A 75-year-old Caucasian man presented to the emergency department following an episode of unresponsiveness and urinary incontinence. Recent history revealed fever, fatigue, generalized weakness, increased urinary frequency, anorexia, and a 10-lb unintentional weight loss over several months. His medical history was significant for previous exposure to asbestos with pleural calcification; recent painless truncal and upper extremity rash with biopsy, demonstrating weak granular deposition of complement C3 (indeterminate for early connective tissue disease manifestation or normal variant); positive antinuclear antibody (ANA) titer of unknown clinical significance; esophageal stricture treated with dilation; type 2 diabetes mellitus treated with metformin; hypertension treated with amlodipine and enalapril; and hyperlipidemia treated with atorvastatin. Vital signs at presentation were the following: temperature, 101.9 °C (14 °F); blood pressure, 121/70 mm Hg; pulse rate, 82 beats per minute; respiratory rate, 20 breaths per minute; and oxygen saturation, 95% on room air. He was ill appearing, poorly groomed, and unable to hold normal conversation. General examination demonstrated dry-appearing mucous membranes. Pulmonary examination revealed basilar crackles. Abdominal and genitourinary examination were negative for suprapubic or costovertebral tenderness. Skin examination demonstrated nontender, nonpalpable, and superficial bruising on the upper extremities bilaterally. Cardiac, neurologic, and musculoskeletal examination were unremarkable. Laboratory work-up revealed the following (reference ranges are provided in parentheses): hemoglobin, 9.7 g/dL (13.5 to 17.5 g/dL); platelets, 142x10^9/L (150 to 450x10^9/L); white blood cells, 3.1x10^9/L (3.5 to 10.5x10^9/L); sodium, 133 mmol/L (135 to 145 mmol/L); bicarbonate, 18 mmol/L (22 to 29 mmol/L); blood urea nitrogen, 64 mg/dL (8 to 24 mg/dL); serum creatinine, 2.9 mg/dL (0.74 to 1.35 mg/dL) with patient’s baseline being 1.5 mg/dL; and an albumin of 2.8 g/dL (3.5 to 5.0 g/dL). Urinalysis showed 2060 mg of predicted 24-hour protein, red blood cell casts, and a negative Gram stain. A chest x-ray demonstrated a new small right pleural effusion. Computed tomography (CT) scan of the abdomen and pelvis with intravenous (IV) contrast material showed irregular mucosal thickening of the bladder wall as well as bilateral pleural effusions.

The patient was admitted to the medicine floor service and treated with IV maintenance fluids and ciprofloxacin for possible urinary tract infection and suspected dehydration. Unfortunately, he became markedly oliguric and progressively confused over the next few days. Repeat electrolyte panel demonstrated: serum creatinine, 4.9 mg/dL; blood urea nitrogen, 97 mg/dL; and bicarbonate, 15 mmol/L, and urgent dialysis was started through a temporary catheter. During his second run of dialysis, he became acutely agitated and tachycardic, requiring transfer to the intensive care unit. Follow-up laboratory test results demonstrated C-reactive protein (CRP), 43.3 mg/L (≤8.0 mg/L) and erythrocyte sedimentation rate (ESR), 32 mm/1 hour (0 to 22 mm/1 hour) as well as total complement, 15 U/mL (30 to 75 U/mL); complement C3, 31 mg/dL (75 to 175 mg/dL); and complement C4, 11 mg/dL (14 to 40 mg/dL). Peripheral smear demonstrated no schistocytes and hypochromic microcytic red blood cells.

1. Given this patient’s clinical presentation, which one of the following is the most likely diagnosis?
   a) Antiglomerular basement membrane (GBM) disease
   b) Thrombotic thrombocytopenic purpura (TTP)
c) Cryoglobulinemia
d) Systemic lupus erythematosus (SLE) with renal involvement
e) Granulomatosis with polyangiitis (GPA) with renal involvement

In the setting of red blood cell casts and acute renal failure, anti-GBM disease may be suspected. However, it is not as likely, given that the patient did not have clinical or imaging evidence of pulmonary hemorrhage. Furthermore, anti-GBM disease is not usually associated with low complement levels; TTP may also be considered, given his altered mental status and acute renal failure. One of the hallmarks of TTP is microangiopathic hemolytic anemia and the presence of schistoocytes on the peripheral smear, which are not seen in our patient. In addition, even though he had mild thrombocytopenia, TTP is typically characterized by marked thrombocytopenia (range 30x10^9/L to 50x10^9/L). Thus, it is not the most likely diagnosis.

