The Nephrotic Syndrome

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Cover Illustration by Andrew Grivas
The glomerulus with its intricate network of delicate capillary loops is one of the most elegant structures in the human body. When the glomerulus is damaged by disease, a range of disparate effects can occur, including pathologic clotting of the blood, an increase in cholesterol and other lipid molecules to abnormally high levels, hypertension, and ultimately, uremia and certain death without dialysis or transplantation. Interestingly, many seemingly different disease processes and environmental stressors cause glomerular pathology. These include malignancies of many types (liquid tumors such as leukemia and solid tumors such as those of the lung [paraneoplastic syndrome]), infections (group A Streptococcus, leprosy, syphilis, HIV, malaria, and Schistosomiasis [parainfectious syndrome]), inflammatory conditions (ranging from systemic lupus erythematosus to an idiosyncratic reaction to a bee sting [parainflammatory syndrome]), medications (from commonly used over-the-counter nonsteroidal anti-inflammatory drugs to seldom used immunomodulators such as gold and penicillamine), and lastly diseases that do not fall neatly into these categories, such as diabetes mellitus, obstructive sleep apnea, and primary systemic amyloidosis. The endocrine-inflammatory, hormone-cytokine milieu induced by these various disease processes appears to have a common final pathway: glomerular damage accompanied by degrees of cellular inflammation. Such damage results in loss of albumin and other small protein molecules through the normally highly size- and charge-selective structure of the capillary loops, and this loss of proteins along with other events, some rooted in altered transcription at the genomic level, ultimately cause the sequelae known as the nephrotic syndrome.

OVERVIEW OF CLINICAL SEQUELAE

The nephrotic syndrome is associated with the classical clinical quartet of (1) albuminuria in excess of 3 to 3.5 g daily, (2) hypoalbuminemia with serum levels less than 3 g/dL, (3) peripheral edema, and (4) hyperlipidemia, most commonly hypercholesterolemia and less often hypertriglyceridemia. The hypoalbuminemia is predominantly due to the heavy albuminuria, which can range from a few grams to 20 g/day. Hepatic synthesis of albumin is appropriately increased in response to urinary loss. What is intriguing is that the liver can produce up to 25 g of albumin per day, far greater than the amount lost in the urine, yet serum albumin levels often remain low in patients with the nephrotic syndrome. It is likely that inflammatory cytokines (eg, interleukin-1) that are present in many disease states that induce the nephrotic syndrome concomitantly reduce hepatic albumin synthesis, causing the serum concentration to fall.1

The peripheral edema is believed to result from a combination of factors that likely vary among patients. Most important perhaps is increased sodium retention, which may result from primary renal retention and possibly reduced sensitivity to atrial natriuretic peptide.2 Although studied extensively, the contribution of decreased serum oncotic pressure to the development of edema remains unclear. What must be kept in mind is that the driving force for edema formation is not just serum oncotic pressure, but the gradient between serum and interstitial tissue oncotic pressure. Both of these pressures likely fall in parallel, suggesting that hypoalbuminemia by itself does not contribute greatly to edema formation.

The hyperlipidemia may also be multifactorial. Hypercholesterolemia seems to result from both upregulation of hepatic production of lipoproteins triggered by hypoalbuminemia, low plasma oncotic pressure, or low plasma viscosity,3 and decreased catabolism and clearance of lipoproteins.4 Decreased catabolism and increased synthesis also likely cause hypertriglyceridemia.4 Interestingly, it has been postulated that the increase in lipoprotein is composed largely of apoprotein B, which has a greater effect on oncotic pressure than other lipoproteins.5

It is important to distinguish between nephrotic glomerular disease and nephritic glomerular disease. Nephrotic disease generally presents with significant proteinuria but usually does not cause generalized renal dysfunction evidenced by a rising serum creatinine level. Conversely, nephritic glomerulopathies often do present with general renal dysfunction with an
increased creatinine level. In addition, hypertension is often present with nephritis, but seldom with the nephrotic syndrome.

