Renal Involvement in Systemic Lupus Erythematosus: Review Questions

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QUESTIONS

Choose the single best answer for each question.

Questions 1 and 2 refer to the following case.

A 25-year-old woman presents to her primary care physician with joint pain and a red rash, which first appeared while vacationing in Florida 2 months ago. The rash started over the bridge of her nose and then spread to her cheeks, and it appears to worsen when she is in the sun. The patient states that she has felt tired for the last 3 months but attributed the fatigue to work-related stress. She also has noticed blood in her urine for the last 3 months but was too busy at work to see her physician. On examination, blood pressure is 160/90 mm Hg. Evaluation of the patient's scalp demonstrates alopecia, and she has significant lower extremity edema. Initial laboratory results demonstrate a hemoglobin level of 9.1 g/dL, a white blood cell count of 4000 cells/μL, a platelet count of 60,000 cells/μL, and a positive antinuclear antibody (ANA) test.

1. **Which test should be performed next?**
   (A) Anti-cyclic citrullinated peptide antibody test
   (B) Anti–double-stranded (ds) DNA test
   (C) Anti-Sm antibody test
   (D) Urinalysis

2. **A 24-hour urine collection reveals 3000 mg of protein. Renal biopsy is performed, which reveals cellular proliferation with increased mesangial, epithelial, and endothelial cells and inflammation in more than 50% of glomeruli. Which of the following is most likely associated with this patient's renal disease?**
   (A) Anti-dsDNA antibodies
   (B) Anti-RNA antibodies
   (C) Anti-Sm antibodies
   (D) Antinuclear antibodies

Questions 3 and 4 refer to the following case.

A 30-year-old woman with fatigue, arthralgia, alopecia, and weight loss for 4 months presents to her primary care physician after going to the beach and developing a red rash on her face. The rash initially developed over the bridge of her nose and later spread to her cheeks but spared the nasolabial fold. Urine dipstick analysis demonstrates 2+ protein, microscopic urinalysis reveals dysmorphic erythrocytes and cellular casts, and a 24-hour urine collection reveals 1500 mg of protein. Renal biopsy is performed, which demonstrates increased mesangial, epithelial, endothelial, and inflammatory cells involving more than 70% of glomeruli.

3. **What is this patient's diagnosis?**
   (A) Diffuse membranous glomerulonephritis
   (B) Diffuse proliferative glomerulonephritis
   (C) Focal segmental glomerulonephritis
   (D) Mesangial nephritis

4. **What is the treatment of choice for this patient?**
   (A) Cyclophosphamide alone
   (B) High-dose intravenous (IV) steroids alone
   (C) High-dose IV steroids with adjunctive cyclophosphamide
   (D) Mycophenolate mofetil

5. **A 22-year-old woman presents to her primary care physician with oral ulcers, arthralgias and myalgias in her hands, and fatigue. Urinalysis demonstrates 10 to 12 red blood cells/high-power field, red blood**

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cell casts, and white blood cell casts. A 24-hour urine collection reveals a protein level of 3500 mg. Anti-Sm and anti-dsDNA tests are negative. What is the next step in this patient's management?

(A) Blood pressure monitoring
(B) Complete metabolic panel
(C) Renal biopsy
(D) Renal ultrasound

6. **Which of the following manifestations of systemic lupus erythematosus (SLE) has been strongly associated with a poor outcome?**

(A) Discoid rash
(B) Lupus nephritis
(C) Myocardial infarction
(D) Pleuritis

7. **Which of the following is the most common cause of death in patients with SLE?**

(A) Cardiovascular disease
(B) Pulmonary hypertension
(C) Renal failure
(D) Vasculitis

ANSWERS AND EXPLANATIONS

1. **(D) Urinalysis.** This patient has 6 of the 11 diagnostic criteria for SLE: malar rash that developed from the bridge of the nose to the cheeks and spared the nasolabial fold, photosensitivity, alopecia, symmetric polyarthritis, anemia, and a positive ANA test. Renal involvement significantly affects the morbidity and mortality of patients with SLE.[1] Glomerulonephritis is clinically silent and may only be suspected if the patient has accompanying hypertension or edema. Urine protein level is a measurement of renal lupus activity. Microscopic analysis of a fresh sample of urine is the most sensitive clinical assay for detecting glomerulonephritis and may reveal dysmorphic erythrocytes and cellular casts before serum creatinine becomes elevated. A baseline 24-hour urine collection also should be performed to measure protein, creatinine, and free cortisol or steroid metabolite levels and to calculate creatinine clearance.

