A 57-year-old woman with a medical history of hypertension, type 2 diabetes mellitus with chronic kidney disease stage 3a, and coronary artery disease presented to the emergency department with a subacute history of progressive fatigue and bilateral leg swelling despite increasing doses of furosemide. Over the next several weeks, she reported feeling generally unwell with profound malaise, frequent urination, and increasing lower-extremity edema despite taking extra doses of her normal diuretic. She otherwise denied chest pain, shortness of breath, orthopnea, redness, or pain in her calves. Home medications included furosemide, losartan, insulin degludec, and liraglutide. The patient had no history of smoking or excessive alcohol use.

On physical examination, the patient was alert and well, appearing to be in no distress. Her vital signs revealed a temperature of 36.6°C, pulse rate 118 beats/min, blood pressure 138/67 mm Hg, and respiratory rate 16 breaths/min with an oxygen saturation of 98% on room air. Her oropharynx was moist and clear. Lung auscultation revealed minimal bibasilar rales without wheezing. Cardiac exam demonstrated regular rhythm with S1, S2, and S4 auscultated, and a systolic murmur best heard at the right upper sternal border. Her distal pulses were intact with bilateral 2+ pitting lower extremity edema noted to the level of the knees, and a normal jugular venous pressure. The remainder of the physical exam was unremarkable.

Laboratory studies revealed (reference ranges provided parenthetically): hemoglobin 11.2 g/dL (12.0 to 15.5 g/dL), white blood cell count 6.1×10^9/L (3.4 to 9.6×10^9/L), and a platelet count 243×10^9/L (157 to 371×10^9/L). Metabolic panel revealed a sodium level 135 mmol/L (135 to 145 mmol/L), potassium 5.1 mmol/L (3.6 to 5.2 mmol/L), bicarbonate 25 mmol/L (22 to 26 mmol/L), blood urea nitrogen level 48 mg/dL (7 to 20 mg/dL), creatinine level 2.32 mg/dL (0.84 to 1.21 mg/dL) increased from a baseline 2 years prior of creatinine level of 1.6 mg/dL, albumin 2.9 g/dL (3.5 to 5.0 g/dL), and a random glucose reading of 394 mg/dL (<140 mg/dL). Liver function tests were within normal limits. Urinalysis revealed a glucose level greater than or equal to 1000 mg/dL (≤15 mg/dL), protein level greater than 600 mg/dL (<150 mg/dL), no ketones, and trace amount of hemoglobin and leukocyte esterase detected. The urine white blood cell count was 5/hpf (0 to 5/hpf), urine red blood cell count was 2/hpf (0 to 2/hpf), bacteria was present as well as squamous epithelial cells and hyaline casts 9/lpf (<2 casts/lpf). Renal ultrasound with Doppler revealed mildly increased cortical echogenicity of the bilateral kidneys without hydronephrosis and no evidence of renal vein thrombosis. Ultrasound with Doppler of the bilateral lower extremities was negative for deep vein thromboses. A chest radiograph showed sternotomy wires and evidence of coronary artery bypass grafting, but no acute findings including edema, effusions, or consolidations.

1. Which one is the most likely etiology of this patient’s presentation?
   a. Decompensated heart failure
   b. Nephrotic syndrome
   c. Diabetic ketoacidosis
   d. Hyperosmolar hyperglycemic syndrome
   e. Nephritic syndrome

Although acute decompensated heart failure would explain worsening edema, the lack of dyspnea, orthopnea, elevated jugular venous pressure, and an unremarkable chest
The patient presents with edema and evidence of proteinuria on urinalysis. This presentation is most consistent with nephrotic syndrome. Nephrotic syndrome is a result of damage at the level of the glomerulus, leading to a constellation of symptoms that consists of heavy proteinuria (>3.5 g/day), edema, lipuduria, hyperlipidemia, and hypoalbuminemia.1,2

Diabetic ketoacidosis could be considered in the setting of hyperglycemia, glycosuria, polyuria, and malaise, but a normal bicarbonate level and lack of ketonuria makes diabetic ketoacidosis less likely. Hyperosmolar hyperglycemic syndrome could be considered, but typically blood glucose levels are greater than 900 mg/dL, and the presentation is associated with changes in mental status.