In addition to having the clinical manifestations described above, patients with nephrotic syndrome are at increased risk for developing thromboembolic phenomena, especially those with membranous nephropathy. The nephrotic syndrome is a hypercoagulable state that predisposes patients to deep venous thrombosis, pulmonary embolism, and clots in other locations (eg, renal vein thromboses) that also are associated with pulmonary embolism. Multiple alterations in the different arms of the coagulation cascade have been postulated to be responsible for the hypercoagulability. Most likely different mechanisms are at work to varying degrees in different patients. Increased levels of fibrinopeptide A and high-molecular-weight fibrin complexes are present in patients with the syndrome and are evidence of an overactive system. Increased levels of several clotting factors have been found in patients with the nephrotic syndrome, including factor V and factor VIII (which both act to ultimately increase thrombin generation) and fibrinogen (which probably contributes to increased viscosity and further propensity to clot). Levels of some fibrinolytic factors have been found to be decreased, including antithrombin III (probably due to urinary excretion) and plasminogen. Hypoalbuminemia itself also may contribute to hypercoagulability, as albumin may be a cofactor in the binding of plasminogen to fibrin and in the interaction of plasminogen with tissue plasminogen activator.

Interestingly, the increased levels of lipoprotein (a) seen in nephrosis also may worsen the hypercoagulable state. Lipoprotein (a) is similar in structure to plasminogen and may compete with it for binding to fibrin or fibrinogen. Several platelet abnormalities, including increased platelet aggregation, increased platelet adhesion to vessel walls, increased levels of von Willebrand factor, and thrombocytosis also have been documented. In patients treated with long-term diuretics, increased viscosity due to volume depletion also may make thromboembolic complications more likely. Renal vein thrombosis may be increased in incidence because glomerular filtration causes the postglomerular venous drainage to become hemoconcentrated, which in an already hypercoagulable patient may predispose further to clot formation in this location.

Patients with the nephrotic syndrome also are more susceptible to infections, especially those caused by bacterial pathogens. There is increased susceptibility to infection because immunoglobulins are lost in the urine, thereby impairing humoral immunity.

### Table 1. Etiologies of Minimal Change Disease (MCD)

<table>
<thead>
<tr>
<th>Primary</th>
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<tr>
<td>Idiopathic MCD (the majority of cases)</td>
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<table>
<thead>
<tr>
<th>Secondary</th>
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</thead>
<tbody>
<tr>
<td>Neoplasm</td>
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<tr>
<td>Hodgkin’s lymphoma (most common)</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Immunizations</td>
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<td>Bee stings</td>
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### MINIMAL CHANGE DISEASE

#### CASE PRESENTATION

A healthy 17-year-old white man presents to his primary care physician with periorbital and pretibial edema that has been present for the past few weeks. The patient reports that his urine is frothy and bubbly, especially upon waking in the morning, but he denies any other symptoms. Physical examination shows a well-developed teenage man who is afebrile and normotensive. The only positive findings are periorbital edema and 2+ to 3+ pretibial pitting edema.

Urinalysis findings include 4+ proteinuria by dipstick and oval fat bodies (“the Maltese cross”) detected on microscopy. Tests for glucose, white blood cells, red blood cells, or casts of any type are negative. The serum concentration of creatinine is 0.9 mg/dL, and the serum albumin is 2.3 g/dL. A 24-hour urine collection shows a total protein excretion of 6.8 g. Renal biopsy is performed, and the specimen shows evidence of minimal change disease (also known as nil disease or lipoid nephropathy).

- What is minimal change disease?
- How should the patient be treated at this time?

#### PATHOLOGIC DIAGNOSIS

Minimal change disease (MCD) is a type of glomerular nephropathy found most often in children and young adults. It accounts for approximately 15% of cases of adult idiopathic nephrotic syndrome. It can be
primary (idiopathic) or secondary to a number of causes (Table 1). The term minimal change disease is derived from the fact that light microscopy shows essentially normal glomeruli. Electron microscopy, however, reveals fusion of epithelial foot processes (Figure 1). It is probably damage to these cells and the resultant loss of the charge selectivity that allows negatively charged protein, such as albumin, to be filtered out of the glomerulus and into Bowman’s capsule.8

