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 systemic lupus erythematosus (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 university hospital.

Three 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 by her primary care physician was 1 month ago. At that visit, a complete blood count and urinalysis were performed; however, the medical records from this visit were not available. She was told that she had anemia and a urinary tract infection. She was prescribed iron supplements for the anemia and an antibiotic for the infection. 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 systemic lupus erythematosus (SLE) often experience at the onset of their symptoms. This patient's history is based on an actual case. Certainly the complaints of rash, muscle pain, and fatigue should have prompted a more extensive evaluation (or closer follow-up) than she received, including a chemistry panel to look at electrolytes and creatinine, and a thyroid-stimulating hormone (TSH) test to screen for thyroid dysfunction. In her age group, Epstein-Barr virus (EBV) should be high on the differential diagnosis as well.

Many clinicians will start antibiotics empirically. While infection is high on the differential diagnosis, considering the epidemiology of lupus and the frequency of skin rashes and musculoskeletal manifestations at the onset of disease, SLE (and other systemic autoimmune diseases) should be on the list also.

Even with the limited data presented, one could make a strong case to include antinuclear antibodies (ANA) in the initial laboratory workup.

Over the last 2 weeks, the patient's fatigue worsened, and she began experiencing 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 emergency department (ED) for further evaluation. She was admitted from the ED 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, and majoring in biology. Denies 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

Head, Eye, Ear, Nose, and Throat (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: Rash on face, and "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 as 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. Some rashes are easily overlooked, such as those located only at the hairline, on the scalp, or in the ear canals.

Physical Exam

Height: 5'6"
Weight: 115 lbs

Vitals: Blood pressure 94/56, heart rate 118/minute, respirations 18/minute (nonlabored), temperature 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: Slightly hyperpigmented scaly rash over malar areas of cheeks, with erythema of palms and soles

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, two 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

Initial Laboratory Data

Complete Blood Count (CBC):

White blood cell count (WBC): 2.8 x 10^3/μL*

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

Hemoglobin: 9.0 g/dL*

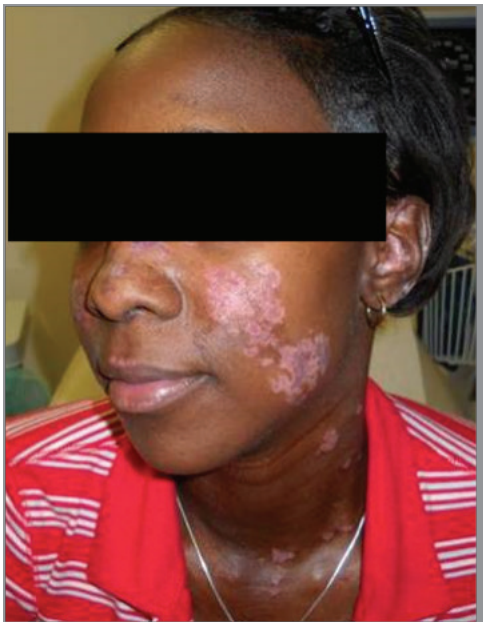

Image courtesy of Dr. Tammy Utset, Section of Rheumatology, University of Chicago.

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

Hematocrit: 25.7%*

Mean cell volume: 86 fL

Platelets: 210/μL

Comprehensive metabolic panel:

Sodium: 133 mEq/L*

Potassium: 4.2 mEq/L

Chloride: 105 mEq/L

Bicarbonate: 21 mEq/L

Blood urea nitrogen: 17 mg/dL

Creatinine: 0.7 mg/dL

Total protein: 7.8 g/dL

Albumin: 2.8 g/dL*

Total bilirubin 0.6 mg/dL

Aspartate aminotransferase: 32 U/L

Alanine aminotransferase: 36 U/L

Alkaline phosphatase: 50 U/L

Urinalysis:

30 mg/dL protein*

No blood

WBC: 3+ hpf*

Red blood cells: none

**Abnormal values*

Two-view chest X-ray: No cardiopulmonary process

Electrocardiogram: Sinus tachycardia

Considering the patient's 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. She is also lymphopenic, with an absolute lymphocyte count of 812 cells/μL. It is important to note that her anemia is normocytic and therefore not characteristic of iron-deficiency anemia as previously suggested. Consider 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 two possibilities, a ferritin should be ordered, as well as hemolysis studies, such as lactate dehydrogenase, haptoglobin, and a Coombs test.

The chemistry panel is notable for being essentially normal, except for a low albumin and increased globulin fraction. Consider possible causes of low albumin in this patient, including renal loss (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 2 x the albumin), which can indicate chronic inflammation, such as in SLE or human immunodeficiency virus (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 a 24-hour urine collection for total protein should be performed. The presence of pyuria should be further evaluated for the possibility of a urinary tract infection (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 serum 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 possibility.

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, testing for EBV, hepatitis C and B, HIV testing, rapid plasma reagin (RPR) for syphilis given the 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 UTI, and treated supportively for presumed sepsis with intravenous (IV) fluids. Blood and urine cultures were ordered, as well as HIV, EBV, hepatitis C and B, 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 temperatures 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 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?

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

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; the dose may need to be adjusted later due to the patient's low body weight.

Complement levels and specific autoimmune serologic tests, such as 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 ED 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 is the cause of this patient's new symptoms? What lab testing and radiographic testing should be pursued to further evaluate these symptoms?

Consider 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, central nervous system vascular disease related to SLE and hypercoagulable state should be on the top of the differential diagnosis.

Since her symptoms are most consistent with an ischemic stroke, she should be evaluated with CT and MRI, and tested for antiphospholipid antibodies. Consider how antiphospholipid antibody syndrome is diagnosed. 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 antibody, lupus anticoagulant, or positive anti-β_2-glycoprotein I 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. You should also be aware 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 partial thromboplastin time on routine coagulation testing because the antibodies interfere with phospholipids used to perform the test.

Additional Hospital Data

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

Additional labs returned as follows:

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

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 as soon as there is no evidence of hemorrhagic stroke and the risk of bleeding complications is acceptable. In this patient, waiting for lupus anticoagulant, anticardiolipin, and anti-β_2-glycoprotein I antibody test results to confirm the clinical working diagnosis of antiphospholipid syndrome (APS) is not acceptable. Immediate treatment should include anticoagulation with heparin or enoxaparin, followed by transition to warfarin for at least 6 months. However, the long-term treatment plan will require confirmatory laboratory testing of APS, and this should be carried out within 6 to 12 weeks of initial testing. If her lupus anticoagulant remains positive, she is a candidate for indefinite anticoagulation after a thorough review of risks.

Also consider the challenges of using warfarin in a patient like this since warfarin is contraindicated in pregnancy. Warfarin's effects require regular monitoring because the degree of anticoagulation can fluctuate widely with certain types of foods and medications. Anticoagulation always carries a risk of life-threatening bleed, particularly from accidental trauma.

Notes:

Refer to the Lupus Initiative Lecture series for more information.

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