

# AAM Case Discussion Guide

## Key Learning Objectives

- List the differential diagnosis for a systemic disease presentation in a young person.
- Discuss the key elements of diagnosing systemic lupus erythematosus and lupus nephritis.
- Determine the appropriate questions to ask consultants in the inpatient setting.
- Discuss how limitations in access to care impact clinical care.
- Summarize treatment options in a patient with lupus nephritis.

## History of Present Illness

A 25-year-old Black male kindergarten teacher presented to the emergency department (ED) with the complaint of “not feeling well.” Specifically, he has had 6 months of fatigue, productive cough, dyspnea on exertion, myalgias, arthralgias, poor sleep, and a painful rash on his legs. He also reported high fevers (40 °C, 104 °F), anorexia with a 15-pound (6.8 kg) weight loss, headache, rash, and dizziness.

He denies recent travel, sick contacts, or animal exposures. Over the past few months, he was seen at multiple EDs for these complaints and has been treated with antibiotics for a series of presumed infections.

Although an ED physician recommended he follow up with a primary care physician, he has not because he has no health insurance and has to pay out-of-pocket.

He denies any past medical history other than this recent illness. His family history is only remarkable for one relative with thyroid cancer. He has no family history of autoimmune disease.

He is a college biology graduate working as an assistant kindergarten teacher in a public school system. As an assistant teacher, he is not eligible for employer-sponsored healthcare benefits.

He drinks alcohol occasionally. He denies tobacco and drug use and lives at home with his mother. He is sexually active and uses protection most of the time. He has no known drug allergies.

With this presentation, what broad disease categories are in your differential diagnosis?

Infections, including human immunodeficiency virus (HIV), viral hepatitis, Epstein-Barr virus, cytomegalovirus, parvovirus, and tuberculosis (TB) should be considered, as well as malignancies like lymphoma or leukemia. Other broad categories of a systemic disease presentation should include lupus and other connective tissue diseases. Other conditions, such as granulomatous diseases like sarcoidosis, should also be considered.

Is a more detailed sexual history important in this case? Why/why not?

Absolutely. This is a young male with a constellation of symptoms that can be seen in the presentation of several sexually transmitted diseases, including HIV and syphilis.

## Physical Exam

Height: 5'10"  
Weight: 150 lbs

Vitals: Blood pressure 130/79, heart rate 118/minute, respiratory rate 22/minute, O<sub>2</sub> saturation 98% on room air, temperature 37.7 °C (99.1 °F)

General: Appears chronically ill, but in no distress

Head, Eye, Ear, Nose, and Throat (HEENT): No mucous membrane lesions, no thrush

Pulmonary: Clear to auscultation bilaterally, no wheezes or rhonchi

Cardiovascular: Normal S1 S2, regular rhythm, tachycardic, no murmurs

Abdomen: Soft, + bowel sounds, nontender, nondistended, no organomegaly

Neurologic: Awake, alert, oriented, no focal deficits

Musculoskeletal: Tenderness and synovitis of metacarpal phalangeal 2–4 bilaterally and subtle bilateral ankle synovitis without tenderness or limited range of motion

Skin: Erythematous and hyperpigmented facial rash with flat scarred central areas. Erythematous lesions on anterior shins and buttocks, some of which are tender, periungual hemorrhages bilateral hands, 1+ bilateral lower extremity edema

Lymph Nodes: Notable for small (approximately 1 cm) bilateral submandibular, epitrochlear, and inguinal nodes, right axilla with firm 4 x 3 cm node and left axilla with multiple palpable lymph nodes, largest about 2 x 2 cm



*Image courtesy of the American College of Rheumatology Image Bank.*

The images included in this case are for example only and are not those of the individual described in the case.

He is admitted to a medical floor. A workup is started, and the patient is given intravenous (IV) fluids. No other empiric treatment is begun since the patient is hemodynamically stable. Dermatology is consulted.

What data would you like to obtain first and why?

Factors such as the time it takes to receive test results and cost should be considered. Basic labs including a comprehensive chemistry, complete blood count (CBC) with differential, urinalysis with microscopy, and blood and urine cultures are reasonable tests to start with as they are relatively low in cost.