TREATMENT

Idiopathic MCD is differentiated from other causes of the nephrotic syndrome by its exquisite sensitivity to glucocorticoids. Prednisone in doses of 1 mg/kg/day causes resolution of nephrotic-range proteinuria and the edema associated with it within 2 to 4 months in up to 90% of adults. Once remission of proteinuria is achieved, doses can be given on alternate days and then tapered slowly over the course of months to prevent relapse.9 The natural history of MCD is quite variable. Between 19% and 63% of patients will recover after steroid therapy with no further episodes of significant proteinuria.9,10 The remaining patients fall across a spectrum of disease severity. Some patients will relapse after steroids are stopped, the so-called frequent relapers. Another portion, the steroid-dependent, will relapse during the tapering of steroids, sometimes at a predictable dose. At the opposite end of the spectrum lie the steroid-resistant patients (approximately 10%), those whose proteinuria does not remit at all after 16 weeks of steroid therapy.9 At least some portion of these patients may not actually have MCD but rather have focal segmental glomerulosclerosis (which is less responsive to steroid therapy) that was missed because of an inadequate biopsy tissue specimen.

Reduction of peripheral edema is an important aspect of therapy. Edema that causes alteration of body image often is a source of distress to patients, especially to a high school student such as this patient. Severe edema also may be painful and cause skin breakdown. Therefore, a low-salt diet and the judicious use of loop diuretics (eg, furosemide) is warranted; however, the physician must closely monitor blood pressure and electrolytes such as potassium and magnesium.

In cases of secondary MCD, therapy is directed at the underlying etiology, whether it is treating an underlying malignancy or withdrawal of an offending medication. The role of steroids or other immunosuppressive medication is unclear.

- Was renal biopsy necessary in this patient?

Renal biopsy does not need to be performed prior to initiation of therapy in every case of nephrotic syndrome. Approximately 90% of cases of idiopathic nephrotic syndrome in children are due to MCD. This number falls to 50% in older children. However, the likelihood prior to biopsy was that this patient has either MCD or focal segmental glomerulosclerosis, both of which are treated initially with steroids. Therefore, a strong case can be made for empiric treatment, with biopsy reserved for those patients with steroid-resistant nephrotic syndrome.

CLINICAL COURSE

The patient is started on prednisone 60 mg/day and furosemide 20 mg/day. At 5 weeks, dipstick urinalysis
reveals 1+ proteinuria, there is almost complete resolution of peripheral edema, and the serum albumin level is 4.0 g/dL. The patient is switched to alternate-day steroid therapy for 1 month, and then the steroids are slowly tapered over 9 months. After 7 months of remission, the patient returns with peri-orbital and pretibial edema. A spot protein-to-creatinine ratio is 3.7. The patient is treated with a second identical course of prednisone, which induces remission for 5 months. However, he returns once again with nephrotic-level proteinuria and significant edema.

- **What course of therapy should be pursued at this point?**

  This patient falls into the category of frequent relapsers, who achieve successive temporary remissions followed by relapse upon cessation of therapy, usually within 1 to 2 years. The optimal therapy for such patients is not clear, mostly because large studies comparing competing therapies head-to-head have not been done. However, a number of immunosuppressive medications are used to treat MCD in frequent relapsers. Alkylating agents such as cyclophosphamide (2–3 mg/kg/day for at least 8 weeks) and chlorambucil have achieved a remission rate of 63% at 10 years of follow-up. Longer courses may be necessary for steroid-dependent cases. Cyclophosphamide has a variety of potentially serious side effects, including hemorrhagic cystitis, bone marrow suppression leading to infection and anemia, sterility, and secondary malignancies such as leukemia.

  Although less toxic therapies can be used, including cyclosporine, mycophenolate mofetil, and azathioprine, the rates of remission and subsequent relapse with these agents are less favorable compared to those with cyclophosphamide. These medications are attractive not only because of their effect on the underlying disease, but also because they are steroid-sparing, helping to avoid the many complications of protracted steroid use (e.g., infection, hypertension, diabetes mellitus, acne, striae, cushingoid body changes, osteopenia/osteoporosis, avascular necrosis, and psychiatric changes).

**CASE RESOLUTION**

The patient is treated with an 8-week course of cyclophosphamide, after which his nephrotic-range proteinuria again remits. He remains disease free for 3 years, after which he is lost to follow-up.