Cryoglobulinemia can be a cause of glomerulonephritis with low complement, and it can occur in the setting of hepatitis B, hepatitis C, or HIV. Patients should have very low C4, but C3 can be normal. In addition, most patients with cryoglobulinemia demonstrate the clinical triad of palpable purpura, weakness, and arthralgia early in the disease course. Our patient had low C3 and C4 levels. Moreover, he had weakness but no characteristic cutaneous signs such as palpable purpura, hemorrhagic crusts, or necrotic lesions.

Constitutional symptoms in SLE can include fever, weakness, and weight loss. Lupus nephritis is a common initial presentation. Characteristic laboratory findings include cytopenias, elevated ESR, and decreased total complement and complement C3 and C4 levels. This patient’s presentation, in addition to serositis (pleural effusions), his history of positive ANA, and skin biopsy with complement deposition are concerning for SLE with lupus nephritis.

Patients with GPA may have a similar presentation as patients with SLE, including fever, malaise, and renal failure. They may provide additional history of ear, nose, throat, and pulmonary manifestations such as nasal bleeding, sinusitis, mucocutaneous ulcers, and alveolar hemorrhage. Certainly, his age and racial background are more associated with GPA rather than SLE. However, the level of complement depression, positive ANA history, low albumin, the presence of pleural effusions, and leukopenia fit best with SLE rather than GPA.

Additional laboratory findings showed the following: double-stranded DNA (dsDNA) IgG antibody with reflex, 482 IU/mL (<30.0 IU/mL); and ANA, 7.8 U (<1.0 U). Results of hepatitis B and C serologies as well as cryoglobulins were negative. The patient’s agitation decreased gradually, but his mental status continued to fluctuate.

2. Which one of the following tests would be the highest yield in diagnosing the cause of this patient’s renal failure?

a) Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP)
b) Renal biopsy
c) Antineutrophil cytoplasmic autoantibodies (ANCA)
d) Anti-glomerular basement membrane (anti-GBM) antibodies
e) Urine cytology

Serum protein electrophoresis and UPEP are used in diagnosis of monoclonal gammopathies. They can cause albuminuria, nephrotic syndrome, and subacute renal dysfunction: monoclonal gammopathy of renal significance. However, the patient’s antibody and complement testing are more concerning for lupus nephritis.

His work-up demonstrates findings of nephritic syndrome, including hematuria, proteinuria, and cellular casts. Renal biopsy is necessary to establish his diagnosis and to guide the next steps in treatment.

Anti-neutrophil cytoplasmic antibody glomerulonephritis and anti-GBM disease should be in the differential for glomerulonephritis (GN). A mild decrease in complement may be seen with ANCA GN (whereas anti-dsDNA elevations are not), but levels of complement are typically normal in anti-GBM, and a renal biopsy can be used to confirm
either of these diagnoses. Urine cytology would be indicated in the setting of suspected bladder or urinary tract malignancy as in the setting of new microscopic or gross hematuria. The patient’s course is not suggestive of genitourinary malignancy.

The patient had findings concerning for GN. Although his laboratory findings were consistent with SLE, it was very unusual that an elderly Caucasian man would have SLE with renal failure as his initial manifestation. He had a kidney biopsy, and it demonstrated a diffuse proliferative glomerulonephritis with 21 of 54 glomeruli that were globally sclerotic. There were mesangial, subendothelial, and subepithelial deposits on electron microscopy and positivity for IgA, IgG, IgM, C1q, and C3 on immunofluorescence. He was diagnosed with SLE and class IV lupus nephritis.

