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 room with complaints of “not feeling well.” Specifically, he has had one and a half months of fatigue, productive cough, dyspnea on exertion, myalgias, arthralgias, poor sleep, and a painful rash on his legs. He also reports high fevers (40 C, 104 F), anorexia with a 15-lb (6.8 kg) weight loss, headache, and dizziness.

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

Although an ER 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 employee-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?

Please refer to the Lupus Initiative lecture series. After reviewing the lectures by Drs. Davidson and Mackay, it should be clear to the students that infections (including HIV) and malignancies (like lymphoma or leukemia) should be considered in this patient. Other broad categories of a systemic disease presentation should include lupus and other connective tissue diseases as well as other conditions, such as granulomatous diseases like sarcoidosis.

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

Vital Signs: BP 130/79, HR 118, RR 22, Sat 98, Temp 37.7C (99.1 F)

General: Chronically ill appearing, but in no distress

HEENT: No mucous membrane lesions, no thrush

Pulmonary: Clear to auscultation bilaterally, no wheezes or rhonchi

Cardiac: Normal S1S2, RR, tachycardic, no murmurs

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

Neurologic: Awake, alert, oriented, no focal deficits

Musculoskeletal: Tenderness and synovitis of MCPs 2–4 bilaterally and subtle bilateral ankle synovitis without tenderness or limited ROM

Skin: Erythematous lesions on anterior shins and buttocks, some of which are tender, periungal hemorrhages bilateral hands, 1+ bilateral lower extremity edema

Lymph Nodes: Notable for small (approximately 1 cm) bilateral submandibular, epitrochlear, and inguinal nodes bilaterally, right axilla with firm 4x3-cm node and left axilla with multiple lymph notes, the largest about 2x2 cm.

PICTURES TO BE INSERTED FOR SKIN LESIONS AND THE PICTURE OF PERIUNGUAL HEMORRHAGES [PLEASE LET US KNOW IF YOU HAVE ANY TO CONTRIBUTE]

He is admitted to a medical floor in "guarded" condition. A workup is started and the patient is given IV fluids. No other empiric treatment is begun since the patient is hemodynamically stable.

What data would you like to obtain first and why?

This is a good opportunity to engage the students in prioritizing a workup for a complicated patient. Considerations such as the timing it takes to receive test results and cost should be considered. Basic labs, including a comprehensive chemistry, CBC with differential, urinalysis with microscopy, and blood and urine cultures, are reasonable tests to start with that are relatively low cost.

Data

WBC **1.6**: Segs 55% (absolute neutrophils **1040/mm^3**), lymphs 23% (absolute **368/mm^3**), Monos 10%, Eos 2%

Hb/Hct **11.3/33.3**, MCV 82

Platelets **114**

PT/INR 12.1/1.0

Urinalysis

2+ protein

2+ blood

WBC 11–25

RBC 25–50

Granular casts 6–10, cellular casts 6–10

BUN/Cr 18/**1.3**

Extended chemistry WNL

CXR –

EKG normal sinus rhythm

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

Review with students that this is a young, previously healthy, male who presents appearing chronically ill, with tachycardia, synovitis, rash, periungal hemorrhages, lower extremity edema, lymphadenopathy and fever. Laboratory abnormalities include: leukopenia, lymphopenia, neutropenia, anemia, thrombocytopenia, and 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? Be more specific.

After the physical exam revealed synovitis and rash, processes like a connective tissue disease could be higher on the list. It is reasonable for the students to maintain their 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 consult any subspecialty services?

It is important for the students 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 also would not be inappropriate to consult infectious diseases, hematology and rheumatology at this point.

The primary team initiates a comprehensive infectious workup, including: hepatitis serologies, Epstein-Barr virus PCR, cytomegalovirus PCR, parvovirus antibodies, RPR, HIV testing, TB testing with PPD, 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.

Given his active urinary sediment, in addition to ordering a renal biopsy, the team wants to order serologic testing to work him up 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?

The students should consider connective tissue diseases, including systemic lupus erythematosus (based on the previous discussion questions answered) and can also consider various forms of systemic vasculitis. Review Drs. Mackay and Davidson's lectures regarding serologic support for a diagnosis of SLE.

Appropriate initial tests to order would be an ANA, anti-Smith and anti-dsDNA antibodies, complements and antineutrophil cytoplasmic antibodies (ANCA). An ANCA could be positive in a patient with several types of vasculitis that can cause renal disease. The pathology of this disease is different, however, from lupus nephritis and is pauci-immune. We will discuss more about lupus nephritis pathology later in the case.

An ANA test can be done by the traditional gold standard immunofluorescence. However, in some labs it is now done by a screening ELISA test as it is more cost effective. However, there are some limitations with both the sensitivity and specificity of the ELISA test compared with immunofluorescence. The take-home point for the students is that serologies, particularly the ANA, is not diagnostic in and of themselves and must be interpreted in the setting of the overall clinical picture. ANA tests can be positive in patients without connective tissue diseases. They can be seen in family members of those with connective tissue diseases and are often seen in other conditions, such as autoimmune thyroid disease.