- **Should the patient be evaluated for secondary causes of MCD?**

  At 17 years old, the patient is at an age when the incidence of Hodgkin’s lymphoma begins to peak. Given the association between Hodgkin’s lymphoma and MCD, must the physician rule out this diagnosis? To answer this question, we must consider the individual patient. The patient was otherwise well, with no complaints of enlarged lymph nodes, fevers, night sweats, or weight loss. Furthermore, physical examination revealed no lymphadenopathy, splenomegaly, or other concerning findings. If any of these signs or symptoms had been present, a computed tomography (CT) scan of the chest would have been warranted. However, in an uncomplicated case such as this with no findings suspicious for malignancy, further workup is unnecessary.

**FOCAL SEGMENTAL GLOMERULOSCLEROSIS**

**CASE PRESENTATION**

A 25-year-old African American man with no past medical history presents to his primary care physician with complaints of fatigue, swelling legs, and frothy urine. He has had multiple sexual partners since he was 18 years old but denies intravenous drug use. He reports testing negative for HIV infection 1 year ago.

Physical examination reveals a blood pressure of 148/92 mm Hg and 2+ pretibial pitting edema. Urinalysis findings include 4+ proteinuria by dipstick and oval fat bodies on microscopy. There are no white blood cells, red
blood cells, or casts. On serum testing, the creatinine concentration is 1.8 mg/dL, albumin is 2.8 g/dL, and total cholesterol is 316 mg/dL, with a low-density lipoprotein (LDL) level of 224 mg/dL and a high-density lipoprotein (HDL) level of 41 mg/dL. A 24-hour urine collection contains 8.3 g of protein. Renal ultrasound shows normal to slightly small kidneys with increased echogenicity, consistent with medical renal disease. A repeat HIV test is negative. Renal biopsy is performed; the specimen shows focal segmental glomerulosclerosis.

- What is focal segmental glomerulosclerosis?
- Why was it necessary to test the patient for HIV infection?

**PATHOLOGIC DIAGNOSIS**

**Idiopathic Form**

Focal segmental glomerulosclerosis (FSGS) is the most common glomerulopathy causing idiopathic nephrotic syndrome in adults, accounting for approximately 35% of such cases. It can be primary (idiopathic) or secondary to a wide variety of etiologies (Table 2). The idiopathic form most commonly affects young African Americans, but it occurs in all races and age-groups. Light microscopy shows sclerosis of some but not all glomeruli (focal), and involved glomeruli are only partially sclerotic (segmental) (Figure 2, see page 9). As a result of this sclerosis, trichrome stains light up, reflecting replacement of functional glomeruli with collagen. Tubulo-interstitial fibrosis can be seen as well.

**HIV-Induced Form**

FSGS secondary to HIV is commonly seen due to the increasing prevalence of HIV infection. The likelihood of FSGS developing is increased with lower CD4 counts, but may be seen at any time. It often presents with rapidly progressive renal failure over a course of months. One of the distinguishing characteristics of HIV-induced FSGS is large kidneys on ultrasonographic examination. It usually causes a variant of FSGS on histology called collapsing FSGS, and this entity has a worse prognosis than typical FSGS. The role of highly active antiretroviral therapy in the treatment of collapsing FSGS is currently under investigation, but it may be appropriate in some patients, especially if therapy is begun before renal function has deteriorated significantly. Other studies show that steroids and cyclosporine may have a role in the treatment of HIV-associated FSGS.

Patients with FSGS do not need to be tested for HIV infection unless there is clinical suspicion for infection. Risk factors such as multiple sexual partners, use of intravenous drugs, especially with shared needles, and history of transfusion of blood products are red flags. Signs and symptoms such as weight loss, lymphadenopathy, diarrhea, or rashes (eg, molluscum contagiosum or Kaposi’s sarcoma) should prompt testing. Patients who do not fit the typical demographic group for idiopathic FSGS should probably also be tested.

This patient’s history of multiple sexual partners is sufficient reason to proceed with testing, although his ultrasonography results and lack of other red flags make it a less likely diagnosis. In addition, because the patient is a young, African-American man, the idiopathic form is a more likely diagnosis.

- How should the patient be treated at this point?

**TREATMENT**

**Prognostic Factors**

Before therapy is initiated, some important prognostic factors for any individual patient need to be considered. Factors that portend a poor outcome include African American race, male sex, older age, nephrotic-range proteinuria (especially > 10 g/day), increased serum creatinine (> 1.3 mg/dL in one study), the presence of interstitial fibrosis at the time of biopsy, and hypertension. The finding of the histological variant collapsing FSGS, most often seen in HIV nephropathy, also is associated with more rapid progression to end-stage renal disease. A lack of response to therapy carries a higher risk of ultimate progression to renal failure.