Nephritic syndrome would classically present with acute hypertension in the presence of a urinalysis showing primarily hematuria, dysmorphic red blood cells, occasionally red blood cell casts, and only mild proteinuria (<1.5 g/day).3

Thus, this patient’s presentation with heavy proteinuria and edema is most suggestive of nephrotic syndrome. She was initially managed with intravenous loop diuretic therapy and salt restriction.

2. Which one of the following would be the most appropriate test to confirm the diagnosis?

a. Echocardiogram
b. Spot urine protein to creatinine ratio
c. 24-hour urine protein and creatinine
d. Serum cystatin c
e. Urine sodium and creatinine

An echocardiogram could be considered if the patient was in decompensated heart failure to evaluate the left ventricular ejection fraction. However, clinically this patient does not have decompensated heart failure, and thus an echocardiogram would unlikely help establish a diagnosis. This presentation with edema and proteinuria is most suggestive of nephrotic syndrome.

Diagnostic evaluation for nephrotic syndrome includes a urinalysis, quantification of urine protein, a basic metabolic, serum albumin, and lipid profile. Quantification of the urine protein would be the most appropriate next step to confirm the diagnosis. A spot urine protein-to-creatinine ratio can be used for this purpose and is commonly ordered as an initial test when the diagnosis is suspected, given its ease of collection and rapid resulting. However, the spot urine test is less reliable than a 24-hour urine collection because there is greater variability with spot testing as the results may be affected by various factors such as exercise, diet, drugs, and time of day.2 A 24-hour urine collection is the gold standard for quantification of proteinuria, and preferred over a spot urine protein-to-creatinine ratio to confirm the diagnosis. Twenty-four-hour collection of urine creatinine can also help correct for under-collection of a specimen. A sample of at least 3.5 g of protein in 1 day would be consistent with nephrotic range proteinuria, which can also occur in the absence of nephrotic syndrome secondary to a number of etiologies.

Cystatin c, in combination with serum creatinine, may be used to better estimate the glomerular filtration rate (GFR). However, it would not be useful in confirming the diagnosis of nephrotic syndrome. Urine sodium and creatinine levels can be used to calculate the fractional excretion of sodium and possibly better characterize the etiology of the acute kidney injury as prerenal or intrarenal. However, because urinary sodium excretion can be affected by diuretic use, fractional excretion of urea is a more reliable test to check in patients taking diuretics.

The patient was found to have a spot urine protein-to-creatinine ratio of 4.71 (<0.18) suggesting an estimated 24-hour urine protein excretion of 4.7 g. The diagnosis of nephrotic syndrome was then confirmed by a 24-hour urine collection which revealed a total urinary protein excretion of 6.28 g/24 h.

To determine the etiology of the nephrotic syndrome, further workup for this patient included hepatitis B and C serologies, HIV serology, serum protein electrophoresis with immunofixation and free light chains, complement levels, antinuclear antibody,
double-stranded DNA, and antibodies to the phospholipase A2 receptor, all of which were negative or normal. The hemoglobin A1c level was 10.0% (<5.7%). Total cholesterol was 291 mg/dL (<200 mg/dL), low-density lipoprotein 209 mg/dL (<70 mg/dL), high-density lipoprotein 46 mg/dL (>50 mg/dL), and triglycerides 178 mg/dL (<150 mg/dL).

3. Given the laboratory studies obtained thus far, what is the most appropriate next step to determine the etiology of this patient’s nephrotic syndrome?

a. Defer renal biopsy and make presumptive diagnosis of diabetic glomerulopathy
b. Defer renal biopsy and make presumptive diagnosis of minimal change disease
c. Obtain percutaneous renal biopsy with light microscopy, immunofluorescence, and electron microscopy
d. Obtain open renal biopsy with light microscopy, immunofluorescence, and electron microscopy
e. Obtain percutaneous renal biopsy with Congo red staining

This patient presents with uncontrolled diabetes (A1C 10.0% and blood glucose 394 mg/dL), chronic kidney disease, and nephrotic syndrome, making diabetic nephropathy the most likely etiology. Typically, patients will develop microalbuminuria followed by heavy proteinuria with a decrease in GFR.4,5 In most patients with diabetes mellitus who develop nephropathy, the diagnosis of diabetic nephropathy is made clinically, often not requiring renal biopsy.6 In some diabetic patients who develop renal disease, biopsy is indicated, particularly when there are atypical features of the presentation suggesting an alternative etiology such as minimal change disease (MCD) or membranous nephropathy. Examples include scenarios where there is evidence of another systemic disease (eg, autoimmune disease), active urinary sediment, rapidly declining renal function, rapidly increasing proteinuria, or well-controlled diabetes or short duration of diabetes. Thus, the most appropriate choice for our patient, with evidence of longstanding uncontrolled diabetes, classic subacute presentation of nephrotic syndrome, and no clinical evidence of other systemic diseases, is to defer renal biopsy and make a presumed diagnosis of diabetic nephropathy.

