AAF Case Discussion Guide

Key Learning Objectives

- List the differential diagnosis for a systemic disease presentation with multisystem involvement
- Identify the key questions from the history to look for when SLE is in the differential diagnosis
- Recognize key physical exam findings that support the diagnosis of SLE
- Summarize the approach to diagnosing SLE using physical exam and laboratory data
- Describe the neurologic manifestations of SLE, and how they are diagnosed and managed

History of Present Illness

The patient is an 18-year-old black female who has been admitted to the hospital.

Two months ago, she noted the slow onset of fatigue and diffuse muscle pains. She also describes a dark-colored rash on her face, hands, and feet. Her most recent evaluation was 1 month ago. At that visit, a complete blood count and urinalysis were performed. She was told that she had "anemia", a "urine infection," and that she had possible "endocarditis." She was prescribed iron supplements for the anemia, and an antibiotic for the infection, and was sent for a transthoracic echocardiogram, which was normal. She was told to follow up again in 2 months.

What other tests would you have ordered when working up this patient's initial complaints?

This patient's initial presentation is meant to highlight the diagnostic delay patients with SLE often experience at the onset of their symptoms. This patient's history is based on an actual case. Certainly the complaints of muscle pain and fatigue should have prompted a more extensive evaluation than she received, including a chemistry panel to look at electrolytes and creatinine, and a TSH to screen for thyroid dysfunction. In her age group, Epstein-Barr virus should be high on the differential diagnosis as well.

The clinician's suspicion of endocarditis demonstrates that a serious condition was suspected, illustrating that in many patients with SLE, clinicians suspect that "something is wrong," but are unsure about what diagnostic steps to take to further evaluate the symptoms. In this case, it is important to discuss with students that her clinical findings are not typical of acute endocarditis (no fever, splinter hemorrhages, Osler's nodes, or murmur on cardiac exam), nor was her evaluation for endocarditis complete. The evaluation of endocarditis includes routine laboratory studies, blood cultures, and a transesophageal echocardiogram to fully evaluate her valve structure. In addition, many clinicians will start antibiotics empirically. Also take this opportunity to highlight the epidemiology of lupus and the frequency of skin rashes and musculoskeletal manifestations at the onset of disease. When making a differential diagnosis, SLE should be on the list.

Over the last 2 weeks, the patient's fatigue worsened to having dyspnea on exertion after 3 minutes of walking. She started feeling feverish every morning and was not eating much due to loss of appetite. She called her physician who advised her to go to the ER for further evaluation. She was admitted from the ER for further workup of her symptoms.

Medications

Iron sulfate as prescribed

Past Medical History

None. No previous pregnancies. No history of blood clots.

Social History

Sophomore in college, lives in a dorm, majoring in biology. Denies use of tobacco, alcohol, illicit drugs, or sexual activity.

Family History

Mother with hypertension. Maternal grandmother with breast cancer. No family history of autoimmune disease.

Review of Systems

General: Positive for fever, chills, and fatigue

HEENT: No photophobia, no oral/nasal ulcers

Cardiovascular: No palpitations, no chest pain, no orthopnea, no paroxysmal nocturnal dyspnea, no lower extremity swelling

Pulmonary: Dyspnea on exertion after 3–5 minutes of walking or activity

Gastrointestinal: Normal

Genitourinary: Normal

Musculoskeletal: Generalized weakness, no swollen joints

Skin: Red rash on face, "different-looking" reddish palms, and soles slightly tender to palpation

Hematologic: No blood clots, no miscarriages

What specific review of systems questions are helpful in evaluating for SLE or other rheumatologic diseases?

Many patients with SLE have longstanding symptoms that they do not recognize are a manifestation of underlying autoimmune disease. These include sicca symptoms, alopecia, chronic fatigue, painless oral or nasal ulcers, Raynaud's phenomenon, synovitis or swollen/puffy joints, and photosensitivity. Rash is often overlooked by patients as a manifestation of a systemic illness, and sometimes it can be easy to overlook—located only at the hairline, on the scalp, or in the ear canals.

Physical Exam

Vitals: BP 94/56, pulse 118, respirations 18 (nonlabored), Temp 38.4 °C (101.4 °F), O2 saturation 100% on room air

General: Thin black female, uncomfortable from fever and acute illness

HEENT: Oropharynx clear, moist mucous membranes, pupils equal and reactive to light bilaterally, conjunctiva clear

Cardiovascular: Tachycardic, regular rhythm, no murmurs or rubs, peripheral pulses palpable and equal

Pulmonary: Clear to auscultation bilaterally without focal dullness to percussion

Gastrointestinal: Nondistended, positive bowel sounds, abdomen soft, nontender, no rebound/guarding, no organomegaly

Skin: Macular hyperpigmented rash over malar areas of cheeks, with erythema of palms and soles

{{PICTURES TO BE INSERTED [PLEASE LET US KNOW IF YOU HAVE ANY TO CONTRIBUTE]}}

What additional areas of the physical exam would you focus on when examining this patient?

