TW Case Discussion Guide

Key Learning Objectives

- Construct a differential diagnosis for a systemic disease presentation with primarily cutaneous manifestations.
- Summarize barriers that impede patient follow-up.
- Describe the complications of pregnancy associated with systemic lupus erythematosus (SLE), and how these are evaluated and managed.
- Discuss the uses of relevant medications in the context of SLE and pregnancy.
- Summarize the importance of a multidisciplinary team approach when caring for patients with SLE.

History of Present Illness

The patient is an 18-year-old White, pregnant female, at 12-weeks gestation, admitted for evaluation of a diffuse skin rash.

She was diagnosed with systemic lupus erythematosus (SLE) 4 years ago at the age of 14. Her original manifestations included positive antinuclear antibodies (ANA), oral ulcers, rash, leukopenia, and swollen fingers. She was followed and treated by a pediatric rheumatologist. Her disease had been under good control with hydroxychloroquine and prednisone.

Three months ago, she became pregnant. As a result, her pediatric rheumatologist felt it was more appropriate for her to be followed by adult physicians. He began the process of transitioning her care to adult rheumatology and high-risk obstetrics. Several referrals were made; however, the patient was reluctant to establish care with new doctors and never made an appointment with either obstetrics or adult rheumatology.

She continued to take prednisone but stopped the hydroxychloroquine out of concern for toxicity to the baby.

Four weeks ago, at 8-weeks gestation, she began feeling fatigued and "run down." She developed oral ulcers typical of her SLE. She decided on her own to increase her prednisone dose in response, from 5 mg/day to eventually 35 mg/day. In spite of this, the ulcers continued to expand. Over about a 10-day period, she developed swollen, puffy lips and an erythematous rash over her cheeks, hands, chest, and feet. She began to feel feverish.

Her symptoms continued to the point that oral intake was severely limited due to odynophagia. She presented to the hospital with weight loss, odynophagia, low-grade fever, and diffuse rash.

What are your concerns regarding her new symptoms? What is your differential diagnosis for what might be causing these new symptoms?

This is a complicated patient with many issues that need to be considered in order to optimize her care. She is a pediatric patient, lost to follow-up care, and now pregnant with fever and mucocutaneous symptoms. One of the largest causes of morbidity in SLE patients is infection, and this should be at the top of their differential. Additionally, a flare of SLE prompted by both the patient's pregnancy and her self-discontinuation of medications should be considered. It is important to recognize that the initial presentation of a lupus flare can be very similar to that of infection (fever, malaise, fatigue, rash) and similar to many of the symptoms that occur in some women as a result of pregnancy.

What is known about pediatric-onset SLE that may make us more concerned about this patient?

A significant portion of SLE patients (15%, predominantly female) present in childhood, usually during adolescence. This patient

certainly fits into that category. Children with SLE are significantly more likely to have a more severe course of disease. Other important issues for consideration are the psychosocial issues stemming from childhood illness, including missed school, altered family dynamics, and compliance, all of which factor into SLE outcomes.

Additional Medical History

Past Medical History: SLE, diagnosed at age 14, with manifestations of oral ulcers, malar rash, arthritis, leukopenia, and positive ANA. No other past medical history. No prior pregnancies. No history of blood clots.

Family History: Mother with type 2 diabetes mellitus; no family history of autoimmune disease. Her father's medical history is unknown, as she has had no contact with him since the age of 5.

Social History: Lives with grandparents and boyfriend. Stopped attending high school when she became pregnant but was previously in her junior year. She intends to resume school after pregnancy. She does not smoke, drink alcohol, or use illicit drugs. Neither she nor her boyfriend is employed. Her mother works as a waitress. No other family members or close contacts have been ill.

How do you think her transition from pediatric to adult caregivers could have contributed to her illness? How might that have been improved?

Poor outcomes in SLE are influenced more by poverty and lack of education than genetics. Two important concepts for consideration are:

First is the concept of "self-efficacy," or the patient's confidence in his or her success in managing a complicated, chronic disease. Self-efficacy is lower in less educated individuals and those with lower socioeconomic status, and this alone is related to outcomes in SLE.