**Corticosteroids and Immunosuppressive Agents**

Optimal therapy for idiopathic FSGS is still a matter of debate, with few evidence-based studies on which to base it. A current approach is to treat patients with prednisone at a dose of 2 mg/kg (up to 120 mg) on alternating days. This dose is continued for 1 or 2 weeks following remission, after which the dose should be very slowly tapered to prevent relapse. Complete remission rates greater than 30% have been achieved in patients receiving steroids for at least 5 to 8 months. Patients who receive steroids for 4 to 6 months without remission are considered steroid-resistant.

Immunosuppressive medications are used in patients with steroid-resistant and steroid-dependent disease. The goal of immunosuppressive therapy is to reverse the underlying inflammatory process driving the disease. Cyclosporine in doses of 5 mg/kg/day for 6 months followed by a slow taper over several months achieved complete or partial remission in 60% of steroid-resistant patients in one study. Experts therefore recommend a
trial of cyclosporine (starting with 3.5 mg/kg/day in divided doses, aiming for trough levels of 125 to 225 μg/L) and low-dose prednisone (maximum of 15 mg/day) for steroid-resistant patients. Data support the efficacy of cyclophosphamide in frequent relapers and steroid-dependent patients (complete or partial remission in 76%), but it is second-line to cyclosporine because of its side-effect profile. Steroid-resistant patients fare far less well after therapy with cyclophosphamide, with only 22% achieving complete or partial remission. Other immunosuppressive agents include tacrolimus, mycophenolate mofetil, and azathioprine. Although far less data are available for these agents, some may assume a more prominent role in therapy after they have been more adequately studied.

Up to 10% of patients who initially respond to therapy will progress to end-stage renal failure at 10 years. This number jumps to approximately 60% in patients who did not have at least a partial remission initially. These patients eventually require dialysis and/or renal transplantation. Even transplantation, however, is not always curative. FSGS recurs in approximately 20% of allografts, requiring further dialysis or transplantation.

In the case of secondary FSGS, therapy is once again directed at the underlying etiology, such as treating malignancy, withdrawal of a causative drug, or weight loss in the case of obesity/sleep apnea. Whether continuous positive airway pressure is effective at reducing proteinuria in the absence of weight loss is not known.

**ACE Inhibitors and Angiotensin II Receptor Blockers**

Another important arm of therapy directed at reducing the degree of proteinuria is treatment with angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers. These key adjunctive medications act by either indirectly or directly blocking the downstream effects of angiotensin II, including systemic and efferent arteriolar vasoconstriction. Blocking the effects of angiotensin II achieves a reduction in systemic and especially intraglomerular blood pressure, and both of these are beneficial in reducing further damage to glomeruli. A reduction in the degree of proteinuria is due to both reduced intraglomerular blood pressure and possibly to preservation of glomerular size-selectivity. These medications should be started at a low dose and titrated up to the maximum dose tolerated by the patient’s blood pressure. Careful monitoring of the patient’s creatinine and potassium levels is also important.

**Statins/Niacin**

Therapy to modulate serum lipid levels is necessary if hypercholesterolemia is present. Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) are good first-line agents since they lower LDL levels and have some effect in raising HDL levels and reducing triglycerides. These medications help prevent accelerated systemic atherosclerosis and may even prevent intraglomerular atherosclerosis. No LDL level has been established as optimal in nephrotic patients. Careful monitoring of liver enzymes is important with the use of these medications. The vitamin niacin (B3) is also a good choice in lipid therapy, especially if low HDL levels are present. Niacin also will achieve a reduction in LDL levels.

**CLINICAL COURSE**

The patient is treated initially with prednisone 120 mg every other day. He also is started on lisinopril 10 mg/day, simvastatin 20 mg at night, and furosemide 20 mg/day for peripheral edema. After 1 month of therapy, he still has proteinuria of 7.9 g/day and his serum creatinine is 1.9 mg/dL. Blood pressure is 136/88 mm Hg, and the peripheral edema is marginally improved. The ACE inhibitor is increased to 20 mg/day.