Special attention should be focused on this patient's musculoskeletal and vascular exam, looking for synovitis and nailfold capillary changes. A thorough exam looking for lymphadenopathy, and neurologic exam focused on muscle strength should be performed.

Additional Data

- Anterior cervical chain lymphadenopathy, 2 nodes approximately 1.5 cm diameter each, nontender, freely mobile
- Synovitis of bilateral wrists and elbows with mild limitation of range of motion
- Periungual telangiectasias and capillary dropout
- Left ear canal with scaly, hyperpigmented rash consistent with discoid SLE

{{PICTURES TO BE INSERTED [PLEASE LET US KNOW IF YOU HAVE ANY TO CONTRIBUTE]}}

Initial Laboratory Data

Complete Blood Count**:** White cell count 2.8

White count differential: 61% segmented neutrophils, 29% lymphocytes, 8% monocytes, no eosinophils

Hemoglobin 9.0/hematocrit 25.7/MCV 86

Platelets 210

Comprehensive Metabolic Panel:

Sodium 133, potassium 4.2, chloride 105, bicarbonate 21

BUN 17/creatinine 0.7

Total protein 7.8/albumin 2.8

Total bilirubin 0.6/AST 32/ALT 36/alkaline phosphatase 50

Urinalysis: 30 mg/dL protein, no blood, 3+ WBC, no RBC

2-view chest x-ray: No cardiopulmonary process

EKG: Sinus tachycardia

Discuss her initial lab results. What findings might be consistent with SLE? What additional studies would you order?

Most notable in her CBC is leukopenia and anemia. It should be pointed out to the students that she is also lymphopenic with an absolute lymphocyte count of 812 cells/mm^3. It is important to note that her anemia is normocytic and therefore not characteristic of iron-deficiency anemia as previously suggested. The students should discuss possible etiologies of the normocytic anemia, including anemia of chronic inflammation, or possibly autoimmune hemolytic anemia related to a new diagnosis of SLE. To further evaluate these 2 possibilities, a ferritin should be ordered, as well as hemolysis studies such as LDH, haptoglobin, and a Coombs test.

The chemistry panel is notable for being essentially normal, except for a low albumin and increased globulin fraction. The students should discuss possible causes of low albumin in this patient, including renal loss (and the urinalysis does show some mild proteinuria), chronic illness, and malnutrition. The normal liver enzymes exclude liver disease as a cause of the hypoalbuminemia. Additionally, she has an increased globulin gap (total protein in general should be roughly 2x the albumin), which can indicate chronic inflammation, such as in SLE or HIV, or the production of a paraprotein, such as in multiple myeloma. To further work up the low albumin and proteinuria, a

spot urine protein: creatinine ratio or 24-hour urine protein collection should be performed. The presence of pyuria should be evaluated for the presence of a UTI. To further evaluate the increased globulin gap, additional workup to evaluate for causes of inflammation should be conducted, and if a paraprotein remains a concern, a protein electrophoresis may be ordered.

In summary, our patient is an 18-year-old black female, with fatigue, rash, and shortness of breath. Her initial evaluation reveals a constellation of clinical findings that includes fever, tachycardia, malar and discoid-appearing rash, lymphadenopathy, arthritis, leukopenia/lymphopenia, anemia, and mild proteinuria. This presentation is strongly suggestive of a new diagnosis of SLE, and an ANA should be sent to further evaluate for this.

It is often difficult to distinguish infection from the initial presentation of SLE, and additional workup for infection is needed. Other studies that may be helpful in this case include blood and urine cultures, EBV testing, HIV testing, RPR for syphilis given rash on palms and soles, creatine kinase to evaluate for muscle breakdown, and TSH to evaluate for thyroid disease. Malignancy, such as lymphoma, may also have a similar presentation that could account for the fever, tachycardia, lymphadenopathy, and cytopenias, but would not usually be associated with arthritis and rash.

Hospital Course

The patient was started on empiric antibiotics for urinary tract infection, and treated supportively with IV fluids for presumed sepsis. Blood and urine cultures were ordered, as well as a HIV, EBV, ANA, and RPR testing.