### Laboratory Data

#### Complete Blood Count (CBC):

White blood cell count (WBC):  $1.6 \times 10^3/\mu\text{L}^*$

White count differential: 55% segmented neutrophils (absolute neutrophils  $1040/\mu\text{L}^*$ ), 23% lymphocytes (absolute  $368/\mu\text{L}^*$ ), 10% monocytes, 2% eosinophils

Hemoglobin: 11.3 g/dL\*

Hematocrit: 33.3%\*

Mean cell volume: 82 fL

Platelets: 114,000/ $\mu\text{L}^*$

Prothrombin time: 12.1 seconds; international normalized ratio: 1.0

#### Urinalysis:

2+ protein\*

2+ blood\*

WBC: 11–25 high power field (hpf)\*

Red blood cells: 25–50 hpf\*

Granular casts: 6–10 hpf\*

Cellular casts: 6–10 hpf\*

Blood urea nitrogen: 18 mg/dL

Creatinine: 1.3 mg/dL\*

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Serum electrolytes and liver tests: Within normal limits

Chest X-ray: Within normal limits

Electrocardiogram: Sinus tachycardia without any ST or T wave abnormalities

Echocardiogram: Normal

*\*Abnormal values*

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Summarize the abnormal findings in this patient's presentation and initial evaluation.

This is a young, previously healthy male who presents appearing chronically ill, with tachycardia, synovitis, rash, periungual hemorrhages, lower extremity edema, lymphadenopathy, and fever. Laboratory abnormalities include: leukopenia, lymphopenia, neutropenia, anemia, thrombocytopenia, and an active urinary sediment.

Here is a young, previously healthy, Black male kindergarten teacher with constitutional signs and symptoms as well as the above other clinical signs. How has your differential diagnosis changed?

After the physical exam revealed synovitis and rash, processes like a connective tissue disease could be higher on the list. It is reasonable to maintain a broad differential diagnosis at this point, since these physical findings can be seen in a variety of diseases, including infectious diseases and malignancies, such as lymphoma.

What workup would you like to do next and/or would you like to consult any subspecialty services?

It is important to initiate a workup, including evaluation for hematologic, infectious, and connective tissue processes. It would be reasonable to start this workup as the primary team, but it would not be inappropriate to consult infectious diseases, hematology, nephrology, and rheumatology at this point.

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The primary team initiates a comprehensive infectious workup, including hepatitis serologies, Epstein-Barr virus polymerase chain reaction (PCR), cytomegalovirus PCR, parvovirus antibodies, rapid plasma reagin, HIV testing, TB testing with purified protein derivative, both routine and fungal blood cultures, and urine culture. In addition, they begin a workup to evaluate the patient's pancytopenia and lymphadenopathy with iron studies and hemolysis labs. They also ask dermatology to see the patient for evaluation and skin biopsy.

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Given his active urinary sediment, in addition to consulting nephrology to request a renal biopsy, the team wants to order serologic testing for a possible connective tissue disease. They ask the rheumatology fellow for assistance in choosing appropriate screening tests.

What serologies would you order to evaluate for a possible connective tissue disease? What connective tissue diseases are you considering and what serologies would support that disease diagnosis? Generally what is the turnaround time for these tests?

You should consider connective tissue diseases, including systemic lupus erythematosus (SLE). Also consider various forms of systemic vasculitis.

Appropriate initial tests to order would be an antinuclear antibodies (ANA) test, anti-extractable nuclear antigens (ENA) and anti-dsDNA antibodies, complements C3 and C4, and antineutrophil cytoplasmic antibodies (ANCA). An ANCA could be positive in a patient with several types of vasculitis that can cause renal disease, but may also be positive in other diseases. However, the pathology of this disease is different from lupus nephritis in that glomerular damage occurs with little to no deposit of antibody and complement; this is referred to as pauci-immune. Lupus nephritis pathology is discussed later in the case.

The traditional ANA test performed by immunofluorescence (IF) has been considered the gold standard and was the technique used when diagnostic criteria for lupus were established for research studies. It has high sensitivity for the diagnosis of lupus but relatively low specificity. Therefore, serologies, particularly the ANA, are not diagnostic when considered alone and must be interpreted in light of the overall clinical picture. The higher the likelihood that someone has lupus based on clinical findings (high pretest probability), the higher the likelihood that a positive ANA is indicative of lupus. ANA tests can be positive in patients without connective tissue diseases. They can also be seen in family members of those with connective tissue diseases and are often seen in other conditions, such as autoimmune thyroid disease. It should also be recognized that in some clinical laboratories, the classic ANA by IF has been supplanted by an enzyme-linked immunosorbent assay (ELISA) based test because it is less costly. However, there are more limitations with both the sensitivity and specificity of the ELISA test compared with the ANA by IF.