The second important concept is the role of the physician in understanding social and economic factors that impact a patient's ability to adhere to a therapeutic plan. In this case, the patient's young age, lack of education, and pregnancy likely impeded appropriate care and management of her SLE. Her physician might have improved the situation by addressing these issues. Specifically, her pediatric physician might have facilitated a visit where both pediatric and adult rheumatologists were present to assist with the patient's transition to adult rheumatology. In other settings, specialists are scarce, and adult rheumatologists, or even generalists, sometimes manage pediatric SLE patients. Therefore, it is important to note that the specific

doctors and specialties involved in the transition of this particular case are not the primary focus. The point is that proper transition of care between a pediatric and adult setting, and between any providers, is critical for all patient outcomes. The physicians might also have asked for the patient's permission to discuss her care with her family members, thereby engaging family members in helping the patient adhere to her treatment plan. It is important for physicians to be aware of the difficulty of the situation.

Physical Exam

Height: 5'8"
Weight: 135 lbs

Vitals: Temperature 38.3 °C (100.9 °F), blood pressure 125/57, pulse 112, respiratory rate 16, O2 saturation 99% on room air

General: Mildly cushingoid, White female, in mild distress from pain

Cardiovascular: Tachycardic, regular rhythm, no murmurs

Pulmonary: Clear to auscultation bilaterally

Abdomen: Gravid uterus, soft; mild epigastric tenderness, no rebound/guarding, palpable fetal movement

Musculoskeletal: Full range of motion of all joints; no evidence of synovitis or deformity

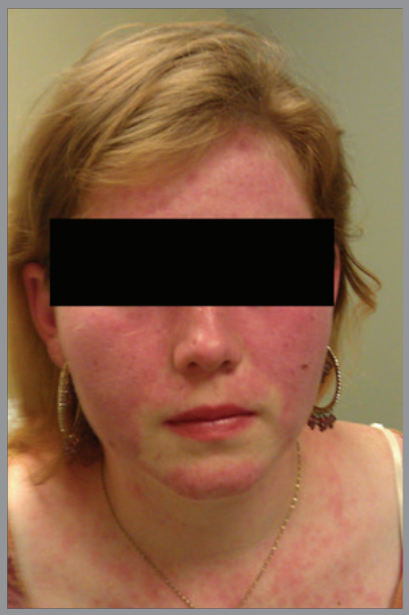

Image courtesy of Dr. Wael Jarjour, Director of the Division of Rheumatology & Immunology, The Ohio State University Wexner Medical Center.

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

Skin and mucous membranes:

- Oropharynx with ulcers on upper hard palate approximately 1.2 cm diameter, and multiple small ulcers on buccal mucosa
- Malar rash with erythematous plaques
- Erythematous patches over bilateral eyelids, chest, biceps (some of the rash over the biceps was ulcerated)
- Periungual hyperpigmentation
- Desquamating erythematous rash over the feet

Laboratory Data

Complete Blood Count (CBC):

- White blood cell count (WBC): 7.8 x 10^3/μL
- White count differential: 2% bands, 73% neutrophils, 18% lymphocytes
- Hemoglobin: 10.0 g/dL*
- Hematocrit: 30.4%*
- Platelets: 179
- Mean cell volume: 83

Comprehensive metabolic panel:

- Total protein: 6.1 g/dL*
- Albumin: 2.7 g/dL*
- All others normal

Urinalysis:

- No proteinuria
- No urine sediment

**Abnormal values*

What is your differential diagnosis for the patient's skin symptoms? What are the data for or against each item on your differential diagnosis? How would you further work this up?

Revisit your original differential diagnosis, which should include infection and SLE flare. At this point, you should be able to state more specifically which infections you are concerned about. Regarding infection, consistent signs and symptoms include fever and erythematous rash. You should be concerned about herpes simplex virus (HSV), which can cause mucocutaneous ulcerations or a

bacterial infection, such as staph. However, the normal WBC is not typical of an infection, which should prompt a discussion of the WBC in SLE. One of this patient's SLE manifestations is leukopenia, so it is important to recognize that a WBC of 7.8 may be relatively elevated in this patient with SLE, which is different than in the general population. Additionally, the increased proportion of neutrophils and presence of bands might suggest infection in this patient. Keep in mind that pregnancy itself, as well as glucocorticoid use may also contribute to leukocytosis. The increased risk of infection due to immunosuppressive medications (ie, glucocorticoid use in this patient) should also be considered.

Signs and symptoms suggestive of an SLE flare include the evolution of the rash, which began in a similar manner to her previous SLE skin flares, as well as oral ulcers, anemia, and hypoalbuminemia. In addition, she recently had two major changes: the advent of pregnancy and the discontinuation of her SLE medications, both of which can increase SLE activity.