Two months later, his proteinuria has decreased to 2.4 g/day, his serum creatinine is down to 1.4 mg/dL, and his blood pressure is 124/80 mm Hg. The steroid dose is tapered slowly, and he continues to have subnephrotic-range proteinuria for the next 8 months. At a follow-up visit, while on prednisone 70 mg every other day, a 24-hour urine collection contains 9.7 g of protein, and his creatinine has risen to 2.1 mg/dL. Increasing his steroid dose achieves partial remission of his proteinuria, but when the dose is tapered to approximately 70 mg every other day, nephrotic-level proteinuria returns. He is started on cyclosporine 100 mg twice daily and his ACE inhibitor is increased to 30 mg/day. He remains on this regimen for 6 months followed by a slow taper. Although he initially has a good response, with proteinuria reduced to less than 2 g/day, he relapses again with massive proteinuria. His creatinine at this time has risen to 4.3 mg/dL. After an unsuccessful trial of cyclophosphamide, he is referred to a transplant center for evaluation.

This patient had many poor prognostic factors at the time of his presentation. He is African American, had a high degree of proteinuria at presentation, had evidence of renal dysfunction with an elevated creatinine, and was hypertensive. His initial response to therapy was encouraging, but he proved to be steroid-dependent, ultimately failing other immunosuppressive regimens and requiring transplantation.
CASE PRESENTATION

A 51-year-old white woman with no significant past medical history presents to her primary care physician with complaints of fatigue, shortness of breath, and pain in her right scapular area when she takes a deep breath. Her symptoms started 3 days prior to presentation. She also reports that her urine is frothy and sometimes pink-tinged, and she has some vague right flank pain.

Physical examination reveals a blood pressure of 132/75 mm Hg, tachycardia to 110 bpm, pulse oximetry of 91% on room air, slightly decreased breath sounds at the right base with dullness to percussion, a widely split S2, right flank/costovertebral angle tenderness, 3+ pretibial pitting edema, and trace heme-positive stool.

An electrocardiogram shows sinus tachycardia and right bundle branch block. Lower extremity Doppler ultrasound is negative for deep venous thrombosis. Results of a ventilation/perfusion nuclear scan indicate a high probability for pulmonary embolism. Urinalysis reveals 4+ proteinuria by dipstick and oval fat bodies on microscopy. On serum testing, creatinine is 0.8 mg/dL, albumin is 2.6 mg/dL, and cholesterol is 301 mg/dL, with an LDL level of 212 mg/dL and an HDL level of 53 mg/dL. A 24-hour urine collection contains 12.2 g of protein. Renal ultrasonography shows an enlarged right kidney with reduced Doppler flow in the right renal vein.

• What is the most likely diagnosis?

PATHOLOGIC DIAGNOSIS

Because of this patient’s urgent need for systemic anticoagulation, a renal biopsy was delayed until this need was addressed. However, based on both her demographics (older age, white race), as well as her thromboembolic complications, she is statistically most likely to have membranous nephropathy as the cause of her nephrotic syndrome. (The diagnosis was confirmed upon biopsy performed after anticoagulation.)

Membranous nephropathy is now the second most common form of idiopathic adult nephrotic syndrome (33% of cases). It is characteristically seen in adults, with a greater predilection for whites than African Americans. There are primary (idiopathic) and secondary forms caused by a wide variety of conditions (Table 3). Light microscopy shows glomerular basement membrane thickening with little or no cellular proliferation or infiltration (Figure 3).

• Does this patient need to be evaluated for malignancy?

Treatment of nephrotic syndrome secondary to neoplasm is directed at treatment of the underlying tumor. In one small case series, there was a correlation between

<table>
<thead>
<tr>
<th>Table 3. Etiologies of Membranous Nephropathy (MN)</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
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<tr>
<td>Idiopathic MN (the majority of cases)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>Solid tumors, most commonly lung, colon, breast</td>
</tr>
<tr>
<td>Leukemia</td>
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<tr>
<td>Non-Hodgkin’s lymphoma</td>
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<tr>
<td>Infectious</td>
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<td>Hepatitis B</td>
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<td>Hepatitis C</td>
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<tr>
<td>Syphilis</td>
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<tr>
<td>Schistosomiasis</td>
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<tr>
<td>Collagen-vascular disease</td>
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<tr>
<td>SLE</td>
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<td>Sjorgen’s syndrome</td>
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<td>Medications</td>
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<td>Penicillamine</td>
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<tr>
<td>Gold</td>
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<tr>
<td>NSAIDs</td>
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NSAIDs = nonsteroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus.
the course of proteinuria and that of the tumor, with proteinuria remitting in successfully treated patients and persisting in patients with progressive disease.

