome. Testing for anti-PLA_2R antibodies may be performed in any patient in whom a diagnosis of membranous nephropathy is considered, particularly if there are increased risks (e.g., anticoagulation) associated with performing a renal biopsy in the patient.

NEPHROTIC SYNDROME AND VENOUS THROMBOPHILIA

This patient's recurrent venous thrombosis suggests a hypercoagulable state. In the absence of an identified heritable defect, the hypercoagulable state is almost certainly due to an acquired defect. The location of the thrombus in the renal vein suggests that the nephrotic syndrome is the primary risk factor. Despite speculation that renal-vein thrombosis might cause the development of proteinuria, more recent evidence suggests otherwise.[20] Several different mechanisms through which the nephrotic syndrome increases the risk of thrombosis have been elucidated, including increased urinary loss of antithrombotic proteins such as antithrombin III and increased synthesis of prothrombotic factors such as factor V and factor VIII.[21]

Among patients with the nephrotic syndrome, the severity of hypoalbuminemia is associated with the risk of venous thromboembolism. One study showed that, in a comparison of patients with a blood albumin level of less than 2 g per deciliter and patients with a blood albumin level of at least 3 g per deciliter, the odds ratio for venous thromboembolism was more than 3.5.[22] As compared with other causes of the nephrotic syndrome, membranous nephropathy has been associated with a particularly high risk of thrombophilia, even in a study that controlled for the severity of proteinuria.[23]

If I consider this patient's clinical presentation to represent simultaneous thrombophilia and subacute proteinuria, both diagnostic paths lead to a diagnosis of primary membranous nephropathy, with a high likelihood of detectable anti-PLA_2R antibodies. A renal biopsy would most likely confirm this diagnosis but would be a somewhat risky procedure, given that the patient was receiving systemic anticoagulation and would be at an increased risk of the development of additional thrombi on discontinuation of therapy. Therefore, to make the diagnosis of membranous nephropathy, I would recommend serologic testing for anti-PLA_2R antibodies as the next step in her evaluation.

Dr. David M. Dudzinski (Medicine): Dr. Fenves, what was your clinical impression when you initially evaluated this patient?

Dr. Andrew Z. Fenves: The patient had a 10-month history of leg edema and had pain in the left flank, hypoalbuminemia, pulmonary emboli, ascites, and renal-vein thrombosis. All these features of her presentation pointed to a diagnosis of the nephrotic syndrome with a hypercoagulable state. This clinical entity usually occurs in the presence of primary glomerulonephritis. Our differential diagnosis included membranous nephropathy, minimal change disease, and membranoproliferative glomerulonephritis, with membranous nephropathy being the most likely diagnosis.

The patient had already had complications from the hypercoagulable state and was receiv-

ing anticoagulation. Stopping anticoagulation in this context was considered to be unsafe, and thus a renal biopsy was not pursued. We recommended obtaining titers of anti-PLA_2R antibodies.

CLINICAL DIAGNOSIS

The nephrotic syndrome with a hypercoagulable state, complicated by pulmonary emboli and renal-vein thrombosis.

DR. CHARLES A. MORRIS'S DIAGNOSIS

Primary membranous nephropathy, complicated by thromboembolic disease.

PATHOLOGICAL DISCUSSION

Dr. Ricard Masia: Serologic testing for circulating anti-PLA_2R antibodies was performed by means of an indirect immunofluorescence assay and an enzyme-linked immunosorbent assay (ELISA). For the indirect immunofluorescence assay, cultured HEK293 cells were transfected with a plasmid encoding human recombinant PLA_2R, and the patient's blood was applied to the cultured cells. Bound anti-PLA_2R antibodies were detected with the use of a secondary fluorescein isothiocyanate–conjugated anti–human IgG antibody, which yielded bright green fluorescence staining of the HEK293 cells in a membranous pattern (Fig. 2A). A control sample of untransfected HEK293 cells yielded no fluorescence staining. The ELISA, in which purified human recombinant PLA_2R was used as substrate, was also positive, at an anti-PLA_2R antibody titer of 424.5 relative units (RU) per milliliter (negative result, <14; borderline result, 14 to 20; positive result, >20). These results indicate the presence of circulating anti-PLA_2R antibodies at high titers. In the clinical context of the nephrotic syndrome, they are diagnostic of membranous nephropathy, PLA_2R type.

Serologic testing for anti-PLA_2R antibodies has become a key component of the diagnostic workup for membranous nephropathy because of its noninvasive nature and very high specificity (99%).[24] A positive serologic test may obviate the need for a kidney biopsy in many patients. The sensitivity of serologic testing for anti-PLA_2R antibodies (78%)[24] is not sufficiently high for a negative test to completely rule out the diagnosis of membranous nephropathy, PLA_2R type. Thus, a kidney biopsy with colocalization studies for PLA_2R within the deposits by means of direct immunofluorescence assay may be necessary when clinical suspicion remains high after negative serologic testing.