Minimal change disease would not be the correct presumed diagnosis in this patient who has obvious risk factors for diabetic kidney disease. Additionally, MCD is more common in pediatric and adolescent cases.

If renal biopsy was indicated, then the less invasive percutaneous renal biopsy would be preferred over open renal biopsy. Light microscopy, along with immunofluorescence and electron microscopy are used to assess for the different histologic subtypes of nephrotic syndrome. Congo red staining is positive in cases of renal amyloidosis.

The patient was diagnosed with nephrotic syndrome secondary to diabetic nephropathy and renal biopsy was deferred.

4. Which one of the following would not be an appropriate next step in management for this patient?

a. Immunosuppressive therapy
b. Pneumococcal vaccine
c. Statin therapy
d. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
e. Optimization of glycemic control

Immunosuppressive therapy would be indicated for treatment of certain primary renal disorders or in cases of renal disease secondary to systemic autoimmune diseases. However, immunosuppressant therapy is not indicated for nephrotic syndrome secondary to diabetic nephropathy. Patients with nephrotic syndrome are at increased risk for infections secondary to loss of immunoglobulins in the urine.7 As recommended by the Centers for Disease Control and Prevention, these adult patients should receive vaccination with both the 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine.8 After obtaining a baseline lipid profile, lipid-lowering medications such as statins should be considered to reduce the risk of long-term effects from atherosclerosis, especially if the nephrotic syndrome is unlikely to resolve.
quickly. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used in most patients with nephrotic syndrome and elevated blood pressure to slow the progression of disease by lowering the intraglomerular filtration pressure and reducing proteinuria. For our patient, one of the next most appropriate steps in management would be to treat the underlying cause for nephrotic syndrome and aim to improve glycemic control.

Over the course of hospitalization, the patient’s insulin regimen was titrated to optimize her glycemic control. In addition, her home doses of losartan and furosemide were up-titrated. She was initiated on a statin, and received pneumococcal vaccination before discharge.

5. What is the most appropriate form of anticoagulation for this patient?
   a. Warfarin with goal international normalized ratio (INR) 2-3
   b. Subcutaneous low-molecular-weight heparin 40 mg daily
   c. Aspirin 75 mg daily
   d. No anticoagulation
   e. Apixaban 5 mg twice a day

Patients with nephrotic syndrome have an increased risk for venous and arterial thrombosis compared with the general population, particularly deep venous thrombosis and renal vein thrombosis. The hypercoagulable state is thought to be secondary to a combination of urinary loss of anticoagulant factors (eg, antithrombin III, plasminogen, and proteins C and S), hemoconcentration, platelet dysfunction, and hypoalbuminemia. In one case series, patients were found to have deep venous thrombosis (up to 15%), symptomatic pulmonary embolism (13%), and acute (4%) or chronic (21%) renal vein thrombosis. Of the different nephrotic histological subtypes, membranous nephropathy has the greatest risk of thromboembolism. Serum albumin levels also serve as an independent risk factor for thromboembolic events, regardless of subtype. There should be consideration for anticoagulation when serum albumin levels are between 2.0 and 3.0 g/dL, with the highest risk in patients with a serum albumin level <2.5 g/dL. Current guidelines recommend prophylactic anticoagulation for patients based on the HAS-BLED bleeding risk, serum albumin, and histologic subtype. For patients with membranous nephropathy, anticoagulation is recommended when serum albumin is less than 3.0 g/dL in low-bleeding-risk patients, and when serum albumin is less than 2.5 g/dL in intermediate-bleeding-risk patients. For patients with any other histologic subtype, including diabetic glomerulopathy, anticoagulation is recommended when serum albumin is less than 2.5 g/dL in low-bleeding-risk patients, and when serum albumin is less than 2.0 in intermediate-bleeding-risk patients. In all patients assessed to have a high risk of bleeding, anticoagulation is generally not recommended.