3. Given his diagnosis, what would be the best management strategy for this patient?
   a) Evaluation for kidney transplant
   b) Initiation of mycophenolate and hydroxychloroquine
   c) Initiation of cyclophosphamide infusion
   d) Initiation of intravenous methylprednisolone, rituximab infusion, and hydroxychloroquine
   e) Initiation of intravenous methylprednisolone, mycophenolate, and hydroxychloroquine

Renal transplantation at this time would not be appropriate. Recommendations for those with rapidly progressive renal failure (as opposed to end-stage renal disease from chronic lupus nephritis and scarring rather than active disease) are to treat with immunosuppression therapy for several months to reduce lupus activity and allow time for renal recovery.1

The goal of initial immunosuppressive therapy in lupus nephritis is induction of complete renal response and preservation of renal function. Hydroxychloroquine is recommended as it improves response to therapy, reduces risk of flare, and delays progression to kidney failure. It is always used in combination with stronger immunosuppressive therapy. Mycophenolate mofetil is a first-line option for lupus nephritis. However, severe disease should be treated as well with high-dose IV glucocorticoids for rapid-acting immunosuppressive effect; therefore, answer “b” would not be the best option.1

Intravenous cyclophosphamide may be used in place of mycophenolate and has shown similar efficacy.2 However, glucocorticoids are again required for rapid effect. Rituximab is a B-cell–directed therapy that may be used in relapsed or refractory lupus nephritis. However, randomized controlled trials failed to show improvement in outcomes when rituximab was added to the standard of care. Therefore, its current role is mostly for the treatment of refractory cases.3

Answer choice “e” would be the most appropriate regimen for this patient; the combination of rapid-acting glucocorticoids with longer-acting immunosuppressive medications will treat his acute illness and induce remission.

The patient was started on induction therapy with high-dose IV methylprednisolone, mycophenolate, and hydroxychloroquine for management of lupus nephritis with rapid improvement in mental status. Following a 3-day course of methylprednisolone, he was transitioned to oral prednisone. His urine production gradually increased, although he did require continuation of dialysis on discharge while awaiting further renal recovery.

4. Which of the following is most appropriate for assessing this patient’s disease activity, response to therapy, and monitoring for relapse in the future?
   a) Serial renal biopsies to assess for histologic remission
   b) Regular ANA levels, anti-Smith antibodies, and anti-dsDNA titer
   c) Regular urine protein, serum creatinine, anti-dsDNA titer, complement C3, and complement C4 levels
   d) Regular serum electrolytes and creatinine
   e) Regular ESR and CRP levels

Monitoring patients during maintenance therapy after hospitalization involves regular
follow-up to evaluate for response and medication toxicity. Serial renal biopsies are not typically indicated, as history, physical examination, and laboratory test results are sufficient for monitoring response and for relapse. In addition, they have high cost and carry risk of bleeding and infection; ANA titers do not correlate with lupus nephritis (or SLE) disease activity, so they are not used for monitoring. Anti-Smith antibodies are highly specific for SLE but also do not correlate with activity.

Anti-dsDNA titers have very high specificity for the diagnosis of SLE, and they have been demonstrated to have utility in monitoring disease activity. These titers in combination with other markers that fluctuate with disease activity, including urine protein and serum creatinine for kidney function and complement C3 and C4 levels for systemic activity, are used to identify flares and inadequate immunosuppression, making "c" the best option.

Although serum electrolytes and creatinine vary with kidney function, they do not fully monitor for SLE activity and may remain stable despite persistent active disease; ESR and CRP levels reveal underlying inflammation but are nonspecific to SLE and elevated in many other inflammatory disorders and in infection.

The patient was continued on mycophenolate, hydroxychloroquine, and prednisone with good response. His renal function improved, enabling him to come off dialysis within a month of hospital discharge. Repeat laboratory tests demonstrated normalization of dsDNA IgG antibody and complements C3 and C4. His urine protein to creatinine ratio was 1.38 compared with 6.59 while hospitalized. There were no dysmorphic red blood cells or casts. He was tapered off prednisone and was continued on hydroxychloroquine and mycophenolate for long-term maintenance therapy.

5. Which one of the following is a common serious complication of this patient's therapy?
   a) Infections
   b) Retinopathy
   c) Acute liver failure
   d) Pancreatitis
   e) Deep venous thrombosis (DVT)

Because mycophenolate and glucocorticoids are effective immunosuppressive medications, infections are 1 of the most common serious side effects related to therapy. Hospitalization rates for serious infections in SLE increased in the last few decades, reaching more than 12 times higher than in patients without SLE. Thus, choice "a" is the best answer. Hydroxychloroquine has been associated with retinal toxicity. Patients are required to have yearly eye examinations for monitoring. However, hydroxychloroquine retinopathy is very rare, particularly in the first 5 years of use. Mycophenolate has been known to cause transient elevations in liver enzymes but is rarely associated with acute liver failure. Gastrointestinal symptoms including diarrhea, stomach upset, and nausea are common with mycophenolate therapy. However, pancreatitis is a very rare side effect of mycophenolate. Finally, thrombosis is not an expected side effect from the therapeutic agents; however, multiple inflammatory diseases are associated with increased risk of DVT.