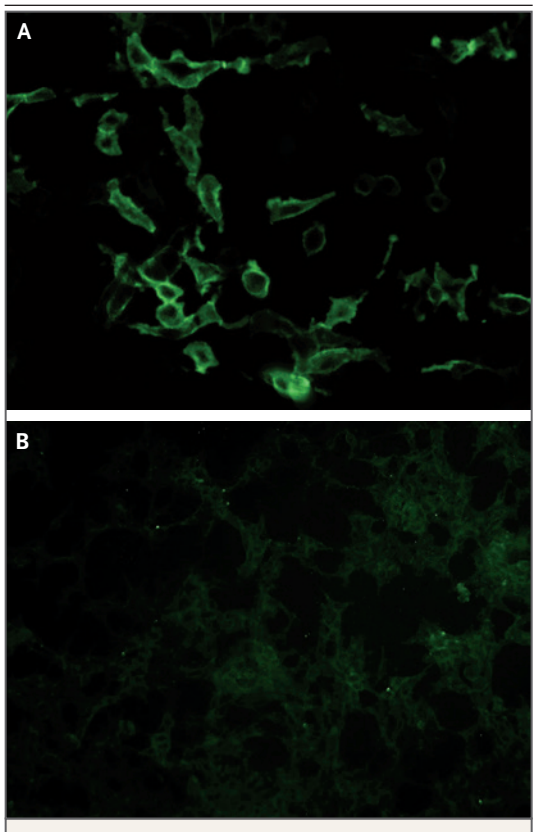

Figure 2. Blood Specimens.
An indirect immunofluorescence assay, performed with cultured HEK293 cells expressing human recombinant M-type phospholipase A_2 receptor (PLA_2R), is positive for circulating anti-PLA_2R antibodies (Panel A). The cells show bright green fluorescence staining in a membranous pattern, which is due to the binding of a fluorescent secondary antibody (fluorescein isothiocyanate–conjugated anti–human IgG antibody) to the anti-PLA_2R antibodies. A repeat assay performed 7 months after the initial evaluation is negative (Panel B).

DISCUSSION OF MANAGEMENT

Dr. Fenves: On the basis of the natural history of membranous nephropathy, approximately one

third of patients have spontaneous remission in the absence of specific therapy, another third remain nephrotic with stable renal function, and the remaining third have progressive renal failure. Therapeutic decisions should be based on certain clinical characteristics that help to predict the group in which the patient will be included. Favorable prognostic features include female sex, white race, normal blood pressure and renal function, an age of 30 to 50 years, and proteinuria with a urinary protein loss of less than 10 g per day, as well as an absence of fibrosis on renal biopsy, when such results are available. Unfavorable features include male sex, black race, the presence of hypertension, abnormal renal function, an age older than 50 years, and proteinuria with a urinary protein loss of more than 10 g per day, as well as the presence of fibrosis on renal biopsy. Immunosuppressive therapy is often used in patients with unfavorable characteristics.

When treating patients who have membranous nephropathy, clinicians weigh the risks and benefits of each treatment method, given the variety of outcomes associated with this condition. There is a strong consensus supporting the administration of lipid-lowering agents, particularly statins, when hyperlipidemia is present; this patient had a triglyceride level of 344 mg per deciliter (3.88 mmol per liter; reference range, 40 to 150 mg per deciliter [0.45 to 1.69 mmol per liter]) and a low-density lipoprotein level of 324 mg per deciliter (8.37 mmol per liter; reference range, 50 to 129 mg per deciliter [1.29 to 3.34 mmol per liter]). Anticoagulation is administered to patients who have definite evidence of thromboembolic disease or to those who have severe hypoalbuminemia, since they have a particularly high risk of the development of venous thrombi. The use of angiotensin-converting–enzyme inhibitors is also accepted widely, since it usually decreases the severity of proteinuria. Diuretics are commonly administered to help with the edema, but they are used with caution, since they are associated with an increased occurrence of acute kidney injury.

The administration of immunosuppressive therapy in patients who are deemed to be at high risk for declining renal function is standard, but the choice of medication or combination of drugs and the dosing schedule are highly variable. Therapy is often guided by the clinical response to treatment, as assessed by changes in edema, proteinuria, or renal function. Because the level of circulating anti-PLA_2R antibodies correlates with disease activity, serial measurement of the anti-PLA_2R antibody level may be used to monitor response to treatment.[25]

In this patient, therapy with atorvastatin, losartan, and furosemide was initiated. In addition, she received a slowly tapered course of prednisone, over a period of 6 weeks. Daily treatment with cyclophosphamide was administered; after 8 weeks, cyclophosphamide was transitioned to daily azathioprine. The patient's edema diminished, and her blood pressure and renal function remained stable.

Dr. Masia: Repeat serologic testing was performed 5 months and 7 months after presentation. Indirect immunofluorescence assays were negative (Fig. 2B), as were ELISAs (anti-PLA_2R antibody titer, <2 RU per milliliter). These findings indicated clearance of the anti-PLA_2R antibodies after treatment.

Dr. Fenves: Our long-term plan was to administer rituximab to this patient at a later point, but for insurance reasons, she transferred her care to a different provider and was lost to our follow-up.

FINAL DIAGNOSIS

Membranous nephropathy, PLA_2R type.

This case was presented at the Comprehensive 2017 Primary Care Update, directed by John D. Goodson, M.D.

No potential conflict of interest relevant to this article was reported.

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

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