In a patient with active urinary sediment secondary to lupus nephritis, we generally would expect to see positive anti-dsDNA antibodies and low complements. Renal involvement occurs in 40%-60% of those with SLE, although the type and severity vary. Anti-dsDNA antibodies are common in SLE, particularly in lupus nephritis, where titers may correlate with the activity of nephritis.

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## Data

The infectious workup is negative, including routine and fungal blood cultures as well as urine culture.

The anemia workup includes laboratory tests and an evaluation of a peripheral blood smear. The workup revealed spherocytes and decreased platelets and white cells, low haptoglobin, elevated lactate dehydrogenase (LDH), and a positive Coombs test. (A Coombs test is an antibody test used to test for hemolytic anemia.) Dermatology evaluated the patient, and the skin biopsy results are pending. They agree with the workup in place.

His pancytopenia is stable. His 24-hour urine protein reveals 3 grams of protein in 24 hours, and his spot urine protein-to-creatinine ratio estimates 2.7 grams/24 hours.

His serologic tests return:

ANA by IF: 1:1280 in a speckled pattern\*

C3: 18 mg/dL\*

C4: <4 mg/dL\*

anti-dsDNA: 546 U/mL\*

anti-Smith: 586 U/mL\* (part of the ENA testing)

anti-SSA: 862 U/mL\* (part of the ENA testing)

anti-SSB: 258 U/mL\* (part of the ENA testing)

ANCA: Not detected

\*Abnormal values.

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What type of anemia is this consistent with? How do you treat it?

The tests performed, including the spherocytes, the Coombs antibody, the low haptoglobin, and elevated LDH, all point to hemolysis, also known as autoimmune mediated hemolytic anemia, which is occasionally seen in lupus.

What conditions lower complement levels? Where is complement made?

Low complements can be seen in several conditions, including SLE, other immune complex mediated conditions, and primary genetic deficiencies. Hypocomplementemia due to complement consumption is highly suggestive of lupus. In the setting of severe hepatic failure, complements can be low as well because they are made in the liver. Conversely, they can be elevated in inflammation as acute-phase reactants.

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The preliminary results of the skin and renal biopsies follow:

#### Skin biopsy

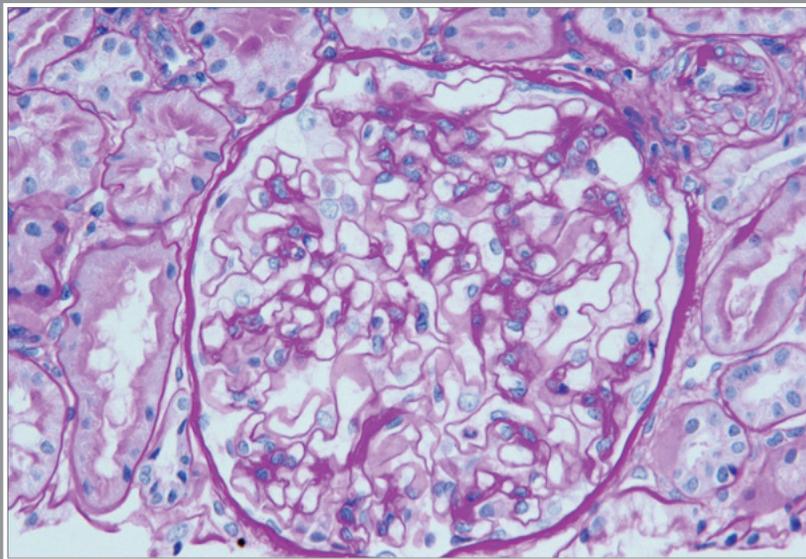
Hyperkeratosis, follicular plugging, epidermal atrophy, and periadnexal lymphocytic infiltrate; the IF is pending. This is consistent with lupus in the appropriate clinical setting.