In patients with nephrotic syndrome who meet criteria for anticoagulation, warfarin (goal INR 2.0 to 3.0) and therapeutic dosing of low-molecular-weight heparin were effective in preventing thromboembolic events and are the most evidence-based options. Warfarin is generally preferred if the patient has fluctuating or unstable renal function. Antiplatelet therapy with aspirin has also been shown to reduce the events of thromboembolism, although this was only demonstrated in very small numbers. Aspirin can be considered on a case-by-case basis in patients who do not meet criteria for full anticoagulation. No anticoagulation would be the correct choice for this patient who has diabetic nephropathy and a serum albumin level greater than 2.5 g/dL. The choice of direct oral anticoagulants (such as apixaban) has not been widely studied for prophylactic anticoagulation in nephrotic syndrome; therefore, it is not recommended as first-line therapy.

After an assessment, anticoagulation was not initiated in our patient. She had improvement in her acute kidney injury and edema during the course of her admission and was discharged with outpatient follow-up with nephrology.
DISCUSSION

In patients presenting with edema and systemic symptoms such as fatigue, a broad differential should be considered, including heart failure, cirrhosis, and portal hypertension, thromboembolic processes, advancing renal disease and causes of low albumin state such as nephrotic syndrome, and malnutrition. Our patient was found to have nephrotic syndrome likely secondary to poorly controlled diabetes mellitus.

Nephrotic syndrome involves glomerular dysfunction that leads to significant proteinuria, renal disease, hypoalbuminemia, and subsequent volume overload. Clinicians should consider nephrotic syndrome when evaluating patients with peripheral edema or anasarca, particularly in the setting of renal dysfunction and underlying systemic disease such as diabetes mellitus or systemic lupus erythematosus. The presence of serum hypoalbuminemia less than 3.0 to 3.5 g/dL, hyperlipidemia, or arterial or venous thromboses are also suggestive of nephrotic syndrome. When routine urinalysis reveals moderate or heavy proteinuria, one should screen for nephrotic syndrome by calculating the protein-to-creatinine ratio in a spot urine sample. This ratio serves as a rough estimate for the total 24-hour urinary protein excretion. If the protein-to-creatinine ratio is close to or greater than 3.5, proceed with confirmatory testing by pursuing 24-hour urine collection. A 24-hour urine protein greater than 3.5 g is diagnostic of nephrotic-range proteinuria.

Once the clinical diagnosis of nephrotic syndrome is made, it is necessary to determine the underlying etiology. The differential for nephrotic syndrome is large, and can be caused by a primary renal disorder or secondary to systemic disease. Primary causes include MCD, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and primary membranous nephropathy. Whereas MCD is the most common cause of nephrotic syndrome in children, in adults, secondary causes occur most frequently, including diabetic glomerulopathy, plasma cell disorder associated glomerulopathies, and secondary membranous nephropathy due to lupus, infections, or malignancy.

Investigations are geared towards uncovering such secondary systemic diseases and can include hemoglobin A1c, antinuclear antibody, anti–double-stranded DNA antibodies, extractable nuclear antigens, rheumatoid factor, syphilis testing, cryoglobulins, complement levels (C3 and C4), hepatitis B and C serologies, HIV screen, serum protein electrophoresis, urine protein electrophoresis with immunofixation, plasma free light chains, and antibodies to the phospholipase A2 receptor. When a secondary etiology is not evident by laboratory workup, renal biopsy is often appropriate to establish the diagnosis. Management of nephrotic syndrome includes identifying and addressing the underlying pathology, renin-angiotensin-aldosterone system blockade, treatment of edema with diuretics and sodium restriction, and mitigating complications associated with the syndrome including consideration of statins, vaccinations, and anticoagulation.

In patients presenting with nephrotic syndrome with long-standing diabetes, diabetic retinopathy, persistent albuminuria, reduced GFR, and without evidence of an alternative etiology, a clinical diagnosis of diabetic kidney disease is established and renal biopsy is not required. If biopsy is pursued in circumstances of an unclear clinical picture, a myriad of pathologic findings can be seen. However, classical diabetic glomerulopathy will include glomerular basement membrane thickening, mesangial expansion, Kimmelstiel-Wilson nodules, and glomerulosclerosis.

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Correct Answers: 1. b. 2. c. 3. a. 4. a. 5. d.