SCREENING TESTS IN PATIENT

The patient undergoes subsequent colonoscopy, mammography, and chest radiograph, all of which are negative for malignancy.

• What is the most appropriate therapy for this patient?

TREATMENT

Membranous nephropathy is the form of nephrotic syndrome most likely to have thromboembolic complications. This patient’s history and physical examination are consistent with the diagnosis of pulmonary embolism. The workup confirmed this suspicion and revealed a renal vein thrombosis as the source, not a lower-extremity deep venous thrombosis. The patient should be treated for pulmonary embolism immediately. She should be hospitalized for intravenous heparin administration until therapeutic levels are achieved on warfarin with an international normalized ratio between 2 and 3. Attention can then be given to her renal disease.

As with FSGS, optimal therapy for idiopathic membranous nephropathy has not been widely studied in large, controlled multicenter trials. The natural history of the disease also makes determining ideal treatment difficult. A small percentage (5%–20%) of patients will have spontaneous remission of proteinuria. A larger portion (25%–40%) will have partial remission (a decrease to < 2 g/day) of proteinuria. Unlike FSGS, where a large proportion of patients will progress to end-stage renal failure if untreated, fewer patients with idiopathic membranous nephropathy will have this result: approximately 10% to 15% at 5 years, 30% at 10 years, and 40% at 15 years.

Because of this more benign course of disease, not all patients with membranous nephropathy need to be treated aggressively. Patients with a more favorable prognosis are women, patients under 50 years,26 and those with sub-nephrotic proteinuria. Men, patients over 50 years,26 those with nephrotic syndrome,26 possibly more so in those with proteinuria of greater than 10 g/day,26 and those who present with an elevated creatinine have a less favorable prognosis.29,30 Patients whose biopsy specimens
show evidence of tubulointerstitial fibrosis and/or glomerular scarring have poorer outcomes. Patients who fall into these categories are candidates for immunosuppressive therapy. Steroids given for at least 2 months at doses of 100 to 150 mg every other day followed by a slow taper may reduce the progression to end-stage renal failure and increase the likelihood of at least a short-term remission of proteinuria, although remission often is not sustained. Cyclophosphamide and chlorambucil (usually in combination with steroids) also affect both proteinuria and progression to renal failure, inducing complete or partial remission of proteinuria in 70% to 100% of patients and reducing the rate of progression to renal failure to 10%, a marked improvement over no therapy at all. Experience with cyclosporine is still limited, but it may eventually have an important role in therapy for membranous nephropathy.

Treatment with an ACE inhibitor or an angiotensin II receptor blocker to treat hypertension and reduce proteinuria, a statin to reduce LDL levels, and a loop diuretic to minimize peripheral edema are once again important considerations.

In cases of secondary membranous nephropathy, treatment is directed at the underlying etiology, whether that is treating a malignancy, giving immunosuppressive drugs for a collagen-vascular disease, giving antimicrobials for an infection, or withdrawing an offending medication.

**CLINICAL COURSE**

Anticoagulation therapy is initiated for the patient’s pulmonary embolism. Because of the high degree of proteinuria and thromboembolic complications, she is started on prednisone 100 mg every other day and low-dose cyclophosphamide (80 mg/day). She also is treated with simvastatin 20 mg at night, enalapril 5 mg/day, and furosemide 20 mg/day. A bisphosphonate also is given to prevent steroid-induced osteoporosis.

After 3 months, a 24-hour urine specimen shows a reduction in protein excretion to 3.3 g. Her cholesterol levels are somewhat improved, and the dose of the statin is doubled. Her blood pressure is 118/68 mm Hg. Her peripheral edema substantially improves.

Follow-up 3 months later shows a further reduction in proteinuria to 1.6 g/day. After a total of 9 months of immunosuppressive therapy, her prednisone is slowly tapered and her cyclophosphamide is stopped. At follow-up 2 years later, her proteinuria is stable at a sub-nephrotic level.