#### Renal biopsy

- Focal lupus nephritis, International Society of Nephrology/Renal Pathology Society Class III, with active and chronic lesions
- Minimal interstitial fibrosis and tubular atrophy
- Minimal segmental glomerular sclerosis
- Active lesions with little evidence of chronicity
- Glomeruli and interstitium fairly well preserved

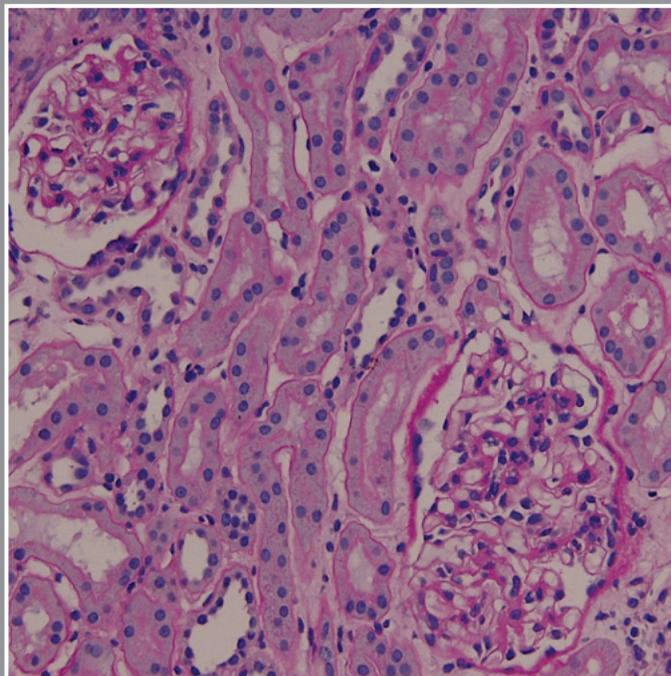
After an extensive workup, SLE is determined to be the unifying diagnosis. Clinical manifestations include lupus nephritis, pancytopenia (autoimmune hemolytic anemia, thrombocytopenia, leukopenia, neutropenia, lymphopenia), arthritis, rash, lymphadenopathy, positive ANA, hypocomplementemia, and elevated anti-dsDNA antibodies.

The following images are from a normal kidney biopsy and affected kidneys with lupus nephritis Class III.



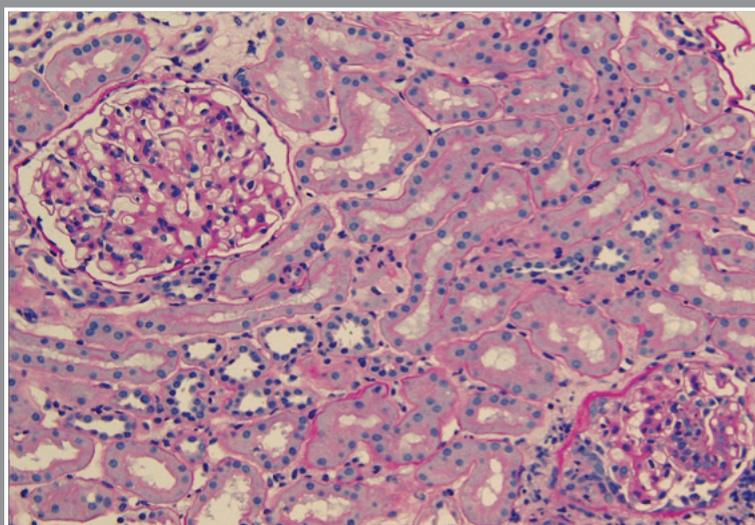
**Normal kidney**

*(Image courtesy of Dr. Anthony Chang, Department of Pathology, University of Chicago).*



**Lupus nephritis Class III**

*(Image courtesy of Dr. Anthony Chang, Department of Pathology, University of Chicago).*



**Lupus nephritis Class III**

*(Image courtesy of Dr. Anthony Chang, Department of Pathology, University of Chicago).*

How is lupus nephritis diagnosed? What is the clinical significance of having lupus nephritis in regard to long-term outcomes?

Lupus nephritis is diagnosed based on kidney biopsy. It is more common in Blacks, Hispanics, males, and children, and is a predictor of morbidity and mortality in patients with lupus.

How does the renal biopsy result direct treatment for lupus nephritis?

The results of the renal biopsy play a key role in directing the treatment course of a patient with lupus nephritis. However, the biopsy results have to be considered when assessing the entire clinical picture, including other manifestations of lupus, comorbidities, concomitant medications, and patient preference. In general, Classes I and II (mesangial) are not treated with cytotoxic agents. Classes III and IV (proliferative) are treated aggressively with immunosuppression, in particular with IV cyclophosphamide or mycophenolate mofetil. Class V (membranous) is treated with immunosuppression for those with significant proteinuria. Class VI (sclerotic) is indicative of irreversible damage and not responsive to treatment. It is important to note that there may be considerable overlap in the various forms of lupus nephritis, and biopsies often contain a mixture of classes.