What specific additional labs would you send given SLE and pregnancy? For which condition are you testing? Consider the pathophysiology of this condition and its potential manifestations.

SLE pregnancies are high risk for mother and baby, with increased C-sections, preterm birth, fetal loss, pre-eclampsia, gestational diabetes, and infection. An additional consideration is neonatal SLE, which is tested for by checking anti-SSA and -SSB autoantibodies, which are common in SLE as well as other conditions. Circulating anti-SSA and -SSB autoantibodies may cross the placenta into the fetal circulation, causing neonatal SLE in the fetus. This is an example of passive transfer of autoimmunity in that the autoantibodies from the mother are causing autoimmune disease in the fetus; the fetus is not producing autoantibodies on his own. The most serious manifestation of neonatal SLE is cardiac disease in which the autoantibodies deposit in developing cardiac tissue resulting in first-, second-, or third-degree heart block. Other manifestations of neonatal SLE include thrombocytopenia and/or a transient, erythematous rash that presents in the newborn infant. Double-stranded DNA antibodies are often elevated and complement levels are often decreased during an acute flare of SLE in both pregnant and nonpregnant patients, so these should be ordered as well.

What services would you consult to optimize this patient's workup and care?

This patient requires coordinated care by high-risk obstetrics and rheumatology, as well as an infectious disease consult to evaluate for the possibility of infection as the cause of the rash.

Hospital Course

The patient was admitted to the obstetrics (OB) service. Infectious disease, rheumatology, dermatology, and maternal-fetal medicine (high-risk OB) services were consulted to assist in her care.

Infectious disease felt that HSV or varicella zoster virus (VZV) skin infections could cause this degree of skin ulceration, or a drug reaction, but that SLE was the most likely cause. They recommended withholding empiric antibiotics unless the patient worsened and sent swabs of ulcers for bacteria and viral culture. Blood cultures were also performed.

Dermatology and rheumatology also felt that her clinical picture was due to a severe mucocutaneous SLE flare. Dermatology performed a skin biopsy. Anti–double-stranded DNA antibodies, anti-SSA and -SSB antibodies, and complement levels were ordered. Because of the severity of her symptoms, intravenous (IV) methylprednisolone sodium succinate 30 mg every 8 hours was started, and hydroxychloroquine was restarted before these labs had returned. Topical corticosteroids were also administered.

Results of Lab Testing

- Blood cultures and HSV, VZV cultures were negative
- Anti–double-stranded DNA antibodies >400 U/mL*; previously was 82 U/mL 3 months ago
- C3 = 110 mg/dL (normal is 75-135 mg/dL)
- C4 = 8 mg/dL* (normal is 15-75 mg/dL)
- anti-SSA antibodies = 8 U/mL (normal <8 U/mL)
- anti-SSB antibodies = 11 U/mL (normal <4 U/mL)
- Anticardiolipin antibody, anti-β_2-glycoprotein I antibody, and lupus anticoagulant were all negative

**Abnormal values*

Skin Biopsy Results

Degeneration of the basal layer of the epidermis. Edema at the dermo–epidermal junction. Some edema and perivascular mononuclear infiltrates. Immunofluorescence microscopy shows granular deposits of immuno–globulin G, C3, and immunoglobulin M, along the dermoepidermal junction.

Given what you know about the pathology of SLE nephritis, how do you interpret this patient's skin biopsy?

Immunoglobulin and complement deposits occur in various parts of the glomerulus, as well as around the glomerular basement

membrane. Consider what you know about kidney biopsies and apply that to the findings of immunoglobulin and complement deposits along the dermoepidermal junction in the skin. There is some homology between the dermoepidermal junction of the skin and the glomerular basement membrane of the kidney. Understanding that SLE is a systemic disease process, you should conclude that what can occur in the kidney can also occur in the skin or other tissues affected by SLE; therefore, this biopsy might be consistent with cutaneous SLE. Certainly the findings on immunofluorescence would not be consistent with an infectious process in the skin.

Given this patient's anti-SSA and -SSB antibodies, what additional testing is necessary to evaluate fetal well-being?