- **What is the optimal duration of anticoagulation in a nephrotic patient with thromboembolic complications?**

The optimal duration of anticoagulation in such a patient is not clear. A minimum of 6 months of warfarin therapy is necessary for deep venous thromboembolism. If resolution of the thrombosis is documented (in the case patient, a Doppler ultrasound showing normal flow and no residual thrombus in her right renal vein), anticoagulation can probably be discontinued provided that the patient’s nephrotic-level proteinuria also is resolved. If the patient is still nephrotic, it is probably wise to continue warfarin until the nephrosis is adequately treated.

**OTHER FORMS OF NEPHROTIC SYNDROME**

There are 2 other important causes of nephrotic syndrome that do not fit neatly into the classification based on histologic examination. The first is diabetes mellitus, the most common cause of nephrotic level proteinuria. Diabetic nephropathy is covered in Volume 4, Part 2 of the *Hospital Physician Nephrology Board Review Manual*, which can be reviewed for detail on the subject.

The other cause is systemic amyloidosis, which is most often seen secondary to multiple myeloma (amyloidosis AL type). In this plasma cell lymphoproliferative disease, a large amount of immunoglobulin is ultimately excreted into the urine as Bence-Jones proteinuria. This urinary immunoglobulin is deleterious to renal function in a number of ways, including the induction of proteinuria, often to nephrotic levels (Table 4). In the case of λ–light chain excretion, amyloid can be deposited in the...

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**Table 4. Types of Renal Involvement in Multiple Myeloma Due to Immunoglobulins**

<table>
<thead>
<tr>
<th>Type of Renal Involvement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidosis</td>
<td>causes albuminuria through deposition of amyloid in the glomerulus (usually caused by λ–light chain excretion)</td>
</tr>
<tr>
<td>Light chain deposition disease</td>
<td>causes albuminuria through deposition of light chains (usually κ–light chain) in the glomerulus</td>
</tr>
<tr>
<td>Heavy chain deposition disease</td>
<td>causes albuminuria through deposition of heavy chains in the glomerulus</td>
</tr>
<tr>
<td>Myeloma kidney: Intratubular casts made up of filtered immunoglobulins and Tamm-Horsfall protein cause obstruction of tubules</td>
<td></td>
</tr>
<tr>
<td>Direct tubular toxicity of immunoglobulins: Proximal tubular cells cannot process the large amount of filtered protein, causing tubular dysfunction, with possible resultant Fanconi syndrome and type 2 renal tubular acidosis</td>
<td></td>
</tr>
</tbody>
</table>

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glomerulus, leading to leakage of albumin and other proteins into Bowman’s capsule and ultimately the urine. In the case of κ-light chain excretion, the more likely result is light chain deposition disease, in which light chains once again are deposited into glomerular (as well as tubular) structures (but not in a β pleated sheet structure as in amyloidosis), causing proteinuria. Heavy chains, if they are secreted by the plasma cell dyscrasia, also can be deposited in a similar way, causing heavy chain deposition disease with resultant proteinuria.

Systemic amyloidosis also can result from other disease states, including chronic inflammatory diseases such as rheumatoid arthritis and chronic infections such as tuberculosis (amyloidosis AA type). Familial forms of amyloidosis also can induce the nephrotic syndrome from glomerular involvement.

**CONCLUSION**

Nephrotic syndrome is a term that covers a broad spectrum of disease states in which there is at least 3 to 3.5 g of protein excreted in the urine daily. A wide range of glomerular diseases cause the nephrotic syndrome. Nephrotic-range proteinuria also can occur in many of the nephritic glomerular diseases, including IgA nephropathy, systemic lupus erythematosus, and the various forms of membranoproliferative nephropathy. It is important to remember that immunosuppression is the mainstay of therapy in the idiopathic forms of MCD, FSGS, and membranous nephropathy. The secondary forms of these pathologic diagnoses are best treated with therapy for the underlying etiology, most commonly malignancy, infection, collagen-vascular disease, and medication. The natural history of these diseases is variable, ranging from spontaneous resolution to successful treatment with subsequent relapse to refractory disease with progression to end-stage renal disease.

**REFERENCES**