What is the general approach to treatment of proliferative lupus nephritis? What are some of the options in induction and maintenance treatments and their pros and cons?

The general approach to treatment is first induction therapy to achieve control of the immune-mediated process causing renal injury. This is done with aggressive immunosuppression. After 6-12 months, the patient is transitioned to maintenance therapy with a less intensive immunosuppressive regimen for a longer period of time to minimize reoccurrence and medication toxicity.

Aggressive treatment is necessary because this form of proliferative lupus nephritis has a high rate of progression to end-stage renal disease, reported in some studies to be 10%–30%. The highest rates are in Blacks.

**Induction Therapy:** Treatment with either IV cyclophosphamide or oral mycophenolate mofetil along with corticosteroids (generally 1 mg/kg tapered over 6 months) for 6–12 months. For details on treatment of lupus nephritis and current guidelines, please see the Lupus Initiative Lecture, Major Causes of Morbidity and Mortality in SLE. Although remission rates are around 50%, relapse is common at 30%–50% by 3 years. The American College of Rheumatology (ACR) guidelines recommend a 3-day IV corticosteroid pulse as part of induction therapy for Class III/IV.

These therapies have good efficacy in some patients but have significant toxicity due to their broad immunosuppression. The potential infectious complications of the immunosuppressive agents and prophylaxis against opportunistic infections during high-dose immunosuppression should be considered. There are no consensus guidelines, but treatment can include prophylaxis for pneumocystis jiroveci. Immunizations, including those against influenza and pneumococcus, should also be considered. Live, attenuated vaccines should not be given in patients on immunosuppressive therapy. All patients should be counseled on the use of reliable forms of contraception given that medications for induction (cyclophosphamide and mycophenolate mofetil) are teratogenic.

It is also important to note that not only are these treatments potentially teratogenic to a fetus, but that pregnancy in the setting of active lupus can adversely affect maternal and fetal health in the peripartum period.

### **Specific Toxicities**

#### Cyclophosphamide includes

- Premature gonadal failure (some treat with gonadotropin-releasing hormone antagonists at the same time for ovarian protection)
- Malignancy:
  - Bladder (pretreat with mesna and aggressive pre- and posthydration.)
  - Other types
- Teratogenicity
- Leukopenia
- Nausea, emesis

#### Mycophenolate mofetil includes:

- Teratogenicity
- Gastrointestinal (cramping, bloating, diarrhea, colitis)

#### Steroids include:

- Osteopenia, osteoporosis
- Diabetes, metabolic syndrome
- Cataracts, glaucoma
- Psychiatric disturbance
- Avascular necrosis
- Weight gain

**Maintenance Therapy:** Treatment is transitioned to either lower doses of mycophenolate mofetil or azathioprine. The length of treatment is not well defined.

Azathioprine includes:

- Hepatotoxicity
- Cytopenias
- Potential malignancy
- It is considered good clinical practice to obtain thiopurine methyltransferase genetic testing to determine the safety of using high-dose azathioprine. This should be done in conjunction with regular lab follow-up.

What are the treatment considerations for proteinuria as a result of lupus nephritis?

Tight control of blood pressure is crucial. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be utilized for blood pressure control and/or management of the proteinuria. Dyslipidemia is treated with statins. In some cases, hypercoagulability from proteinuria can be treated with anticoagulation or antiplatelet agents.

Ultimately he was started on a course of monthly IV cyclophosphamide, and the first dose was given in the hospital. (The ACR guidelines suggest mycophenolate mofetil in Blacks over cyclophosphamide as the drug of first choice for the initial agent.) He was given methylprednisolone sodium succinate while an inpatient, and switched to tapering doses of oral prednisone, calcium, and vitamin D supplementation as an outpatient. Additionally, hydroxychloroquine was started. His blood pressure was controlled. Approximately 6 months into treatment, his renal function recovered significantly, and he was switched to mycophenolate mofetil. He was feeling generally well and was able to return to work.

### **Notes:**

Refer to the Lupus Initiative Lecture series for more information.

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