Within a year after starting immunosuppressive therapy, the patient was hospitalized again because of sepsis from a urinary tract infection. He responded rapidly to antibiotics and was continued on the same maintenance therapy. He remained in serologic remission with significant improvement in renal function through the next 2 years. As a result, outpatient nephrology and rheumatology jointly decided to taper him off mycophenolate completely to reduce side effects, especially given the history of sepsis. To this day, he has remained in remission while only on hydroxychloroquine.

DISCUSSION
Systemic lupus erythematosus is an autoimmune disease of unknown cause that can affect any organ system in the body. Kidney involvement is common with approximately 40% of all patients with SLE developing lupus nephritis. Pathogenesis involves glomerular injury caused by the deposition of immune
complexes, primarily anti-dsDNA antibodies bound to DNA. These complexes trigger the activation of complement leading to an influx of neutrophils and other mononuclear cells. As a result, proliferative glomerulonephritis occurs with proteinuria and an acute decline in renal function. Diagnosis and classification of lupus nephritis are established via kidney biopsy and histology. Histopathologic features may be varied in lupus nephritis, but some are highly characteristic. These include the “full house” immunofluorescence pattern of glomerular deposits staining for IgG, IgA, IgM, complement C3, and complement C1q; subepithelial glomerular deposits seen at the same time; and extraglomerular immune deposits.

Medical management of lupus nephritis involves an induction phase and a maintenance phase and depends on classification. Class I and II lupus nephritis has no or mild clinical and histopathological manifestations; thus, they do not typically require medical therapy. Class III and IV patients commonly have more severe clinical signs and symptoms including hematuria, proteinuria, decreased glomerular filtration rate, and hypertension. These patients require prompt medical treatment to preserve renal function. Class V can be treated with renin-angiotensin-aldosterone system (RAAS) blockers if the patient has subnephrotic proteinuria. Those with nephrotic-range proteinuria of more than 1 g/24 hour of urine protein despite adequate RAAS blockade are treated with immunosuppression. Class IV patients typically have more advanced sclerosing disease that can be irreversible, and they benefit more from renal transplant rather than medical management. The induction phase typically involves glucocorticoids and either cyclophosphamide or mycophenolate. The Aspreva Lupus Management Study (ALMS), one of the largest randomized control trials studying lupus nephritis, compared the efficacy of cyclophosphamide and mycophenolate, both in combination with glucocorticoids during induction therapy. The study showed comparable responses to mycophenolate and cyclophosphamide (56.2% vs 53%, respectively) with response defined as a decrease in proteinuria and an improvement or stabilization in serum creatinine. For the maintenance phase, mycophenolate is often continued. Hydroxychloroquine has been a mainstay in SLE treatment given its safety profile and reversibility and should be used adjunctively. It has been associated with higher rates of response to therapy and lower rates of relapse. Hydroxychloroquine has been classically associated with retinal toxicity, but this has been demonstrated to be rare. Mycophenolate has been used more frequently in recent times owing to its efficacy and fewer side effects compared with cyclophosphamide: in particular, the risk of secondary malignancy and infertility.

Even after induction and maintenance therapy, a subset of patients will continue to have worsening renal function. Eventually, they will require dialysis or renal transplant. In these patients, there was concern for recurrent lupus nephritis in the transplanted kidney with risk of graft failure. A large case-control study encompassing 6850 kidney allograft recipients for lupus nephritis demonstrated that recurrence was uncommon, with only 2.44% developing recurrent lupus nephritis, whereas 25.8% experienced rejection. Although lupus nephritis can recur after transplant, it contributes far less than rejection to graft failure. Moreover, the outcomes of patients with SLE who undergo renal transplants are significantly better than those who receive dialysis. Thus, patients with SLE that progress to end-stage renal disease are appropriate candidates for renal transplant.

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CORRECT ANSWERS: 1. d. 2. b. 3. e. 4. c. 5. a.