This brings up the topic of neonatal SLE again. Positive anti-SSA and -SSB antibodies place the fetus at risk for first-, second-, or third-degree heart block that may be irreversible if not detected early. In practice, the fetus is monitored with regular ultrasound and fetal echocardiograms looking for any cardiac abnormalities that might suggest the evolution of congenital heart block. Once heart block is detected, treatment options are limited. Often the patient is treated with betamethasone, a steroid that can cross the placenta to reach the fetus. However, in the majority of cases of SLE-related neonatal heart block, this damage to the cardiac tissue is irreversible in spite of steroid treatment. Therefore, the focus is on awareness, early detection, and planning neonatal care for a baby born with a heart block.

Consider what medications can be used to treat SLE during pregnancy. What medications are contraindicated?

Some of the more common medications used in SLE include: hydroxychloroquine, corticosteroids, and azathioprine. These can all be used during pregnancy, if clinically warranted. Methotrexate, mycophenolate mofetil, cyclophosphamide, and warfarin must not be used during pregnancy due to known teratogenic effects. In some cases the risk of certain immunosuppressives, such as cyclophosphamide, may be justified in the third trimester.

Hospital Course *(cont'd)*

The patient's skin biopsy is read as consistent with SLE. There is no viral cytopathic effect or other infiltrate to indicate concomitant infection.

By Hospital Day-4 on methylprednisolone sodium succinate, the patient's muco–cutaneous lesions had improved, and she was able to tolerate some oral intake.

She is started on azathioprine 50 mg daily to serve as a steroid-sparing agent, with a plan to increase this dose to 2 mg/kg over several weeks' time.

It is reasonable clinical practice to obtain thiopurine methyltransferase (TPMT) genetic testing to determine the safety of using high-dose azathioprine. The patient should also have regular lab follow-up.

Fetal ultrasound and echocardiogram are normal.

The patient continues to improve. Skin lesions show signs of healing, although there continue to be desquamating lesions on her feet. On Hospital Day-7, she feels slightly worse, with fatigue and malaise. She is noted on vitals to have a temperature of 38.4 °C (101.4 °F). The on-call obstetrics resident for the primary team is notified, and acetaminophen is given for fever.

The next morning, the patient is afebrile on morning rounds after two doses of acetaminophen; however, she continues to feel poorly. When the rheumatologist sees her in the afternoon, she is again febrile to 39.0 °C (102.2 °F).

Consider your differential diagnosis for the patient's fever and malaise. Why was she at risk for developing further complications? What needs to be sent for further evaluation?

At this point, infection again needs to be at the top of the differential diagnosis. The patient's admission diagnosis of mucocutaneous SLE flare is being treated, and she was showing signs of improvement. With this sudden deterioration, she must be evaluated for a new problem. Given her immunosuppression with high-dose steroids and prolonged hospital stay, she is at high risk for infection. She should have immediate blood and urine cultures and a chest X-ray for further evaluation. IV sites and skin should be examined for signs of infection. Also note the delay in evaluation of her fever by the primary team. While low-grade fever in a pregnant patient without SLE is often transient, responsive to acetaminophen, and not requiring further evaluation, fever in a complicated patient with active SLE should always prompt a full exam and evaluation for underlying infection. Infection is an even more serious concern given her fever developed while on glucocorticoids, which impair the immune system's response to infection.

Case Follow–Up

Within 8 hours, the patient's blood cultures returned positive with gram positive cocci in clusters.

Vancomycin was started for presumed *Staphylococcus aureus* bacteremia.

Twenty-four hours later the microbiology lab confirms methicillin-resistant *S. aureus* in the blood.

Given her staph bacteremia, she is at high risk for bacterial endocarditis. Trans-esophageal echocardiogram is ordered to evaluate her valves for endocarditis; however, given her oropharyngeal ulcerations, this is deferred in favor of a trans-thoracic echocardiogram.

The patient's rash begins to worsen, with new oral ulcerations presumably precipitated by the new infection.

By Hospital Day-9, the patient had responded well to antibiotics with negative follow-up blood cultures. Her rash began to heal again without any change in steroid dose, and she was slowly able to tolerate a full oral diet.

By Hospital Day-14, she was stable and ready for hospital discharge. She was discharged home with close outpatient follow-up with infectious disease, rheumatology, dermatology, and high-risk obstetrics. She was continued on prednisone, hydroxychloroquine and azathioprine, and had home health nursing visits arranged to complete a 14-day course of vancomycin for staph bacteremia.

In spite of a very complicated hospital course, the patient did well with her post-discharge care and at 38-weeks gestation, delivered a healthy newborn.

Notes:

Refer to the Lupus Initiative Lecture series for more information.

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