She improved slightly with IV fluids and empiric antibiotics and was less tachycardic by Hospital Day 2, but still felt persistently fatigued. She continued to have temps up to 38.7 C (101.6 F) daily.

By Hospital Day 3, her full infectious workup was negative, including blood and urine cultures. Her ANA returned to positive at 1:1280 in a speckled pattern. Urine studies showed less than 1 g/day of proteinuria.

Given her negative infectious workup, clinical findings characteristic of SLE, and a positive ANA, she was diagnosed with probable SLE.

What additional tests would you send to make a definitive diagnosis of SLE?

Specific autoimmune serologies, such as complement levels, anti-double-stranded DNA, and extractable nuclear antigens should be sent to help make a definitive diagnosis of SLE.

Hospital Course (Cont'd)

The patient was started on prednisone 40 mg daily. By Hospital Day 4, her arthritis had improved and she felt less fatigued. She defervesced and had no further fevers. She was started on hydroxychloroquine 400 mg daily. Specific autoimmune serologies, such as complement levels, anti-double-stranded DNA, and extractable nuclear antigens, were sent.

After being afebrile for 24 hours, the patient was discharged home, with instructions to follow up with rheumatology and primary care to obtain the results of pending studies and have any additional workup as an outpatient.

Three weeks after hospital discharge, the patient returned to the ER with a 1-day history of left arm, leg, and face weakness with a mild headache and nausea. She reported that earlier that morning she had transient difficulty speaking. She had been compliant with all her medications and had been feeling better until 1 day ago.

Physical exam revealed left-sided facial droop, decreased strength in the left upper and lower extremities, symmetric reflexes, and an unsteady, wide-based gait.

What do you suspect as the cause of this patient's new symptoms? What lab testing and radiographic testing should be pursued to further evaluate these symptoms?

Please refer to the Lupus Initiative lecture series. Dr. Davidson's lecture focused on the major causes of morbidity and mortality in SLE. One of these is neuropsychiatric manifestations of SLE, and in this young patient presenting with symptoms of a stroke, CNS vascular disease related to SLE and hypercoaguable state should be on the top of the differential.

Since her symptoms are most consistent with an ischemic stroke, she should be evaluated with CT and MRI, and also tested for antiphospholipid antibodies. Use this opportunity to discuss how antiphospholipid antibody syndrome is diagnosed. As per Dr. Aranow's lecture, this diagnosis is made based on clinical evidence of clot (ie, stroke, deep venous thrombosis, or pulmonary embolus) with laboratory evidence of hypercoagulability (ie, positive anticardiolipin 1 antibody, lupus anticoagulant, or positive anti-beta-2 glycoprotein 1 antibody). These tests should be sent to evaluate if laboratory evidence of hypercoagulability is present now that she has clinical evidence of clot based on her symptoms. This is also a good opportunity to re-emphasize that the term "lupus anticoagulant" is a misnomer because it is actually associated with hypercoagulability. Its name is derived from its tendency to cause a prolonged PTT on routine coagulation testing because the antibodies interfere with phospholipids used to perform the test.

Additional Hospital Data

Our patient received a CT of the head that was normal, followed by an MRI that showed a left lateral medullary infarction. MRA the following day showed a thrombus of the distal left vertebral artery.

Additional labs returned as follows:

- Double-stranded DNA >400
- SSA (Ro) +, SSB (La) –
- Low C3, low C4
- Lupus anticoagulant +

How should this patient's stroke be treated? Does she require anticoagulation, and if so, for how long?

Given this patient's MRA showing a thrombus in the vertebral artery, she should begin anticoagulation with warfarin for at least 6 months. Clinical judgment could support the use of indefinite anticoagulation. Her positive lupus anticoagulant establishes initial laboratory criteria for antiphospholipid antibody syndrome (APS); it is important to discuss with the students that an official diagnosis of APS requires both clinical evidence of hypercoagulability (which this patient has manifested as thrombotic CVA) and lab evidence of hypercoaguable serologies on two separate occasions, at least 12 weeks apart. Therefore, this patient should begin anticoagulation with warfarin now, and have her labs checked for lupus anticoagulant, anticardiolipin, and anti-beta-2 glycoprotein 1 antibody again at least 12 weeks later. If her lupus anticoagulant remains positive, she would meet criteria for antiphospholipid antibody syndrome and be a candidate for indefinite anticoagulation.

The discussion can also be balanced with discussing the challenges of using warfarin in a patient like this. Warfarin is contraindicated in pregnancy and this young patient may want to have a family someday. Warfarin levels require regular monitoring and can fluctuate with certain types of foods and medications. Anticoagulation always carries a risk of life-threatening bleed, particularly from accidental trauma.