2. **(A) Anti-dsDNA antibodies.** Anti-dsDNA antibodies are associated with the immunopathologic events in SLE, especially glomerulonephritis. This association has been demonstrated by correlating anti-DNA serum levels with periods of disease activity, isolating anti-DNA from glomeruli of patients with active nephritis, and inducing nephritis by administering anti-DNA antibodies to normal animals.[2] The occurrence of nephritis without anti-DNA may be explained by the pathogenicity of other autoantibodies, such as anti-Ro or anti-Sm antibodies.

3. **(B) Diffuse proliferative glomerulonephritis.** Based on this patient's 24-hour urine collection (1500 mg protein) and renal biopsy results, she has diffuse proliferative glomerulonephritis, or World Health Organization (WHO) class IV disease. The WHO classifies lupus nephritis into 5 categories based on histology and location of the immune complexes. In WHO class I, the kidney is considered normal; there is no immune complex deposition or bland urine sediment, and 24-hour urine collection yields proteinuria less than 200 mg. WHO class II (mesangial nephritis) is characterized by immune complex deposition only in the mesangium. Red blood cells may be present in the urine sediment or the sediment may be bland. The 24-hour urine collection reveals proteinuria ranging from 200 to 500 mg. WHO class III (focal segmental glomerulonephritis) is characterized by mesangial and subendothelial immune complex deposition, urine sediment that includes both red blood cells and white blood cells, and proteinuria ranging from 500 to 3500 mg on 24-hour urine collection. In patients with class III disease, serum creatinine and blood pressure may be normal to mildly elevated. Testing for anti-dsDNA antibodies is positive and C3/C4 levels are decreased. WHO class IV (diffuse proliferative glomerulonephritis) consists of mesangial and subendothelial immune complex deposition. The urine sediment is filled with red blood cells, white blood cells, and red blood cell casts. The 24-hour urine collection reveals proteinuria ranging from 1000 to 3500 mg. Serum creatinine ranges from normal to extremely elevated to the extent that the patient is dialysis-dependent. Patients with class IV disease are usually hypertensive, have low serum complement levels, and test positive for anti-dsDNA antibodies.[3] In WHO class V (diffuse membranous glomerulonephritis), global or segmental subepithelial deposits are present. The urine sediment is bland, 24-hour urine collection demonstrates more than 3000 mg of protein, serum creatinine is normal to mildly elevated, and blood pressure is normal.

4. **(D) Mycophenolate mofetil.** In the past, glucocorticoids and cyclophosphamide were the treatments of choice in patients with proliferative nephritis. High-dose steroids given as IV boluses (pulse therapy) were effective for rapidly controlling acute

glomerular inflammation. Cyclophosphamide is an important adjunct to steroid therapy and has effectively preserved renal function over the long term as compared with steroids alone.[4] Cyclophosphamide administered as an IV bolus is as efficacious as oral therapy and appears to be less toxic. The currently recommended initial regimen for a patient with proliferative nephritis is mycophenolate mofetil 1 g twice daily for the first 6 months followed by 0.5 mg for 6 months. The patient should be treated for lupus nephritis for 1 year with the goals of inducing remission, maintaining effective prophylaxis against relapse, and prevention of renal failure. Mycophenolate mofetil has been proven to be better tolerated than IV cyclophosphamide.[5]

5. **(C) Renal biopsy.** Biopsies are not required to diagnose lupus nephritis but are extremely helpful when the diagnosis is highly suspected but symptoms are not suggestive.[6] This patient has several manifestations of SLE (ie, joint pain, oral ulcers, proteinuria), but at least 4 criteria should be met to make a diagnosis. Although both anti-dsDNA and anti-Sm antibody tests are negative in this case, these tests are 100% specific for SLE but are not very sensitive.[7] Tissue biopsy can confirm the diagnosis and assess disease severity. Given the importance of identifying pathologic features suggestive of more aggressive disease (eg, crescents), some use results of renal biopsy to guide therapeutic decisions.

6. **(B) Lupus nephritis.** The kidney appears to be one of the main organs affected by SLE. Renal disease is present in one half to two thirds of patients with SLE. Essentially all studies of prognosis have identified lupus nephritis as an important predictor of poor outcome.[6]

7. **(A) Cardiovascular disease.** Accelerated atherosclerosis is an important cause of morbidity and mortality in SLE. Patients with SLE are 10 times more likely to die from myocardial infarction as compared with the general age- and sex-matched population. Autopsy studies support the clinical data, demonstrating severe coronary artery atherosclerosis in up to 40% of patients with SLE compared with 2% of control patients matched for age at the time of death.[8]

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