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

Data

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

Anemia workup includes an evaluation of a peripheral blood smear and reveals a positive Coomb's test, low haptoglobin and elevated LDH. 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.

During this time, he has become volume overloaded and his creatinine has steadily increased. Despite careful diuresis, he has refractory hyperkalemia and ultimately requires dialysis.

His serologic tests return:

ANA by immunoflorescence **1:1280 in a speckled pattern**

C3 **18**, C4 **<4 (low)**

anti-dsDNA **546 (high)**

anti-Smith **+ 586 (high)**

anti-SSA + **862 (high)**

anti-SSB + **258 (high)**

ANCA not detected

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

This is most likely a combination of an anemia of chronic disease and an autoimmune-mediated hemolytic anemia. However, the students should be sure to recognize that for complete assessment, iron studies should be done as well. In an anemia of chronic disease, treatment of the underlying condition should be emphasized. In a hemolytic anemia, appropriate assessment (including peripheral smear) for etiology must be done first (ie, evaluation for TTP). Autoimmune hemolytic anemia without evidence of TTP is treated initially with steroids.

What conditions lower complements 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.

A preliminary result of the skin and renal biopsies report:

Skin

"Interface dermatitis seen at dermal-epidermal junction, immunofluorescence pending. This could be consistent with lupus in the appropriate clinical setting."

Renal Biopsy

- **Focal lupus nephritis, ISN/RPS Class III (A/C)**
- **Minimal interstitial fibrosis with approximately 5% tubular atrophy**
- **Approximately 5% segmental glomerular sclerosis**
- **Mild activity without much evidence of chronicity**
- **The glomeruli and interstitium are fairly well preserved**

After an extensive workup, systemic lupus erythematosus 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.

PICTURE TO BE INSERTED OF NORMAL RENAL BIOPSY AND THAT OF CLASS III LUPUS NEPHRITIS [PLEASE LET US KNOW IF YOU HAVE ANY TO CONTRIBUTE]

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

The discussion at this point should focus on Dr. Davidson's lecture on lupus nephritis. As Dr. Davidson points out, lupus nephritis is more common in blacks, males, and children, and is a predictor of morbidity and mortality in patients with lupus.

The classification criteria for lupus nephritis should be reviewed, as should the classification for chronicity of lupus nephritis and how this classification can help predict response to treatment.

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

The results of the renal biopsy do not independently direct the treatment course of a patient with lupus nephritis. 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 intravenous cyclophosphamide or mycophenolate mofetil. Class V (membranous) is sometimes treated with immunosuppression, particularly those with significant proteinuria. Class VI (sclerotic) is indicative of damage and not responsive to treatment. It is important to note that there is 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?

Refer to Dr. Davidson's lecture on lupus nephritis.

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 to 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 lupus nephritis has a high rate of progression to end-stage renal disease (reported in some studies to be 10% to 30%; the highest rates are in blacks).

Induction therapy: Treatment with either cyclophosphamide or mycophenolate mofetil along with steroids (generally 1 mg/kg tapered over 6 months) for 6 to 12 months. Although remission rates are around 50%, relapse is common at 30% to 50% by 3 years.

These therapies have good efficacy in some patients, but have significant toxicity due to their broad immunosuppression. Discuss the potential infectious complications of the immunosuppressive agents and prophylaxis against opportunistic infections during high-dose immunosuppression. There are no consensus guidelines but can include prophylaxis for pneumocystis carinii. Immunizations, including those against influenza and pneumococcus, should also be considered. All patients should be counseled on the use of reliable forms of contraception given that the 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 active lupus can adversely effect maternal and fetal health in the peripartum period.

Specific Toxicities

Cyclophosphamide:

- Premature gonadal failure (some treat GnRH antagonists at the same time for ovarian protection)
- Malignancy: Bladder (pretreat with mesna and aggressive pre- and posthydration), lymphoma, cervical cancer
- Teratogenicity
- Leukopenia
- Nausea, emesis

Mycophenolate mofetil

- Teratogenicity
- Gastrointestinal (cramping, bloating, diarrhea)

Steroids

- Osteopenia/osteoporosis
- Diabetes/metabolic syndrome
- Cataracts/glaucoma
- Psychiatric disturbance

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

Azathioprine

- Hepatotoxicity
- Cytopenias

Discuss the approach to treatment of proteinuria as a result of lupus nephritis.

Tight control of blood pressure is crucial. ACE-inhibitors and angiotensin-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 the patient was started on a course of monthly intravenous cyclophosphamide, and the first dose was given in the hospital. He was given Solu-Medrol 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, and outpatient dialysis was arranged near his home.

Approximately 4 months into treatment, his renal function recovered significantly and he was taken off dialysis. After completing 6 months of IV Cytoxan, he was switched to mycophenolate mofetil. His renal function stabilized. Although he was left with chronic renal impairment with a glomerular filtration rate of 35, he was feeling generally well and was able to return to work.

Notes